TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

PAEDIATRIC ENCEPHALITIS AND NEUROBORRELIOSIS

Studies on Diagnostics, Treatment and Outcomes

Heidi Pöyhönen

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1620 | MEDICA – ODONTOLOGICA | TURKU 2022

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

PAEDIATRIC ENCEPHALITIS AND NEUROBORRELIOSIS

Studies on Diagnostics, Treatment and Outcomes

Heidi Pöyhönen

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1620 | MEDICA – ODONTOLOGICA | TURKU 2022

University of Turku

Faculty of Medicine
Paediatric Neurology
Doctoral Programme in Clinical Research

Supervised by

Docent, Tuire Lähdesmäki, MD, PhD
Department of Paediatric Neurology
Turku University Hospital
Turku, Finland

Professor, Ville Peltola, MD, PhD
Department of Paediatrics and
Adolescent Medicine
Turku University Hospital
Turku, Finland

Reviewed by

Docent, Päivi Vieira, MD, PhD
Clinic for Children and Adolescents
Oulu University Hospital
Oulu, Finland

Docent, Tuula Pelkonen, MD, PhD
Children´s Hospital
Helsinki University Hospital
Helsinki, Finland

Opponent

Docent, Eeva-Liisa Metsähonkala MD, PhD
Children´s Hospital
Helsinki University Hospital
Helsinki, Finland

The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-951-29-8808-2 (PRINT)
ISBN 978-951-29-8809-9 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2022

To paediatric patients

UNIVERSITY OF TURKU
Faculty of Medicine
Paediatric Neurology
HEIDI PÖYHÖNEN: Paediatric Encephalitis and Neuroborreliosis: Studies on Diagnostics, Treatment and Outcomes
Doctoral Dissertation, 132 pp.
Doctoral Programme in Clinical Research
February 2022

ABSTRACT

The confirmed diagnosis of neuroborreliosis and encephalitis is essential, because safe and focused treatment may improve neurological outcomes. The prediction of outcome helps to guide support and rehabilitation.

We performed four separate studies to investigate the utility of cerebrospinal fluid samples in the diagnostics of facial palsy etiology in children; the dental safety of doxycycline in the treatment of neuroborreliosis and encephalitis in children under 8 years; and the predictive factors for long-term neurological outcomes after paediatric encephalitis. The studies were performed at the Department of Paediatrics and Adolescent Medicine, Turku University Hospital.

Our results revealed that borreliosis is a common etiology of acute facial nerve palsy in children and that the elevated levels of leucocytes, protein and CXCL13 chemokine in cerebrospinal fluid were signs of *Borrelia* infection. Doxycycline given at young age was found not to cause permanent teeth staining. The recovery from facial palsy was good, but recovery after encephalitis was poorer: More than a quarter of children suffered from moderate or severe disability. The complexity of acute phase neuroimaging findings associated with long-term disability. We also found that 71% of children without evident disability had minor neurological dysfunction, which associated with lower cognitive performance. These deficits related to difficulties in everyday life performance. Young age at encephalitis was associated with lower cognitive performance.

According to our results, cerebrospinal fluid sample analysis is a valuable tool in the diagnostics of facial palsy. Our data strengthen the previous knowledge of the safety of doxycycline in the treatment of neuroborreliosis and encephalitis in children and underline the high disability rates and the need for long-term follow-up after paediatric encephalitis.

KEYWORDS: borreliosis, cognitive performance, CXCL13 chemokine, dental staining, doxycycline, encephalitis, facial nerve palsy, lumbar puncture, neuroborreliosis, neuroimaging, neurological performance

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Lastenneurologia
HEIDI PÖYHÖNEN: Lasten enkefaliitit ja neuroborrelioosi: tutkimuksia diagnostiikasta, hoidosta ja ennusteesta
Väitöskirja, 132 s.
Turun kliininen tohtoriohjelma
Helmikuu 2022

TIIVISTELMÄ

Neuroborrelioosin ja enkefaliitin diagnostiikka voi olla haastavaa. Turvallinen ja oikein kohdennettu hoito voi parantaa potilaiden ennustetta. Ennustetta heikentävien tekijöiden tunnistaminen auttaa kohdentamaan seurantaa ja kuntoutusta oikeille potilaille.

Teimme neljä erillistä tutkimusta selvittääksemme selkäydinnestetutkimuksen käyttökelpoisuutta kasvohermohalvausten etiologian diagnostiikassa, doksisykliinihoidon hammasturvallisuutta neuroborrelioosin ja enkefaliitin hoidossa alle 8-vuotiailla lapsilla, ja neurologista pitkäaikaisennustetta enkefaliitin jälkeen. Tutkimukset toteutettiin Tyksin lasten ja nuorten klinikalla.

Tulokset osoittivat, että borrelioosi on lasten kasvohermohalvausten yleinen aiheuttaja, ja siihen viittasivat selkäydinnesteen kohonnut valkosolu-, proteiini- ja CXCL13-pitoisuus. Doksisykliinihoitoa saaneilla lapsilla ei todettu pysyvien hampaiden värjäytymistä. Toipuminen kasvohermohalvauksesta oli hyvä lähes kaikilla, mutta aivotulehduksen jälkeen kohtalainen tai vaikea vamma jäi yli neljännekselle. Vaikeampi löydös aivojen magneettikuvassa oli yhteydessä vaikeampaan vammautumiseen. Lievempiä neurologisia jäännösoireita havaittiin 71 %:lla tutkittavista, ja ne olivat yhteydessä heikompaan kognitiiviseen suoriutumiseen. Nuori sairastumisikä lisäsi riskiä heikommalle suoriutumiselle.

Tutkimuksemme osoitti, että selkäydinnestetutkimus on hyödyllinen kasvohermohalvauksen diagnostiikassa. Löydöksemme vahvistavat aiempia tuloksia doksisykliinihoidon hammasturvallisuudesta lapsilla, ja korostavat enkefaliitin sairastaneiden lasten pitkäaikaisseurannan tarpeellisuutta suuren vammautumisriskin vuoksi.

AVAINSANAT: borrelioosi, CXCL13-kemokiini, doksisykliini, enkefaliitti, hammasvärjäymät, kasvohermohalvaus, kognitiivinen ennuste, magneettitutkimus, neuroborrelioosi, neurologinen ennuste, selkäydinnestenäyte

Table of Contents

Abbreviations

AAN	American Academy of Neurology
ADEM	Acute disseminated encephalomyelitis
AED	Antiepileptic drug
ANE	Acute necrotizing encephalopathy
BRIEF	Behavior Rating Inventory of Executive Function
CMV	Cytomegalovirus
CNS	Central nervous system
CRP	C reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
CXCL13	C-X-C motif chemokine ligand 13
EBV	Epstein-Barr virus
EEG	Electroencephalogram
EFNS	The European Federation of Neurological Societies
ELISA	Enzyme-linked immunosorbent assay
ENMG	Electroneuromyogram
FNGS 2.0	Facial nerve grading system 2.0
FIRES	Febrile infection-related epilepsy syndrome
GOS	Glasgow outcome scale
GOS-E	Glasgow outcome scale extended
H-B FNGS	House-Brackmann Facial Nerve Grading System
HHV	Human herpesvirus
HSV	Herpes simplex virus
ICD-10	The international classification of diseases, 10th Revision
ICH	Intracranial hemorrhage
ICU	Intensive care unit
IQ	Intelligence quotient
LOS	Liverpool Outcome Scale
cMND	Minor neurological dysfunction; complex
sMND	Minor neurological dysfunction; simple
MRI	Magnetic resonance image; magnetic resonance imaging

mRS	Modified Ranking Scale
PCPC	Paediatric Cerebral Performance Category
PCR	Polymerase chain reaction
PROMIS	Patient-Reported Outcomes Measurement Information System
TBE	Tick-borne encephalitis
VZV	Varicella zoster virus
WAIS	Wechsler Adult Intelligence Scale
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Heidi Pöyhönen, Tuire Lähdesmäki, Jukka Hytönen, Ville Peltola. Cerebrospinal Fluid Pleocytosis and Elevated C-X-C Motif Chemokine Ligand 13 Value Predict Lyme Borreliosis in Children With Facial Palsy. *The Pediatric Infectious Disease Journal,* 2019; 38: 1195–1198.

II Heidi Pöyhönen, Mirka Nurmi, Ville Peltola, Satu Alaluusua, Olli Ruuskanen, Tuire Lähdesmäki. Dental Staining After Doxycycline Treatment in Children. *Journal of Antimicrobial Chemotherapy*, 2017; 72: 2887–2890.

III Heidi Pöyhönen, Sirkku Setänen, Nea Isaksson, Mikko Nyman, Anna Nyman, Ville Peltola, Tuire Lähdesmäki. Neurological and Cognitive Outcome after Childhood Encephalitis. *Frontiers in Pediatrics*, 2021; 6: 9: 646684.

IV Heidi Pöyhönen, Mikko Nyman, Ville Peltola, Eliisa Löyttyniemi, Tuire Lähdesmäki. Acute Phase Neuroimaging and the Neurological Outcome after Pediatric Encephalitis (manuscript).

The original publications have been reproduced with the permission of the copyright holders.

1 Introduction

The most frequent presentation of neuroborreliosis in children is mononeuritis affecting the facial nerve (Mygland et al., 2010). *Borrelia* infection causing facial nerve palsy cannot be distinguished from idiopathic facial nerve palsy by clinical examination. Thus, specific and sensitive diagnostic methods during acute symptoms are needed to help select the focused treatment based on the etiology of the nerve palsy.

Oral doxycycline has been proven to be as effective as intravenous ceftriaxone in neuroborreliosis treatments (Dotevall & Hagberg, 1999) and is effective for macrolide resistant *Mycoplasma pneumoniae* infections as well (Lung et al., 2013). Oral doxycycline treatment does not necessitate hospitalization, which makes it a more cost-effective and patient-friendly treatment. Despite these benefits, the fear of dental staining linked to tetracyclines has limited the use of doxycycline in small children.

Encephalitis is a severe infection or inflammation of the brain with several clinical subtypes and etiologies. The neurological sequelae after paediatric encephalitis can be severe, and the means to predict outcome are limited. Certain microbial etiologies, such as *M. pneumoniae* (Lehtokoski-Lehtiniemi & Koskiniemi, 1989) and herpes simplex virus (Ward et al., 2012), increase the risk for neurological sequelae. Early management may improve outcome (Titulaer et al., 2013). The etiology is usually confirmed later during the course of the disease, if ever, so the empiric treatment should cover all treatable microbial agents of major importance.

This study aimed to investigate the accuracy of cerebrospinal fluid pleocytosis, elevated protein level and elevated CXCL13 chemokine level in the diagnostics of neuroborreliosis and facial palsy recovery in children. Furthermore, we wanted to study the overall, long-term neurologic outcomes after paediatric encephalitis and, separately, the neurological and cognitive performance in children surviving encephalitis with milder sequelae. The dental safety of doxycycline used in the treatment of encephalitis and neuroborreliosis of small children was also studied.

2 Review of the Literature

2.1 Neuroborreliosis presenting as facial palsy

2.1.1 Epidemiology

Neuroborreliosis, or Lyme neuroborreliosis, is a tick-mediated central nervous system (CNS) infection caused by the *Borrelia burgdorferi* spirochete. Southwest Finland is an endemic area of *B. burgdorferi*. In *Borrelia* endemic areas, such as northern and central Europe, the annual incidence of neuroborreliosis in children is reported to be 2.8 to 28 per 100 000 (Christen, 1996; Jenke et al., 2011; Södermark et al., 2017). Acute peripheral facial nerve (seventh cranial nerve) palsy affects 21 to 25 per 100 000 children annually (Jenke et al., 2011; Tveitnes et al., 2007). Previous Finnish studies reported that the annual incidence of facial palsy in children has been 8.6 per 100 000, and *Borrelia* was the causative agent in about one third of those cases (Kanerva et al. 2013; Peltomaa el al. 1998). However, neither of these studies reported the incidence of facial palsy or neuroborreliosis in the *Borrelia* endemic area of Southwest Finland.

Facial palsy is the most common clinical manifestation of neuroborreliosis in children in Europe, presenting in 23 to 90% of cases (Berglund et al., 1995; Bingham et al., 1995; Mygland et al., 2010; Skogman et al., 2015). Other neurological manifestations of borreliosis, such as acute myelitis, painful radiculitis, other cranial neuropathies or encephalitis, which present with symptoms like hemiparesis, opsoclonus-myoclonus or ataxia, are less frequent (Belman et al., 1997; Dutta et al., 2021; Huisman et al., 1999; Knudtzen et al., 2017; Vukelic et al., 2000; Wilke, 2000; Ylitalo & Hagberg, 2009). Meningitis symptoms are also rare (0–10%) despite commonly occurring cerebrospinal fluid (CSF) lymphocytic pleocytosis (Albisetti et al., 1997; Belman et al., 1997; Knudtzen et al., 2017). Common coexisting symptoms presenting with facial palsy are headache, malaise, fatigue and fever (Mygland et al., 2010; Peltomaa et al., 1998; Skogman et al., 2015; Södermark et al., 2017). Early neurological manifestations of borreliosis, such as facial palsy or meningitis, usually present from one to twelve weeks after tick bite, and late manifestations, such as encephalitis or myelitis, may present even several months after tick bite (Mygland et al., 2010).

2.1.2 Diagnostic criteria

The European Federation of Neurological Societies (EFNS) guidelines stated the criteria for Lyme borreliosis and Lyme neuroborreliosis. All three criteria should be fulfilled for definite Lyme neuroborreliosis, and two of them should be fulfilled for possible Lyme neuroborreliosis. The criteria are 1) neurological symptoms, 2) CSF pleocytosis, and 3) *B. burgdorferi* specific antibodies produced intrathecally (Mygland et al., 2010).

2.1.3 Differential diagnostics

Borrelia infections are the cause for acute facial palsy, even in endemic areas, in only 17 to 65% of children (Christen et al., 1990; Engervall et al., 1995; Munro et al., 2020; Peltomaa et al., 1998; Tveitnes et al., 2007). Other pathogens, such as varicella zoster virus (VZV), herpes simplex virus (HSV) 1 and 2, human herpes virus (HHV) 6, Epstein-Barr virus (EBV), or cytomegalovirus (CMV), can also cause acute facial palsy in children (Aydoğdu et al., 2015; Genizi et al., 2019; Peltomaa et al., 1998). The etiology can also be structural, such as trauma, tumor, or acute otitis media; inflammatory or related to a systemic disorder such as multiple sclerosis, sarcoidosis, Kawasaki disease, polyradiculitis or leukemia; or genetic in rare cases, such as Melkerson-Rosenthal syndrome (Cha et al., 2008; Ellefsen & Bonding, 1996; Grundfast et al., 1990; May et al., 1981; Pavlou et al., 2011; Peltomaa et al., 1998). The etiology remains unknown in 16 to 66% of cases (Cha et al., 2008; Grundfast et al., 1990), diagnosed as idiopathic facial palsy or Bell´s palsy.

Facial palsy caused by neuroborreliosis cannot be distinguished from idiopathic facial palsy with clinical examination. However, there are some features that predict neuroborreliosis in patients with facial palsy: presentation of illness mainly during the second half of the year and associated neurological symptoms outside the facial nerve (Bremell & Hagberg, 2011; Nigrovic et al., 2008). Only 14–63% of patients can recall a tick bite, and not more than 10–36% have noticed earlier local skin infection, erythema migrans (Albisetti et al., 1997; Backman & Skogman, 2018; Belman et al., 1997; Knudtzen et al., 2017; Mygland et al., 2010; Skogman et al., 2012; Skogman et al., 2015; Södermark et al., 2017; Tveitnes et al., 2007). Therefore, these factors cannot be used as independent predictive markers for neuroborreliosis. However, a score to assess the possibility of neuroborreliosis by the presence of certain symptoms and findings (facial palsy, fever, fatigue, erythema migrans or lymphocytoma and CSF pleocytosis) has been developed. The diagnostic accuracy of this score in children with suspicion of neuroborreliosis (presenting with facial palsy in 49% of patients) was 90% (Skogman et al., 2015).

2.2 Encephalitis

2.2.1 Epidemiology

Encephalitis affects 16 per 100 000 children annually worldwide (Johnson, 1998). The overall incidence in children in Finland is reported to be 10.5 per 100 000 and 18.4 per 100 000 among <1-year-old children (Koskiniemi et al., 1997).

2.2.2 Diagnostic criteria

Encephalitis is an inflammatory disease of the brain causing neurological dysfunction. The international definition of encephalitis includes the presence of encephalopathy (altered level of consciousness, lethargy or change in personality) lasting at least 24 hours and exclusion of encephalopathy from other causes. Additional criteria, such as seizures and focal neurological signs, and CSF, neuroimaging and electroencephalography (EEG) changes consistent with encephalitis, are required for possible (at least two criteria) and confirmed (at least three criteria) diagnosis (Venkatesan et al., 2013).

2.2.3 Differential diagnostics

The symptoms of encephalitis can resemble any brain dysfunction caused by, e.g., febrile seizures, hypoglycemia or electrolyte disturbances during viral infections. Objective methods are needed to detect infection or inflammation in the CNS.

The etiology of encephalitis includes microbial organisms causing direct CNS infection and pathologic mechanisms mediated by the immune system (Thompson, C. et al., 2012). The infective organisms causing encephalitis in developed countries are respiratory and herpes group viruses, enteroviruses, tick-borne encephalitis (TBE) virus and *M. pneumoniae* (Britton et al., 2020; Fowler et al., 2008; Iff et al., 1998; Kolski et al., 1998). The previously common mumps, measles and rubella encephalitis have become rare due to vaccination programs (Koskiniemi et al., 1991). The etiology remains unknown in 25 to 66% of cases overall and in 44 to 54% of cases in previous Finnish studies (Bykowski et al., 2015; DuBray et al., 2013; Elenga et al., 2020; Fowler et al., 2020; Galanakis et al., 2009; Glaser et al., 2003; Hon et al., 2016; Koskiniemi et al., 2001; Pillai et al., 2015; Rantala et al., 1991).

Encephalitis can be classified into different clinical subtypes. Autoimmune encephalitis is a group of disorders presenting with an acute or subacute onset of neuropsychiatric symptoms due to an abnormal immune response affecting the CNS (Cellucci et al., 2020; Dalmau & Graus, 2018; Hacohen et al., 2013). Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease

of the CNS that involves mostly white matter of the brain and spinal cord (Esposito et al., 2015). Acute cerebellitis has characteristics of cerebellar dysfunction such as ataxia or nystagmus, accompanied by other encephalitis-related symptoms and magnetic resonance imaging (MRI) abnormalities of the cerebellum (Kornreich et al., 2016; Lancella et al., 2017; Yildirim et al., 2020). Infection-related encephalopathies, such as acute necrotizing encephalopathy (ANE) due to RANBP gene mutation (Neilson et al., 2009) and febrile infection-related epilepsy syndrome (FIRES) (Hon et al., 2018; van Baalen et al., 2010), are often considered acute encephalitis because they fulfill the diagnostic criteria of encephalitis during the acute phase of illness.

2.3 Diagnostic tools

2.3.1 Neuroimaging

An MRI reveals encephalitis-related abnormalities in brain parenchyma in an earlier phase of acute illness better than does computed tomography (CT) (Aygun et al., 2001; Koelfen et al., 1996; Kolski et al., 1998) and is nowadays a primary neuroimaging method used in children. MRI does not cause any radiation exposure, but it requires sedation in small children due to the longer scanning time (Artunduaga et al., 2021).

A brain MRI can be normal or abnormal according to encephalitis-related pathology in paediatric encephalitis. The rate of abnormal MRI varies by etiology: In the California Encephalitis Project, including adults and children, MRI showed abnormal findings in 100% of the HSV and VZV cases but in only 40% of the enterovirus cases (Gable et al., 2012). The MRI findings associated with ADEM are typically multiple, bilateral, asymmetric, poorly marginated, demyelinated lesions of deep gray and white matter. The abnormal MRI is pathognomonic for diagnosis in ADEM, while the MRI is abnormal in only less than half of the cases in anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis (Howarth et al., 2019; Messacar et al., 2018). The findings can also vary in complexity, ranging from barely meningeal enhancement or focal nonenhancing lesions to multifocal or confluent lesions, or at worst, to diffusion restriction, hemorrhage or hydrocephalus (Bykowski et al., 2015).

Typical locations of neuroimaging findings in encephalitis caused by certain viruses are, e.g., temporal lobe for HSV, thalamus and basal ganglia for influenza and other respiratory viruses, cerebellum for VZV, and brainstem for enterovirus 71 and HSV. Reductions of whole brain, gray matter, hippocampal and basal ganglia volumes were seen in children with NMDAR encephalitis in volumetric MRI analyses (Howarth et al., 2019).

Imaging findings in paediatric encephalitis differ from those in adults. Multifocal lesions and extratemporal and deep gray matter involvement are reported to be more common in children than adults in HSV encephalitis (Beattie et al., 2013; De Tiège et al., 2008; Elbers et al., 2007; Galanakis et al., 2009; Koelfen et al., 1996; Kolski et al., 1998; Leonard et al., 2000; Schlesinger et al., 1995; Ward et al., 2012), especially in the youngest patients (Schleede et al., 2013). The thalami and basal ganglia were predominately affected in a small study of children with TBE (von Stülpnagel et al., 2016).

Neuroimaging is not necessary in the diagnostics in neuroborreliosis presenting as typical mononeuritis, peripheral facial nerve palsy. The neuroimaging is needed to exclude brain pathologies like ischemic or hemorrhagic stroke in central facial nerve palsy.

2.3.2 Electroencephalogram and electroneuromyogram

EEG findings related to encephalitis are often nonspecific, such as generalized slowing or epileptiform discharges (Venkatesan et al., 2013). More specific abnormalities can be seen in some entities, e.g., repetitive sharp wave complexes over the temporal lobes or periodic lateralizing epileptiform discharges in HSV 1 encephalitis (Lai & Gragasin, 1988).

Electroneuromyogram (ENMG) may be used in diagnostics and follow-up of facial palsy. It may help when assessing the nature (myelinic or axonal) and severity of nerve damage (Benaim et al., 2015).

2.3.3 Cerebrospinal fluid analysis

Pleocytosis and elevated protein level in the CSF are signs of CNS infection or inflammation (Belman et al., 1997; Bremell & Hagberg, 2011; Hébert et al., 2020; Venkatesan et al., 2013). Pleocytosis is defined as a CSF leucocyte count above 5 x 10^6 /L and an elevated protein level as a value above the normal range according to the child´s age (Kahlmann et al., 2017; A. Venkatesan et al., 2013). Oligoclonal banding or specific autoimmune antibodies can be found in the CSF in autoimmune encephalitis (Cellucci et al., 2020).

A normal CSF sample does not exclude CNS inflammation in the early phase of the disease and in immunocompromised patients. The CSF leucocyte count is <1000 x 10^6/L and lymphocytes predominate in the majority of encephalitis and neuroborreliosis cases. The leucocyte count in a traumatic lumbar puncture has to be adjusted to the red blood cell count in the CSF. The following formula can be used:

True leucocyte count in CSF = actual leucocyte count in CSF – (red blood cell count in CSF x leucocyte count in blood) / red blood cell count in blood (Venkatesan et al., 2013).

Mononuclear pleocytosis is a strong predictive factor for the diagnosis of neuroborreliosis in adults and children with facial palsy in *Borrelia* endemic areas (Albisetti et al., 1997; Belman et al., 1997; Bremell & Hagberg, 2011; Skogman et al., 2015; Tveitnes et al., 2007). The positive predictive value of pleocytosis for microbiologically proven neuroborreliosis has been reported as 68% and has a negative predictive value for a normal CSF leucocyte count of 92% to rule out neuroborreliosis (Ogrinc et al., 2013).

2.3.4 Microbiological diagnosis

2.3.4.1 Microbiological diagnosis of neuroborreliosis

The microbiological diagnosis of borreliosis is based on detecting specific antibodies in serum or CSF. The positive polymerase chain reaction (PCR) test for *B. burgdorferi* in a CSF sample is a strong indicator for neuroborreliosis, but the sensitivity of the PCR is only 10–30% (Wilske et al., 2007). The antibody testing for *B. burgdorferi* is performed by a two-step procedure: 1) a sensitive Enzyme-linked immunosorbent assay (ELISA) differentiating IgM and IgG, and 2) immunoblots (IgM and IgG) if ELISA is reactive (Sanchez et al., 2016; Steere et al., 1990; Wilske, 2003).

2.3.4.2 Microbiological diagnosis of encephalitis

Encephalitis-related pathogens can be detected in blood, CSF, throat, nasopharyngeal, tracheal or fecal samples by a PCR test and/or in CSF and serum by detecting specific antibodies. The detection of pathogens in brain tissue sample collected by brain biopsy is rarely used (Ellul & Solomon, 2018). The International Encephalitis Consortium's guideline for evaluating microbial etiology was published in 2013 (Venkatesan et al., 2013). HSV 1 and 2 and VZV should be tested by the PCR and can also be considered to be tested by antibodies in the CSF due to the low sensitivity of PCR testing. Enterovirus can be tested by the PCR in CSF and PCR and/or stool culture or throat sample, and evaluating both CNS and extra-CNS samples is essential. Epstein-Barr virus (EBV) may be found by antibodies in serum and PCR test in CSF, and *M. pneumoniae* may be found by PCR test in CSF, nasopharyngeal or throat sample or by antibodies in serum or CSF. Serology or PCR testing alone may be unreliable in encephalitis diagnostics due to a high incidence of *M. pneumoniae* in the respiratory tract of healthy children and the limited

specificity of available tests (Christie et al., 2007). Thus, it is recommended to use both PCR testing and serology. Additionally, TBE virus antibodies in serum and CSF and tests for neuroborreliosis are recommended in endemic areas. Specific signs, symptoms, and laboratory test or neuroimaging findings can guide the diagnostic evaluation to study certain pathogens, e.g., cerebellar signs, or a typical rash may raise a suspicion of a VZV infection. However, the approach to evaluate the microbial etiology of encephalitis varies widely in clinical practice.

2.3.5 C-X-C motif chemokine ligand 13

C-X-C motif chemokine ligand 13 (CXCL13) is produced by CNS monocytes as a part of the innate immune response to *B. burgdorferi* outer surface proteins. Its function is to recruit B cells to the site of the CNS infection (Rupprecht et al., 2008). CXCL13 is a useful marker of an active neuroborreliosis; its CSF concentration rises at the early disease phase and decreases after treatment. Thus, it reacts much faster than specific antibodies, which can have several weeks´ delay before their rise from the beginning of the disease and remain elevated for months or even years after neuroborreliosis (Hytönen et al., 2014). CXCL13 can also be detected by point-of-care testing (Pietikäinen et al., 2018).

An elevated CSF CXCL13 level has predicted Lyme neuroborreliosis in children with 88% sensitivity and 89–99% specificity with 55–160 ng/L cut-off levels. The median CXCL13 concentration in children with definite or possible Lyme neuroborreliosis has varied from 686 to 7303 ng/L. (Henningsson et al., 2018; Remy et al., 2017; Sillanpää et al., 2013). CSF CXCL13 has also been positively associated with CSF leucocyte and protein levels, as well as with the detected CSF *Borrelia* antibodies in children with Lyme neuroborreliosis (Barstad et al., 2019). However, there are no previous studies of accuracy of CXCL13 chemokine predicting *Borrelia* infection in children with facial palsy.

CXCL13 concentration can be elevated in certain other diseases causing neuroinflammation, e.g., neurosyphilis and autoimmune disorders such as multiple sclerosis. The elevation of CXCL13 concentration in autoimmune disorders has been less than in neuroborreliosis. Instead, a single neurosyphilis patient included in the study had a markedly elevated CXCL13 concentration, indicating that spirochetal infections other than neuroborreliosis may also raise the CXCL13 concentration (Hytönen et al., 2014; Leypoldt et al., 2015).

2.4 Treatment

2.4.1 Antimicrobial treatment

The treatment of suspected encephalitis should be empirical due to delay in microbiologic results. According to the Association of British Neurologists and British Paediatric Allergy Immunology and Infection Group's National Guidelines, intravenous acyclovir should be started immediately if the CSF analysis or neuroimaging findings suggest viral encephalitis and at least within six hours of admission (Kneen et al., 2012). The early initiation of acyclovir is suggested to improve neurological outcomes in paediatric HSV encephalitis (Cameron et al., 1992; Lahat et al., 1999). Acyclovir treatment is usually initiated if there is a strong clinical suspicion of VZV or HSV encephalitis, even if the first CSF analysis or neuroimaging findings are normal. However, in VZV cerebellitis, acyclovir treatment is not necessarily needed, because it is suggested to a be post-infectious, immunomediated and typically self-limited illness (Hausler et al., 2002; Kneen et. al, 2012). Intravenous ceftriaxone is recommended in the case of suspected bacterial meningitis or *Borrelia* encephalitis (Mygland et al., 2010; Thompson, C. et al., 2012). Other antimicrobial drugs are recommended to be used when a specific etiology is confirmed, e.g., oseltamivir for influenza virus encephalitis and ganciclovir or foscarnet for HHV6 and CMV encephalitis. Azithromycin, doxycycline or a fluoroquinolone can be considered for *Mycoplasma* encephalitis, though there is no evidence of effects on outcomes (Britton et al., 2015; Daxboeck et al., 2004; Tunkel et al., 2008).

Intravenous ceftriaxone and penicillin have been reported to have similar efficacy in the treatment of Lyme neuroborreliosis in children (Müllegger et al., 1991). Several studies suggest good response to intravenous penicillin, ceftriaxone and cefotaxime, and oral doxycycline (Hansen & Lebech, 1992; Krbkova & Stanek, 1996; Thorstrand et al., 2002).

The EFNS guidelines and the Clinical Practice Guidelines by the Infectious Diseases Society of America, American Academy of Neurology (AAN) and American College of Rheumatology recommend that children with definite or possible Lyme neuroborreliosis with symptoms of inflammation of meninges, cranial nerves, nerve roots or peripheral nerves should be treated with a 14-day course of oral doxycycline or intravenous penicillin, ceftriaxone or cefotaxime; children with late CNS manifestations such as encephalitis, myelitis or vasculitis should be treated with a 14- to 21-day course of intravenous ceftriaxone (Lantos et al., 2021; Mygland et al., 2010). According to the EFNS guidelines, doxycycline is contraindicated in children under 8 (or in some countries 9) years (Mygland et al., 2010).

2.4.1.1 Doxycycline

Doxycycline is a member of tetracycline-class antibiotics. Doxycycline is effective against *B. burgdorferi* and *M. pneumoniae* (Karlsson et al., 1994; Ljøstad et al., 2008; Lung et al., 2013), both of which can cause CNS infections. Resistance of *M. pneumoniae* to macrolides has increased in some countries (Lung et al., 2013; Okada et al., 2012), but resistance to doxycycline has not been reported. Doxycycline is also a useful antimicrobial agent in the treatment of anthrax and Rocky Mountain spotted fever, as well as brucellosis, pasteurellosis, rickettsioses, treponematosis, cholera, leptospirosis, Q fever, gonococcal infections, pulmonary and urinary infections caused by *Chlamydia* species, and acne, and in prophylaxis of malaria (Aupee et al., 2009; Benavides & Nahata, 2002; Cale & McCarthy, 1997). According to experimental animal studies, doxycycline may have neuroprotective properties in pneumococcal meningitis, neurodegenerative conditions and hypoxic-ischemic brain injury (Lazzarini et al., 2013; Meli et al., 2006; Wang et al., 2012; Widerøe et al., 2012).

Classical tetracyclines bind calcium ions, which leads to accumulation of tetracycline-calcium complexes in teeth. Tetracycline treatment during the rapid calcification phase of teeth results in permanent dental staining (Committee on Infectious Diseases; American Academy of Pediatrics., 2015; Demers & Fraser, 1968; Sánchez et al., 2004; Shwachman et al., 1958). Teeth staining is typically first yellow, and finally, upon exposure to light, brown and grey (Forti & Benincori, 1969; Moffitt et al., 1974). The location of the staining coincides with the part of the tooth calcifying at the time of tetracycline administration. Discoloration can be seen as diffuse bands at different levels of the crown in permanent teeth.

Figure 1 shows tetracycline-like dental staining. (Weyman, 1965)**.**

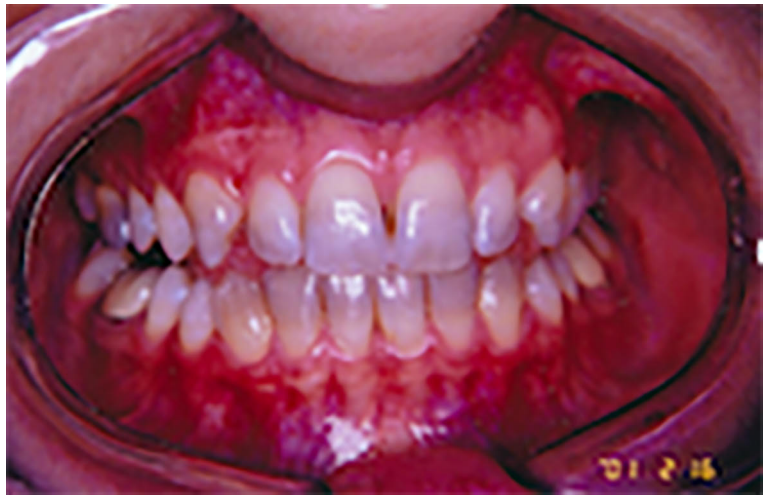

Figure 1. Tetracycline-related dental staining. Photograph by professor S. Alaluusua.

Furthermore, it has been suggested that tetracyclines could cause enamel hypoplasia, but this is somewhat controversial (Salanitri et al., 2013; Seow, 1991).

The thickness of the pigmented bands in teeth relates to the duration of administration, the intensity of discoloration to dose, and the number of pigmented bands to number of courses. The discoloration rate varies from 23 to 92% (Ayaslioglu et al., 2005; Boast et al., 2016; Conchie et al., 1970; Grossman et al., 1971; Moffitt et al., 1974). Prenatal and neonatal time are high-risk periods for a child´s molar teeth pigmentation. Permanent dentition is not that vulnerable for intense pigmentation due to its thicker enamel and slower mineralization (Guggenheimer, 1984; Hamp, 1967). Calcification of permanent teeth begins around 3–4 months of life and is largely complete by 5–6 years of age. This puts children under 4 years of age at the highest risk for dental staining. The risk of cosmetically disruptive dental staining is considered low after the age of 5 years, especially if treatment duration is short and multiple courses are not used (Ayaslioglu et al., 2005; Grossman et al., 1971; Shetty, 2002).

Doxycycline is a second-generation tetracycline and differs from classical tetracyclines in several aspects. It can be used in lower doses and with less frequent administration than, e.g., oxytetracycline (Agwuh & MacGowan, 2006; Cross et al., 2016; Cunha et al., 1982). It has lower calcium binding capacity, is more fat-soluble with better ability to penetrate through the blood–brain barrier, and is more potent against anaerobic bacteria than classical tetracyclines. Furthermore, doxycycline is cost effective, fully absorbed enterally, well tolerated, and importantly, most pathogens have not acquired resistance against it (Aupee et al., 2009; Dotevall & Hagberg, 1989; Eckman et al., 1997; Forti & Benincori, 1969; Karlsson et al.,1996; Von Wittenau, 1968). **Figure 2** shows the chemical formula of oxytetracycline and doxycycline.

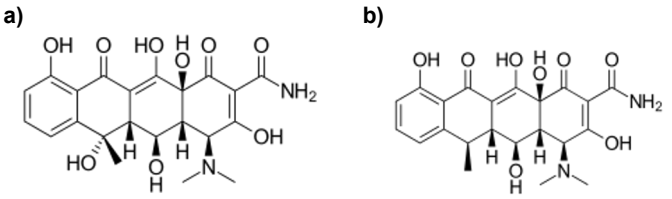

Figure 2. The chemical formula of a) oxytetracycline and b) doxycycline

Like other tetracyclines, doxycycline has been recommended to be avoided in children under 8 years (Committee on Infectious Diseases; American Academy of Pediatrics., 2015; Mygland et al., 2010). Two of the latest studies showed that doxycycline did not cause dental staining in children (Todd et al., 2015; Volovitz et al., 2007). Cale and McCarthy stated already in 1997 that up to five courses of

doxycycline could be used in children younger than 9 years with minimal risk of dental staining, and a literature review published in 2016 stated that doxycycline courses up to 10 days of duration have <1% risk for dental staining in children younger than 8 years (Boast et al., 2016; Cale & McCarthy, 1997). Most paediatric studies include mainly peroral use of doxycycline, and only a minority of studies also report the rate of dental staining after intravenous administration of doxycycline. The American Academy of Pediatrics stated in 2018 that a single course of doxycycline for up to 3 weeks is safe for children, for any indication, without regard to the age (Committee on Infectious Diseases; American Academy of Pediatrics, 2018, 2021). However, some authors still consider insufficient data exist for doxycycline safety and advise care in prescribing doxycycline for young children (Wormser et al., 2018).

2.4.2 Immunotherapy

The first- or second-line immunotherapy is needed in management of encephalitis with unknown or immunologic etiology and in patients with clinical or radiological deterioration. High-dose corticosteroids (e.g., methylprednisolone 30 mg/kg/day up to 1g), intravenous immunoglobulin (usually 2 g/kg) and plasma exchange can be used as the first-line immunotherapy. Second-line immunotherapy with agents such as rituximab or cyclophosphamide can be used in cases resistant to first-line therapies (Britton et al., 2015). The main pharmacological mechanism of immunotherapies is to modify immunological response of the host. Corticosteroids may also improve the brain oedema in the treatment of encephalitis.

In immunological encephalopathies, such as autoantibody mediated encephalitis, ADEM and ANE, the first-line immunotherapies, especially given early in the disease course, improve the neurological outcomes and associate with higher rates of complete recovery or reductions in disability scores (Hacohen et al., 2013; Okumura et al., 2009; Titulaer et al., 2013). The use of corticosteroids in the treatment of HSV encephalitis is controversial: It may be beneficial in the treatment of cerebral oedema, but in theory, it could also enhance viral replication in CNS. Poor outcome (moderate or severe sequelae or death) was independently associated with the lack of corticosteroid treatment in one study in adults with HSV encephalitis (Kamei, 2005). The knowledge of HSV triggering autoimmune encephalitis has recently increased, which could explain the possible effect of corticosteroid treatment in prevention of poor outcomes in HSV encephalitis (Stahl & Mailles, 2019). There is limited evidence of the advantages of corticosteroid treatment in VZV encephalitis. It may be beneficial if VZV encephalitis causes vasculopathy, e.g., stroke (Kneen et al., 2012). However, the lack of studies in children limits the use of immunotherapy in these conditions. Intravenous immunoglobulin is widely

used in Asia in severe enterovirus 71 associated CNS infections without strong evidence. A beneficial effect has generally not been shown for intravenous immunoglobulin as an adjuvant therapy for viral encephalitis (Britton et al., 2015; Iro et al., 2017). Second-line immunotherapy has improved outcomes in patients who have persisting symptoms or relapse of anti-NMDAR encephalitis (Titulaer et al., 2013).

The Australian guidelines recommend considering immunotherapy if microbiologic etiology for which a targeted treatment is available cannot be confirmed, and a child continues to be symptomatic (Britton et al., 2015).

2.4.3 Supportive treatment

Supportive treatment of encephalitis consists of assessment of airway, breathing, circulation, glucose or electrolyte imbalance, raised intracranial pressure and epileptic seizures (Kneen et al., 2012; Messacar et al., 2018; Thompson, C., et al., 2012). Anticonvulsants, sedative drugs, antipsychotics or medication for movement disorders can be used in symptomatic care (Mohammad & Jones et al., 2016), and ventriculostomy or even further neurosurgical interventions may be needed to treat raised intracranial pressure (Venkatesan & Geocadin, 2014). Children with a falling level of consciousness, need for ventilator therapy, circulation support, or treatment of raised intracranial pressure or seizures should be transferred to an intensive care unit (ICU) (Kneen et al., 2012). Consultation with a neuropaediatric specialist should be arranged during the hospitalization, and the assessment of need for rehabilitation and an agreement for out-patient follow-up should be arranged at discharge (Kneen et al., 2012).

2.5 Outcome

2.5.1 Outcome of facial palsy

The recovery rate of facial palsy in children is excellent, between 90 and 100% (Arnason et al., 2020; Chen & Liu, 2005; Drack et al., 2013; Inamura et al., 1994; Jenke et al., 2011; Karalok et al., 2018; Karatoprak & Yilmaz, 2019; Peitersen, 2002; Wolfovitz et al., 2017; Yoo et al., 2018). Some studies report a 20 to 50% rate of residual symptoms when a slight dysfunction (House-Brackmann Facial Nerve Grading System [H-B FNGS] grade II) and/or any subjective residual symptoms of facial nerve paresis have also been classified as poor recovery (Bagger-Sjöbäck et al., 2005; Biebl et al., 2013; Kanerva et al., 2021; McNamara et al., 2013; Peltomaa et al., 1998).

The etiology of facial palsy has been variable in most studies reporting outcomes. Residual symptoms are found in 5.5 to 21% of children in neuroborreliosis-related facial palsy (Knudtzen et al., 2017; Peltomaa et al., 1998; Skogman et al., 2012). Subjective, parent-rated or objectively detected residual symptoms or signs are described in 27 to 37% in studies reporting a wider range of neuroborreliosis-related symptoms (e.g., impaired fine motor skills, poor balance or pain) (Knudtzen et al., 2017; Skogman et al., 2012; Södermark et al., 2017). However, nonspecific symptoms, such as headache, fatigue, and memory or concentration problems, were as common after neuroborreliosis as in children without neuroborreliosis in a Swedish study (Skogman et al., 2012).

The average recovery time of facial palsy is 3 to 7 weeks, ranging from a few days to seven months (Albisetti et al., 1997; Boulloche et al., 1993; Dhiravibulya, 2002; Micheli et al., 1996; Peitersen, 2002; Peltomaa et al., 1998; Tang et al., 2009). The recurrence rate of facial palsy in children ranges from 9 to 14% (Chen et al., 2005; Kanerva et al., 2021; Micheli et al., 1996).

2.5.1.1 Methods for assessing outcome of facial palsy

2.5.1.1.1 Grading of facial nerve function

H-B FNGS is a classical six-point scale to evaluate facial nerve function. It was first presented in 1985. Grades I and II represent a good outcome, grades III and IV represent moderate dysfunction and grades V and VI represent a poor outcome (House & Brackmann, 1985). (**Table 1**.) The graphic-visual adaptation of House-Brackmann facial nerve grading was introduced by Lazarini et al. (2006).

Facial Nerve Grading System 2.0 (FNGS 2.0) was developed from original H-B FNGS for the purpose of providing more exact information on regional facial movement. It has a better ability to state the exact grade of facial nerve function and especially to differentiate between grades III and IV (Vrabec et al., 2009). The Burres-Fisch and Sunnybrook facial grading systems evaluate facial function through continuous quantitative scoring, allowing finer distinctions compared to H-B FNGS (Burres & Fisch, 1986; Ross et al., 1996), while the Nottingham system is based on objective measurements of two distinct facial distances (Murty et al., 1994).

Thereafter, several computer-assisted facial nerve grading systems were described (Meier-Gallati et al., 1998; Yuen et al., 1997). Self-report instruments have been created to take account of social and mental disabilities caused by facial palsy (Kahn et al., 2001; Mehta et al., 2007; VanSwearingen & Brach, 1996). The grading of facial nerve function is essential in clinical work for objective review of facial nerve palsy recovery. However, the newer grading systems may be laborious to use, and the precise separation between different grades of facial palsy that they offer is rarely needed.

Table 1. House-Brackmann Facial Nerve Grading System.

Grade	Description	Characteristics
I	Normal	Normal function in all areas
II	Mild dysfunction	Gross: slight weakness noticeable on close inspection, may have very slight synkinesis At rest: normal symmetry and tone Motion: forehead – moderate to good function; eye – complete closure with minimum effort; mouth – slight asymmetry
III	Moderate dysfunction	Gross: obvious but not disfiguring difference between two sides; noticeable but not severe synkinesis, contracture, and/or hemifacial spasm At rest: normal symmetry and tone Motion: forehead – slight to moderate movement; eye – complete closure with effort; mouth – slightly weak with maximum effort
IV	Moderately severe dysfunction	Gross: obvious weakness and/or disfiguring asymmetry At rest: normal symmetry and tone Motion: forehead – none; eye – incomplete closure; mouth – asymmetric with maximum effort
V	Severe dysfunction	Gross: only rarely perceptible motion At rest: asymmetry Motion: forehead – none; eye – incomplete closure; mouth – slight movement
VI	Total paralysis	No movement

2.5.1.2 Factors predicting outcome of facial palsy

The severity of facial palsy at the acute phase affects its final recovery. Complete palsy (H-B grade V–VI) and electroneurographically detected facial nerve degeneration of 90% or more predict poor outcome (Gantz et al., 1999; Mantsopoulos et al., 2011; Peltomaa et al., 1998). Early recovery (< 1 month), start of recovery in 3 weeks, and milder palsy (H-B FNGS grade II–III vs. IV–VI) at the tenth day from facial palsy onset may predict good outcome and better final facial nerve function (Biebl et al., 2013; Karatoprak & Yilmaz, 2019; Shargorodsky et al., 2010). Young age may predict poorer outcome (Özkale et al., 2015).

Etiology can affect facial palsy recovery. Infectious and idiopathic vs. traumatic etiology predicted earlier recovery (Arnason et al., 2020; Chen & Wong, 2005; Evans et al., 2005) and neuroborreliosis vs. otitis media or idiopathic etiology are related to a higher recovery rate (Drack & Weissert, 2013). However, a Finnish study reported a tendency for better outcomes in children with unknown etiology compared to an obvious viral etiology (Peltomaa et al., 1998).

Early treatment with prednisolone predisposed complete facial palsy recovery in adults, and the AAN guidelines recommend the use of corticosteroids in the treatment of new-onset Bell´s palsy (Gronseth & Paduga, 2012; Sullivan et al., 2007). Corticosteroid treatment in children, especially if administrated within 24 hours from the onset of symptoms, could possibly shorten the recovery time of facial palsy (Karatoprak & Yilmaz, 2019), but it has no effect on final recovery (Karalok et al., 2018; Shih et al., 2009; Ünüvar et al., 1999; Yoo et al., 2018). Prednisolone is the corticosteroid mainly used at 1–2 mg/kg/day for 7 to 10 days, when reported. According to Arican et al., the dose of 1 mg/kg/day was as effective as the dose of 2 mg/kg/day in the treatment of facial palsy. This study only included patients who received corticosteroid treatment without a control group, making it impossible to evaluate the effect of corticosteroid treatment on recovery (Arican et al., 2017). Previous studies have shown a tendency exists for a better prognosis in children receiving corticosteroid treatment compared to those without treatment, but the differences were not statistically significant, probably due to the small sample sizes, variable etiologies and severity of palsy. It is currently unclear if there is an age limit when children start to benefit from corticosteroids and there is not enough data for corticosteroid treatments in different age groups.

The effect of physical therapy to improve the recovery result is controversial (Pereira et al., 2011; Teixeira et al., 2011). Patients are sometimes advised to try training of expressive muscles at home. However, families should be informed about the lack of knowledge of its real efficiency to avoid unnecessary stress for them.

An early start of antimicrobial treatment may hasten the recovery from acute symptoms and prevent the risk of neurological sequelae (Knudtzen et al., 2017; Wormser et al., 2006), but this effect is not reported in all studies (Skogman et al., 2012; Södermark et al., 2017).

Female gender, lower CSF leucocyte count and shorter length of hospital care were related to permanent sequelae, and infection-associated facial palsy was related to lower relapse risk in one study (Papan et al., 2019). Most paediatric studies evaluating facial palsy recovery are small and retrospective. Larger, prospective and controlled studies are needed to discover factors affecting the prognosis of facial palsy.

2.5.2 Outcome of encephalitis

Outcomes after paediatric encephalitis vary from full recovery to death. Its potential long-term consequences were described first in 1925 (Hall, 1925). Long-term neurological sequelae among survivors can be motor impairment, mental retardation, epilepsy, attention and learning disorders, emotional and behavioral changes, speech

difficulties, memory loss, hearing loss and chronic headaches (Fowler et al., 2010; Kaga et al., 2003; Mailles et al., 2012; Michaeli et al., 2014; Wang et al., 2007).

Previous studies have reported that the overall rate of neurological sequalae after paediatric encephalitis has been up to 83%. The mortality rate is mostly 2 to 6% (Aygun et al., 2001; Britton et al., 2020; Clarke et al., 2006; Ebaugh, 2007; Fowler et al., 2010; Galanakis et al., 2009; Iff et al., 1998; Khandaker et al., 2016; Klein et al., 1994; Kolski et al., 1998; Michaeli et al., 2014; Mohammad & Soe et al., 2016; Rao et al., 2017; Rautonen et al., 1991; Wang et al., 2007), but in a recent study from French Guayana, as high as 13% (Elenga et al., 2020). The rate of severe disability, defined as dependence on others, is reported to be 7 to 17% (Chen & Liu, 2018; DuBray et al., 2013; Iff et al., 1998; Mailles et al., 2012; Pillai et al., 2015; Rautonen et al., 1991).

The rate of certain severe neurological disorders has been remarkably higher after encephalitis compared to the general child population. The risk of postencephalitic epilepsy is 6–35% (Amin et al., 2008; Chen & Liu, 2018; Elenga et al., 2020; Fowler et al., 2010; Fowler et al., 2020; Khandaker et al., 2016; Lee et al., 2007; Rao et al., 2017; Rismanchi et al., 2015b; Wang et al., 2007), and risk for intractable or drug-resistant epilepsy 11–16% (Lee et al., 2007; Michaeli et al., 2014; Mohammad & Soe et al., 2016). The risk of severe cognitive delay (full-scale intelligence quotient [IQ] <70) has been up to 22%, compared to 2% in the general population (Khandaker et al., 2016; Michaeli et al., 2014), and the rate of severe motor disability (hemiparesis or tetraparesis) is 1–12% (Amin et al., 2008; Chen & Liu, 2018; Elenga et al., 2020; Michaeli et al., 2014; Wang et al., 2007). Additionally, the reported risk for milder sequelae, such as attention deficit and hyperactive disorder and learning disorders, seems to be elevated, 50 and 20%, respectively, compared to a 5–10% rate in the general population (Michaeli et al., 2014).

Only a minority of studies have used standardized outcome scales (Armangue et al., 2013; Britton et al., 2020; Chen & Liu, 2018; DuBray et al., 2013; Elenga et al., 2020; Y. Hacohen et al., 2013; Kalita et al., 2017; Ma & Jiang, 2013; Mailles et al., 2012; Mohammad & Soe et al., 2016; Pillai et al., 2015; Ramanuj et al., 2014; Sasaki et al., 2014) or standardized questionnaires (Blum et al., 2020; Engman et al., 2012; Fowler et al., 2013; Ramanuj et al., 2014) to assess outcomes after paediatric encephalitis. The duration of follow-up also varies: Some authors report outcomes at discharge or shortly after it (Britton et al., 2020; Ma & Jiang, 2013; Sasaki et al., 2014), while some others report outcomes even after 12 years of follow-up (Lahat et al., 1999). Only four previous studies report the standardized outcome results at least 12 months from hospital discharge (Chen & Liu, 2018; DuBray et al., 2013; Mailles et al., 2012; Pillai et al., 2015).

2.5.2.1 Definition of minor neurological dysfunction

Minor neurological dysfunction (MND) is a deviant of normal brain function that can be considered an indicator of brain damage. It can be divided into two distinct forms, simple MND (sMND) and complex MND (cMND), and into several types by dysfunctional domains (Hadders-Algra, 2010). MND, especially cMND, is associated with behavioral, cognitive and neuropsychiatric problems at school age (Arnaud et al., 2007; Broström et al., 2018; De Jong et al., 2011; Ferrari et al., 2012; Kikkert et al., 2011; Punt et al., 2010; Soorani-Lunsing et al., 1993) and with psychiatric morbidity at adolescence (Shaffer et al., 1985). The most important domains of dysfunction associated with motor, cognitive and behavioral problems are fine manipulative and coordination problems. Male gender and several prenatal and perinatal determinants such as preterm birth and intrauterine growth-retardation are risk factors for MND (Hadders-Algra, 2010).

MND has been widely used as an outcome parameter of, e.g., preterm birth and intrauterine growth retardation (Ley et al., 1996; Setänen et al., 2016). The Touwen neurological examination was used to define a "neurological profile" by dysfunction of domains but not to assess MND in a study of children with TBE encephalitis (Schmolck et al., 2005).

The assessment of MND could offer a useful tool to detect children at risk of developing learning or behavioral problems after encephalitis. By means of training skills and educational support, these children could achieve age-level opportunities for participation in schooling and leisure-time hobbies despite of MND.

Table 2 shows the definitions of simple (sMND) and complex MND (cMND).

Table 2. The definitions of simple and complex MND (sMND, cMND) by Hadders-Algra (2010).

Definition of MND	From 4 years until puberty	After the onset of puberty
sMND	Dysfunction in 1–2 of 8 domains (except reflexes)	Dysfunction in one of the next 5 domains: posture and muscle tone, choreiform movements, associated movements, sensory function, cranial nerve function
cMND	Dysfunction in >2 of 8 domains	Dysfunction in one of the next 2 domains: coordination, fine manipulation

2.5.2.2 Methods for assessing outcome of encephalitis

The methods to report outcomes of encephalitis have varied widely in previous studies. Some studies have focused on one specific category of sequelae (Lee et al., 2007; Rismanchi et al., 2015a), whereas others have reported different categories (Aygun et al., 2001; Galanakis et al., 2009; Rismanchi et al., 2015b; Wang et al., 2007). Some authors have reported mostly physical symptoms (Ilias et al., 2006), and some others also reported mental illness (Galanakis et al., 2009; Kolski et al., 1998; Wang et al., 2007). Health-related quality of life (Ramanuj et al., 2014) or psychosocial outcome, such as ability to return to work or school, performing activities of daily living, or financial loss are used as outcome indicators in some studies (Blum et al., 2020; Ding & Hong, 2007; Engman et al., 2012).

Methods to assess residual symptoms vary from surveys or telephone interviews with caregivers (Ilias et al., 2006; Ward et al., 2012) or clinicians' medical reports (Aygun et al., 2001; Lancella et al., 2017; Yildirim et al., 2020) to study visits consisting of clinical neurological examinations and/or cognitive assessment of participants (Fowler et al., 2013; Kennedy et al., 1987; Lahat et al., 1999; Rantala et al., 1991; Rautonen et al., 1991; Wang et al., 2007). The methods to define the outcomes, e.g., “developmental delay”, are not exactly reported in some studies (Amin et al., 2008; Elbers et al., 2007). The outcome categories have ranged from two to several. Studies that report only two outcome categories, e.g., survivors and non-survivors, or sequelae and no sequelae, cannot make the difference between mild symptoms and severe disability. The interpretation of a good or poor outcome has also varied: In some studies, e.g., slight learning disorders are defined as a good recovery, while in some others, equally mild symptoms are defined as a poor outcome (Aygun et al., 2001; Clarke et al., 2006; Fowler et al., 2020; Kornreich et al., 2016; To et al., 2014).

2.5.2.2.1 Glasgow outcome scale for assessment of functional outcome

The Glasgow Outcome Scale (GOS) (**Table 3**) and its revision, Glasgow Outcome Scale Extended (GOS-E), have been the gold standards for a long time in assessing functional outcome after brain injury (Jennett et al., 1981; Jennett & Bond, 1975). The GOS has subsequently been found to be a useful tool to assess outcome after encephalitis (Britton et al., 2020; T. Chen & Liu, 2018; Elenga et al., 2020; Granerod et al., 2010; Mailles et al., 2012; McGrath et al., 1997; Raschilas et al., 2002). The original score evaluates major life functions (consciousness, independence at home and outside the home at work, social and leisure activities, family and friendship functions, and returning to normal life) to characterize the overall disability with a categorial scale of 1 to 5. Thus, it focuses on how the injury has affected function rather than on certain symptoms caused by injury.

Table 3. Glasgow Outcome Scale according to Jennet et al. 1975.

GOS score	Clinical meaning	Outcome
5	Death	Poor
4	Neurovegetative state; patient unresponsive and speechless for weeks or months	Poor
3	Severe disability; patient dependent for daily support	Poor
2	Moderate disability; patient independent in daily life	Poor
1	Good recovery; resumption of normal life with minor neurological and psychological deficits	Favorable

The GOS-E was developed due to a high variability of function within the category scores. For example, a severe disability can range from total dependency to the need for assistance with only one activity. The scores 3–5 are each divided into 2 categories in this version, resulting in the categorial scale of 1–8: 8) death, 7) vegetative state, 6) lower severe disability, 5) upper severe disability, 4) lower moderate disability, 3) upper moderate disability, 2) lower good recovery and 1) upper good recovery.

The validated version for children, Paediatric Glasgow Outcome Scale Extended (GOS-E Peds), was later generated to meet the need to evaluate children at different stages of development. Only problems that have emerged or become markedly worse after the brain injury should be considered, as the child´s premorbid status is weighed in evaluation. The GOS-E Peds score has a strong association with everyday function, behavior and intelligence. It is highly correlated with the original GOS and is sensitive to severity of injury and recovery over time (Beers et al., 2012).

Other scoring systems, including Paediatric Cerebral Performance Category (PCPC), Liverpool Outcome Scale (LOS) and Modified Ranking Scale (mRS) have also been developed to assess neurological disability after brain insult (Fiser, 1992; Lewthwaite et al., 2010; van Swieten et al., 1988).

2.5.2.2.2 Touwen neurological examination for detection of minor neurological dysfunction

The Touwen neurological examination is a standardized and age-specific examination to detect MND (**Table 2**) in children from 4 years of age. The examination includes eight domains: posture and muscle tone, reflexes, involuntary movements (athetoticform movements, choreiform movements, and tremor), coordination and balance, fine manipulation, associated movements, sensory function and cranial nerve function. The domains are classified as dysfunctional

according to the manual's criteria using computerized scoring (Hadders-Algra, 2010).

The Touwen neurological examination has been developed for clinical practice but is also used in clinical research (Hadders-Algra, 2010; Peters et al., 2008). However, the Touwen examination may take 30–45 minutes to be performed, so it may be too time consuming to use in clinical practice. The reliability of this examination is moderate or good (Peters et al., 2008).

2.5.2.3 Factors predicting outcome of encephalitis

2.5.2.3.1 Neuroimaging

There are few studies of the relation of specific neuroimaging findings or the complexity of findings to neurological outcomes. An association has been reported between abnormal brain MRI findings and severe clinical presentation and poor short-term outcomes of encephalitis (Ilias et al., 2006; Klein et al., 1994). The increasing complexity of brain MRI findings correlates with the length of hospitalization (Bykowski et al., 2015). Poor long-term outcome is associated with an abnormal brain MRI (DuBray et al., 2013; Howarth et al., 2019; Lancella et al., 2017; Michaeli et al., 2014; Rao et al., 2017), as well as with parenchymal involvement (Chen & Liu, 2018), areas with diffusion restriction (Pillai et al., 2015) and focal cortical findings (Lee et al., 2007; Wang et al., 2007) on the brain MRI. Parenchymal involvement on the brain MRI is also related to postencephalitic epilepsy (Chen & Liu, 2018). In a small study of children with TBE, all six children with neurological sequelae had bilateral thalamic involvement in MRI (von Stülpnagel et al., 2016), whereas demyelination was an independent risk factor for relapse in children with anti-NMDAR encephalitis (Weihua et al., 2021). Some studies evaluating the relation of neuroimaging findings and neurological outcomes are small and do not allow statistical evaluation. The study of Bykowski et al. (2015) included a larger number of patients but focused only on short-term outcomes after encephalitis.

2.5.2.3.2 Etiology

There are plenty of studies reporting the risk of poor prognosis after encephalitis linked to specific viruses or bacteria. HSV was first described as causing high rates of mortality and disability (Meyer et al., 1960) and is still an important pathogen predisposing children to poor outcomes (Britton et al., 2020; Chen & Liu, 2018; Committee on Infectious Diseases; American Academy of Pediatrics., 2015; Elbers et al., 2007; Granerod et al., 2010; Michaeli et al., 2014; Pillai et al., 2015; Rautonen

et al., 1991; To et al., 2014; Ward et al., 2012). Up to 53–100% rates of severe disability or death have been reported after HSV encephalitis (Cameron et al., 1992; Kimura et al., 1992). According to the current knowledge, the poor prognosis of HSV encephalitis may be linked to early relapses by immunological mechanisms (Schleede et al., 2013). *M. pneumoniae* can cause severe CNS manifestations with long-term neurological sequelae (Daxboeck et al., 2004; Lehtokoski-Lehtiniemi & Koskiniemi, 1989; Rautonen et al., 1991), including drug-resistant epilepsy (Mohammad & Soe et al., 2016). Encephalitis caused by the influenza A or B virus or enterovirus 71 is also related to poor outcome (Britton et al., 2017; Britton et al., 2020; Huang et al., 1999). VZV cerebellitis, but not encephalitis, is considered a benign disorder with a good recovery (Bozzola et al., 2014; Granerod et al., 2010). TBE is usually more benign in children than in adults (Stähelin-Massik et al., 2008); however, mild to significant long-term sequelae after paediatric TBE are noted (Engman et al., 2012; Fowler et al., 2013; Schmolck et al., 2005; von Stülpnagel et al., 2016).

2.5.2.3.3 Clinical subtypes of encephalitis

Clinical subtypes of acute encephalitis and encephalopathy differ from each other by the sequelae risk. The group of antibody-positive autoimmune encephalitis has a poor prognosis with a 56% rate of mortality or severe disability (Granerod et al., 2010) and a high risk for drug-resistant epilepsy (Mohammad & Soe et al., 2016). The long-term outcome after paediatric ADEM is reported to be much better than in adults, despite its severe acute course of disease (Absoud et al., 2011; Granerod et al., 2010; Ketelslegers et al., 2011; Paolilo et al., 2020). However, ADEM with relapsing episodes can predispose the child to a more unfavorable long-term outcome (Baumann et al., 2016; Hacohen et al., 2018). FIRES has over a 10% mortality rate and over a 90% rate of neurological sequelae in survivors (Kramer et al., 2011; van Baalen et al., 2009), including an elevated risk for drug-resistant epilepsy (Mohammad & Soe et al., 2016). The ANE outcomes range from complete recovery (<10%) to 30% risk of death (Lee et al., 2019; Levine et al., 2020). The risk of persistent deficits in survivors is 90-100% (Mohammad & Soe et al., 2016). The course of cerebellitis can range from benign self-limiting disorder to fulminant brain damage, and outcomes have also been variable. The rate of residual symptoms has ranged from 5% in a large study (Lancella et al., 2017) to 27–54% in smaller studies (Hennes et al., 2012; Kornreich et al., 2016; Yildirim et al., 2020). The residual symptoms have mainly been motor or coordination problems, but cognitive defects have also been reported in these studies.

2.5.2.3.4 Patient-related factors

Multiple patient-related factors can affect encephalitis outcome. A poor outcome, defined as death or disability affecting daily skills, has been linked in several studies to young age (mostly <1 or <3 years) at time of encephalitis (Clarke et al., 2006; Elenga et al., 2020; Iff et al., 1998; Kennedy et al., 1987; Rautonen et al., 1991). Studies focusing on certain etiologies reported that young age has predisposed the child to more unsatisfactory outcome in HSV, enterovirus and anti-NMDRA encephalitis, but in contradiction, to better outcome in *Mycoplasma* encephalitis (Daxboeck et al., 2004; Sells et al., 1975; Ward et al., 2012; Weihua et al., 2021). It is known that children with premorbid developmental challenges may be most vulnerable for residual symptoms after brain damage. This seems to also be congruent in encephalitis: The need for extra support at school before encephalitis may predispose them for a longer hospital stay (Fowler et al., 2020). Female gender was related to development of postencephalitic epilepsy in one study, but the number of children suffering epilepsy was small, and there was a lack of discussion of the possible effect of gender in this study (Fowler et al., 2010).

2.5.2.3.5 Laboratory parameters

Some laboratory findings are reported to affect outcome. Pleocytosis and higher CSF leucocyte and protein levels compared to the control group (Aygun et al., 2001; Fowler et al., 2008) have been risk factors for unfavorable outcomes in some studies but not in others (Iff et al., 1998; Rismanchi et al., 2015b). A high CSF cell count and protein elevation are associated with unfavorable outcomes in *M. pneumoniae* encephalitis. Clarke et al. suggested that the degree of blood-brain barrier impairment, defined as a high CSF–blood albumin ratio, was associated with poor outcome and persistence of interferon alpha in CSF with good outcome (Clarke et al., 2006). Blood leucopenia (Wang et al., 2007) and increased erythrocyte sedimentation rate, and serum increased aspartate aminotransferase level (Aygun et al., 2001) have been related to adverse outcome in single reports. These laboratory parameters are nonspecific markers of systemic diseases and infectious or inflammatory CNS disorders, which may cause major differences between results of separate studies and restrict their use as predictive factors of encephalitis.

2.5.2.3.6 EEG findings

Several studies have tried to find EEG patterns that could predict outcomes in paediatric encephalitis. An abnormal EEG, a greater degree of slowing, focal slow waves, continuous generalized delta waves, pure spikes in EEG, and deterioration of an EEG from normal to generalized slow activity may predict a more severe, acute

illness (Rao et al., 2017) or later neurological sequelae and death (Aygun et al., 2001; Britton et al., 2020; Chen & Liu, 2018; Clarke et al., 2006; Kennedy et al., 1987; Wang et al., 2007). An abnormal EEG and certain findings, including focal slow waves or generalized delta waves, may be risk factors for postencephalitic epilepsy (Aygun et al., 2001; Rismanchi et al., 2015a), and a shifting focal seizure pattern in EEG is a risk factor for drug-resistant epilepsy (Mohammad & Soe et al., 2016). An abnormal EEG correlates to problems in concentration, attention and fluency, as well as lower scores in 4 of 10 neurologic subsystems in the Touwen neurological examination in patients with TBE (Schmolck et al., 2005).

2.5.2.3.7 Clinical signs and symptoms

Clinical signs and symptoms at the acute phase of encephalitis can be linked to poor outcomes. According to several reports, a low level of consciousness and seizures (and at least recurrent seizures) at presentation are predictors of adverse outcomes in the short-term (discharge or <12 months) (Aygun et al., 2001; Britton et al., 2020; Hatachi et al., 2021; Kalita et al., 2017; Rautonen et al., 1991) and long-term (>12 months) follow-up (Chen & Liu, 2018; DuBray et al., 2013; Fowler et al., 2010; Ma & Jiang, 2013; Rao et al., 2017; Rismanchi et al., 2015b; Wang et al., 2007). Certain focal signs in neurological examination, e.g., limb weakness or cranial nerve paralysis (Kalita et al., 2017; Michaeli et al., 2014; Wang et al., 2007), movement disorders (Pillai et al., 2015), or abnormal oculocephalic responses (Kennedy et al., 1987) may also be predictors of poor outcomes. From a clinical aspect, a focal neurological sign often relates to a focal lesion in a brain MRI, movement disorders are symptoms of autoimmune encephalites or basal ganglia injury, and abnormal oculocephalic responses reveal brain stem dysfunction, which probably explain these associations with adverse outcomes. Pillai et al. made a finding that infectious prodrome at acute illness onset can predict more favorable outcome (Pillai et al., 2015). The authors did not discuss this finding, but the infectious prodrome may be linked, e.g., to ADEM-like disorders (Weng et al., 2006), which are mostly associated with a good prognosis.

Additionally, markers of severe acute illness, e.g., a longer hospital stay (Michaeli et al., 2014; Rismanchi et al., 2015a; Rismanchi et al., 2015b), admission to ICU (Britton et al., 2020; Chen & Liu, 2018; Fowler et al., 2010; Pillai et al., 2015; Titulaer et al., 2013), need for mechanical ventilation (Chen & Liu, 2018), need for anti-epileptic drugs (AED) at discharge (Rismanchi et al., 2015a; Rismanchi et al., 2015b), medically induced coma, and a higher extent of organ and cardiopulmonary failure (Chang et al., 2007; Kalita et al., 2017) are risk factors of neurological sequelae. Status epilepticus is an independent risk factor for a longer stay in the ICU (Sasaki et al., 2014), poor short- and long-term outcomes (Kalita et al., 2017; Pillai

et al., 2015; Sasaki et al., 2014) and postencephalitic epilepsy (Chen et al., 2018; Lee et al., 2007). The same factors predicted poor outcomes in studies of encephalitis of certain etiologies or subtypes, such as HSV, *M. pneumoniae* and Japanese encephalitis, enterovirus 71 brain stem encephalitis, anti-NMDAR encephalitis, and cerebellitis (Daxboeck et al., 2004; Hennes et al., 2012; Huang et al., 2006; Lahat et al., 1999; Ma & Jiang., 2013; Weihua et al., 2021).

The factors effecting encephalitis outcomes have been under active research during the past decades. The relation of certain factors to outcomes is quite clear, but the relation of many others is much more controversial. Some factors may be related to a prognosis only under certain environmental circumstances and are invalid globally. It is obvious that more studies are needed to discover the predictors of good and poor prognoses. This could help clinicians to inform their patients and their families about the long-term prognosis more individually.

3 Aims

The objective of this thesis was to study diagnostic methods, treatment safety and outcomes in two types of paediatric CNS infections: encephalitis and neuroborreliosis presenting as facial palsy. The specific aims were:

1. To study the predictive value of CSF pleocytosis, elevated protein concentration and CXCL13 chemokine level, the need for lumbar puncture in diagnostics of neuroborreliosis as the cause of facial palsy, and facial nerve palsy recovery in children (I).
2. To study the dental effects of doxycycline given to children under eight years of age for treatment of CNS infection (II).
3. To study the long-term neurological and cognitive performance after childhood encephalitis (III).
4. To study the complexity of acute-phase MRI findings and their association with long-term neurological disability after childhood encephalitis (IV).

4 Materials and Methods

4.1 Study population

We identified and retrospectively reviewed the children hospitalized due to encephalitis, neuroborreliosis and facial palsy or due to related conditions during the years 1994 to 2016 at the Department of Paediatrics and Adolescent Medicine, Turku University Hospital, Turku, Finland. The Department of Paediatrics and Adolescent Medicine in Turku University Hospital serves a population of 70 000 children and adolescents 0 to 16 years and serves as a level III hospital for three level II hospitals. Children were identified from the medical record system by the International Classification of Diseases, 10th Revision (ICD-10) codes, referring to CNS infection or related conditions: encephalitis, meningoencephalitis, acute encephalopathy, cranial nerve palsy, Lyme borreliosis and Lyme neuroborreliosis. The medical records of the subjects with one or several of the above-listed diagnoses were examined to meet the inclusion criteria for separate studies. **Figure 3** shows a flowchart of the participants.

4.1.1 Facial palsy (Study I)

We included all the patients diagnosed with facial palsy during 2002–2016 in Study I. The years 2002–2016 were included to improve the availability of information from medical records; the year 2002 was the first year after transition to electronic medical record system. Only the first episode of subjects with more than one episode of facial palsy was included.

4.1.2 Treatment safety (Study II)

We included in Study II the children with suspected encephalitis or neuroborreliosis, treated empirically with doxycycline at the age of 0–7.9 years, who reached the minimum age of 8 years at the time of study catch-up. 2015 was the last year of doxycycline treatment included in the study. These age limits were selected based on the known dental mineralization timeline of tooth development with the aim of studying the dental staining after permanent teeth eruption (Kraus, 1959).

4.1.3 Encephalitis outcomes (Studies III and IV)

All hospitalized children meeting the encephalitis criteria defined next during years 1995–2016 were included in Studies III and IV.

Subjects without severe developmental delay (motor or learning disabilities) or any neurological or neuropsychiatric disease before the encephalitis and without evident disability or death caused by encephalitis were invited to participate in Study III in the follow-up evaluation. Thus, 74 subjects were invited to participate in the study visits in Study III; of them, 42 (57%) participated.

4.2 Definition of encephalitis

Encephalitis was defined as acute encephalopathy (altered level of consciousness or altered behavior) or ataxia lasting ≥24 hours, occurring with or without findings of acute neurological defect, with previous or concurrent symptoms of infectious disease (fever, respiratory tract symptoms or gastrointestinal symptoms) and either CSF, EEG or neuroimaging findings consistent with encephalitis. CSF findings consistent with encephalitis were pleocytosis, elevated protein concentration, or a positive PCR test for a known causative microbial agent of encephalitis. The CSF leucocyte count above 5 x 10^6 /L was regarded as pleocytosis. CSF protein concentrations greater than 400 mg/L in ≤13.9 year old children and 450 mg/L in ≥14.0 year old children were regarded as elevated. General and/or focal disorders with or without epileptiformic activity were regarded as EEG findings consistent with encephalitis. Cortical or basal ganglia oedema, diffusion restriction, hemorrhage, hydrocephalus, and parenchymal, meningeal or cranial nerve enhancement were considered encephalitis-related pathology on an MRI.

Different subtypes of encephalitis were determined based on the clinical features of illness during hospitalization and clinical follow-up. The subtypes included were autoimmune encephalitis, ANE due to RANBP gene mutation, ADEM, cerebellitis with or without a confirmed microbial causative agent, encephalitis with a confirmed microbial causative agent, encephalitis without a microbial causative agent and FIRES. Intrathecal immunological reaction, observed as an elevated CSF IgG index or oligoclonal bands, with or without specific autoimmune antibodies, was indicative of autoimmune encephalitis in our data.

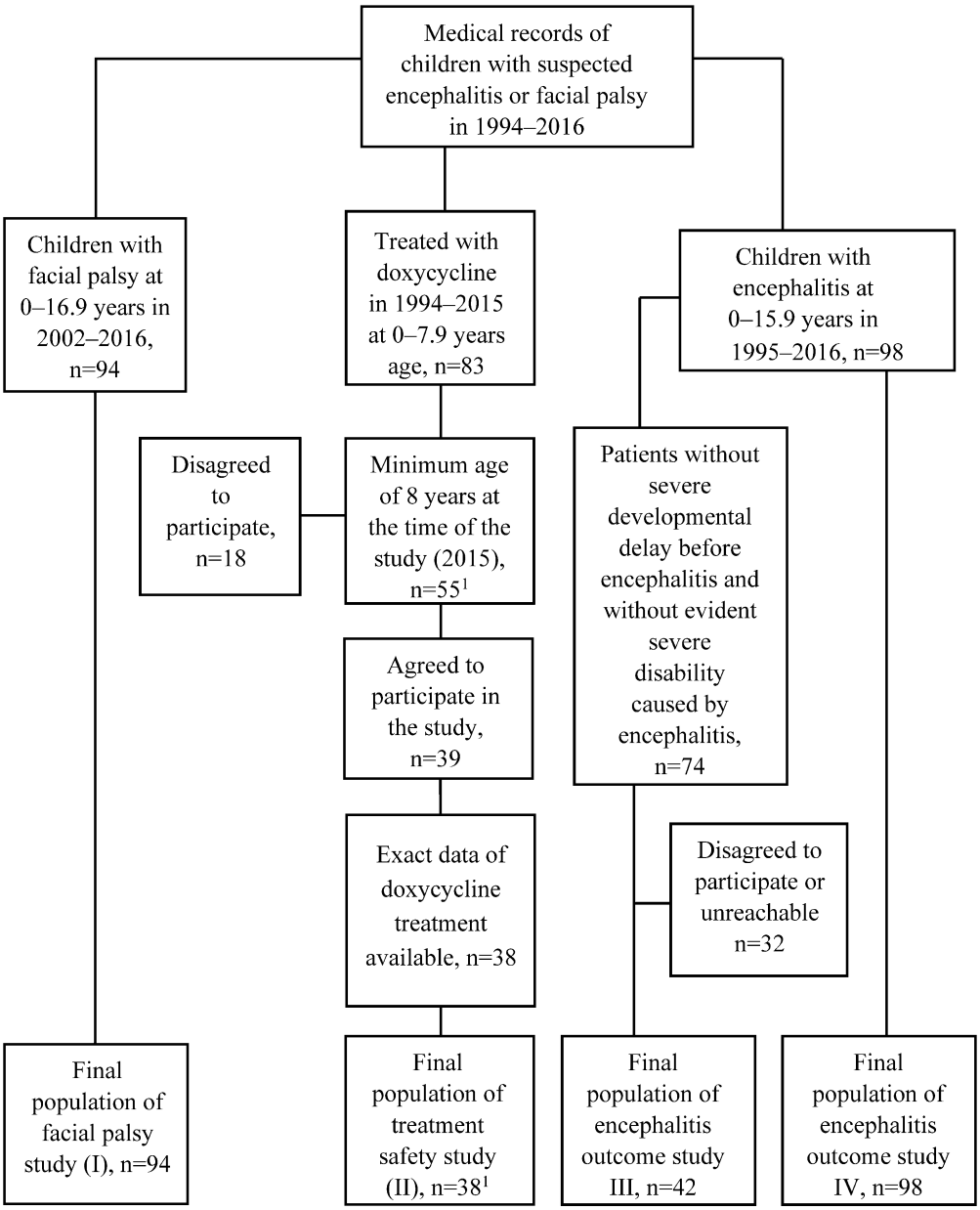

Figure 3. Flowchart of the study. [1]One subject had received two separate courses of doxycycline before the age of eight years: the number of doxycycline courses was 39.

4.3 Definition of neuroborreliosis as a cause of facial palsy

Neuroborreliosis was defined as clinically detected facial palsy with a confirmed microbiologic diagnosis of borreliosis in Study I. The microbiologic diagnosis of borreliosis was based on a serologic diagnosis in a serum sample, detection of an intrathecal-specific antibody production, or a positive *B. burgdorferi* PCR in CSF.

4.4 Background data

Clinical data were collected from medical records. The study subjects' medical history, signs and symptoms, microbiologic and other laboratory test results were documented. We collected the information related to facial nerve function recorded during clinical follow-up in the facial palsy study (I). We recorded all the details of doxycycline treatment: the child´s age at treatment, duration of the course, and the dose and administration route of the doxycycline treatment in the treatment safety study (II). We recorded the history of neurological development, EEG and neuroimaging results, the results of neurological and physical examinations, and the cognitive assessments in the encephalitis outcome studies (III, IV).

4.5 Dental examinations

The study subjects were contacted by letter and telephone and asked to participate in one 30-minute study visit. The study visit included a dental examination and a questionnaire on their medical and dental history. The dental examination was performed by an experienced paediatric dentist, the teeth were photographed, and the dental developmental stage was noted. The focus of the clinical examination was to detect tetracycline-like staining in the forms of diffuse discolored bands of tooth crowns and enamel hypoplasia. The photographs were re-evaluated by another experienced paediatric dentist blind to the results documented by the first examiner.

4.6 Diagnostic methods

4.6.1 Re-evaluation of neuroimaging studies

Brain MRIs were re-evaluated for any encephalitis-related pathology by an experienced neuroradiologist to confirm the radiological findings consistent with encephalitis. Cortical or basal ganglia oedema, diffusion restriction, hemorrhage, and parenchymal or meningeal enhancement were considered to be encephalitis-related pathology in MRI. The neuroimaging findings in Study IV were categorized

by the complexity of findings: 1) no imaging abnormality, 2) meningeal or single cranial nerve enhancement and/or focal nonenhancing lesion, 3) multifocal lesions, 4) confluent lesions, and 5) lesions plus diffusion restriction, hemorrhage, or hydrocephalus (Bykowski et al., 2015).

4.6.2 Microbiologic diagnostics

Standard laboratory methods in use at the time of a patient´s disease were used in routine diagnostics of the microbial etiology of encephalitis or facial palsy. Microbial etiology was defined as "confirmed" when there was a positive PCR or an IgM antibody result in the CSF for a typical encephalitis-causing pathogen. The etiology was defined as "probable" when there was a positive CSF antigen test for any pathogen, an antibody response in the CSF for an atypical encephalitis pathogen, or a positive IgM antibody result in a single serum sample, a seroconversion, or an increase in IgG antibody levels in paired sera for a typical encephalitis-causing pathogen. The etiology was also defined as probable in a case with an onset of clinically diagnosed varicella four days before development of encephalitis. The etiology was defined as "uncertain" when a potentially encephalitis-causing pathogen was detected by a PCR or antigen test from a nasopharyngeal, pharyngeal, tracheal or fecal specimen or by high IgG antibodies in a single serum sample.

The microbial etiology was divided into two groups: 1) confirmed or probable and 2) uncertain or unknown. The probable and confirmed cases positive for a respiratory virus (rhinovirus, enterovirus, adenovirus, parainfluenza virus, or influenza A or B virus) were defined as one category in the statistical analyses of Study IV.

4.6.3 Diagnostics of neuroborreliosis

The microbiologic definition of confirmed Lyme neuroborreliosis was based on a serologic diagnosis in a serum sample, detection of intrathecal-specific antibody production, or a positive *B. burgdorferi* PCR in the CSF. Serum and CSF samples were analyzed using a two-tiered testing approach. Samples were screened for *B. burgdorferi*-specific IgM and IgG antibodies by an in-house whole *Borrelia* antigen (*B. burgdorferi* B31 sonicate) ELISA (Viljanen & Punnonen, 1989), as the second-tier test, IDEIA *B. burgdorferi* IgM/IgG enzyme immunoassay (Oxoid, Basingstoke, UK) was used in 2002–2010, and a C6-peptide-based assay (C6 Lyme ELISA; Immunetics, Boston, MA) was used in the years 2001–2016. Intrathecal *B. burgdorferi* antibody production was determined using the IDEIA Lyme Neuroborreliosis kit. *B. burgdorferi*-specific PCR was performed using the method

described by Ivacic et al. (2007) in 2008–2016. A nested PCR targeting the flagellin gene of *B. burgdorferi* was used before the year 2008 (Schmidt, 1997).

CXCL13 levels in CSF samples were measured by using the human CXCL13 kit (Quantikine; R&D Systems, Minneapolis, MN) (Hytönen et al., 2014). This test was used in 2014–2016. The analyses were performed according to the manufacturer's instructions. Samples with concentrations greater than the upper limit of the assay's standard curve (>500 ng/L) were further diluted 10 to 100 times with the calibration diluent buffer of the kit and re-analyzed. A CXCL13 level <7.8 ng/L was regarded as normal.

4.7 Outcome assessment methods

4.7.1 House-Brackmann Facial Nerve Grading System (I)

Facial palsy recovery was assessed retrospectively from medical records with H-B FNGS (House & Brackmann, 1985). Recovery was regarded as good if the facial palsy recovered totally (grade I) or almost totally (grade II). Facial palsy symptoms of grades III–VI lasting for more than one year were regarded as a permanent poor recovery.

4.7.2 The Touwen neurological examination (III)

The latest version of the Touwen neurological examination was used to assess MND in Study III (Hadders-Algra, 2010). The examination was performed by an experienced physician using the manual's instructions. Examinations were videotaped and classified together with other experienced physicians to ensure a consensus regarding the assessments' details. Patients were divided by neurological examination into groups of normal and MND (simple and complex).

4.7.3 The cognitive assessments (III)

The cognitive outcomes in Study III were assessed by an experienced psychologist using Finnish or Swedish translations of age-appropriate Wechsler intelligence scales: Wechsler Preschool and Primary Scale of Intelligence – Third Edition, WPPSI-III (Wechsler, 2005, 2009) (n=10); Wechsler Intelligence Scale for Children – Fourth Edition, WISC-IV (Wechsler, 2007, 2010) (n=17) or Wechsler Adult Intelligence Scale – Fourth Edition, WAIS-IV (Wechsler, 2012) (n=11). Full-scale IQ (mean ±SD, 100 ± 15 in the normative population), a composite score of more specific cognitive domains, was used as a measure of general intelligence. Abbreviated versions were used for estimating full-scale IQ for 32 of 38 (84%)

subjects. An abbreviated version of the WPPSI-III (Wechsler, 2005, 2009) included two of three subtests (Information and Word Reasoning) from the verbal scale, two of three subtests (Block Design and Picture Concepts) from the performance scale and one (Coding) from the processing speed scale. The abbreviated versions of the WISC-IV (Wechsler, 2007, 2010) and the WAIS-IV (Wechsler, 2012) included two of three subtests (Similarities and Vocabulary) from the verbal scale, two of three subtests (Block Design and Matrix Reasoning) from the perceptual scale, one of two subtests (Digit Span) from the working memory scale and two subtests (Coding and Symbol Search) from the processing speed scale. Subtests were selected according to general clinical practice (Crawford et al., 2010), and the scores for abbreviated assessments were assigned according to test manuals (Wechsler, 2005, 2007, 2009, 2010, 2012). A cut-off of average full-scale IQ 85 (-1 SD) was chosen based on clinical experience as a sign of clear decline in overall cognitive performance. The cognitive outcomes were divided into two groups: <85 and ≥85.

4.7.4 Glasgow Outcome Scale (IV)

GOS at discharge, at short-term follow-up (<3 months after acute encephalitis), and at long-term follow-up (≥1 year after acute encephalitis) was used as the neurological disability measurement. The outcome score was retrospectively classified based on medical records from the clinical follow-up period. The age-appropriate level of function in children was defined according to paediatric validation (Beers et al., 2012). The degree of disability was defined in 5 categories (GOS 1–5). Outcomes were divided into two groups: good recovery (GOS 1) and poor recovery (GOS 2–5).

4.7.5 Questionnaires (II, III)

Studies' II and III participants or their parents were asked to fill out and return a questionnaire regarding comorbid diseases, medications, neurological development, learning ability, school performance and educational information before and after the CNS infection. The treatment safety study (II) also asked about previous problems in dental health; the encephalitis outcome study III asked about the difficulties in motor skills and daily performance, residual symptoms, and leisure-time sporting activities at the time of the follow-up. Daily performance included the ability to dress, eat, wash up, move outside the home, and outline times or value for money independently or at an age-appropriate level. The definition of difficulties was a subjective experience for the participants or their parents. The questionnaires were designed for the present study's purposes. Appendices 1 and 2 show the questionnaires for the treatment safety study (II) and the encephalitis outcome study III.

4.8 Ethics

The Institutional Review Board at the Clinical Research Centre of the Turku University Hospital approved all the studies. The study subjects participating in the teeth examination in treatment safety study (II) and the neurological and cognitive assessment in encephalitis outcome study III and/or their parents gave their informed, written consent. The Ethics Committee of the Hospital District of Southwest Finland (T7/2015 and 71/2016) approved both studies with clinical study visits. An Ethics Committee review was not needed for studies I and IV with retrospective analyses of data collected during routine patient care.

4.9 Statistical analyses

The cases in the facial palsy study (I) were divided into groups by diagnosis of Lyme borreliosis, and these two groups were compared. The compared groups were participants and non-participants, participants with normal Touwen neurological examination and MND, and participants with full-scale IQ <85 or ≥85 in the encephalitis outcome study III. The variables studied were gender, age at disease onset, C reactive protein (CRP) >40 mg/l, CSF pleocytosis, abnormal MRI, abnormal EEG, seizures, need for ICU, length of hospital stay and duration of symptoms ≥1 and ≥3 months. The responses studied in the encephalitis outcome study IV were poor and good recovery, degree of disability, and neuroimaging complexity category. The variables studied were need for ICU, need for ventilator therapy, need for AED, detected CSF pleocytosis, abnormal EEG, gender, age at acute illness onset, length of hospital treatment, category of the probable/confirmed microbial agent, microbial etiology category, and encephalitis subtype.

The continuous variables were summarized using mean with standard deviation (SD) when data were normally distributed and median with lower (Q1) and upper (Q3) quartile when not normally distributed. The categorical variables were summarized with counts and percentages.

The differences in categorical variables between two groups were compared by using the chi-square test or Fisher´s exact test, as appropriate. The differences in continuous variables between two groups were compared using the two-sample t-test (when data were normally distributed) or Mann-Whitney U-test, when the data were not normally distributed. Differences between more than two groups were compared using Kruskal-Wallis test. The association between poor long-term recovery and the need for ventilator therapy, age and neuroimaging complexity categories were examined with cumulative ordinal logistic regression. The neuroimaging complexity categories are defined in 4.6.1. A similar model was built for degree of disability according to neuroimaging complexity categories.

Study I calculated sensitivities, specificities, and positive and negative predictive values with 95% confidence intervals (CI) of pleocytosis or abnormal CSF (defined as pleocytosis or elevated protein value) for borreliosis.

Significance level 0.05, two-tailed, was used. Statistical analyses were performed in Studies I and III by using SPSS, versions 23.0 and 27.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) and in Study IV by using SAS software, Version 9.4 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

5 Results

5.1 Background and clinical characteristics

5.1.1 Facial palsy (Study I)

We identified 94 children or adolescents with a confirmed diagnosis of an acute peripheral facial palsy. The mean age of all patients was 9.1 years (SD, 4.3; range 2.0–16.9). Children with borreliosis (n=34) were younger than children without borreliosis (n=60): 7.2 years (SD, 3.7; range, 2.7–16.3) vs. 10.1 years (SD, 4.3; range, 2.0–16.9) (p=0.001).

5.1.2 Safety of doxycycline treatment (Study II)

We identified 55 children who had received doxycycline before the age of 8 years and were aged 8 years or older at the study time. A total of 39 subjects participated in a dental examination. Reliable information on doxycycline treatments was found for 38 of 39 study subjects. Thirty-seven subjects had received one course of doxycycline, and one had received two courses. Twenty-four of the subjects (63%) were male. The mean age at the time of doxycycline treatment was 4.7 years (SD, 2.3; range, 0.6–7.9 years). The mean length of the treatment was 12.5 days (SD, 6.0; range, 2–28 days,). The mean follow-up time was 9.3 years (SD, 3.1; range, 3.3–15.5 years), and the mean age at the dental examination was 14.2 years (range, 8.3–22.6 years).

The doxycycline dose was exactly reported in 30 of 39 courses. The loading dose for the first 2–3 days was 10 mg/kg/day (varied from 8 to 10 mg/kg/day). The average dose thereafter was 5 mg/kg/day (varied from 2.5 to 10 mg/kg/day). Doxycycline was administered once or twice daily. The administration route was first intravenous and later oral in 18 (46%), only oral in 12 (31%) and only intravenous in 9 (23%) courses. The indication of doxycycline treatment was suspicion of CNS infection in 38/39 cases and *Borrelia* uveitis in one case. The final diagnosis was CNS infection in 28 cases (72%): Of these, 16 met the criteria of encephalitis, 3 met the criteria of meningitis (meningismus and pleocytosis) and 6 met the criteria of neuroborreliosis.

5.1.3 Encephalitis (Studies III, IV)

We found 98 paediatric encephalitis patients hospitalized in Turku University Hospital between 1994–2016. The median age was 6.8 (IQR, 3.0–11.5) years. A total of 59 (60%) of those patients were male. One child had nephrotic syndrome and immunosuppressive treatment, whereas others had no significant somatic diseases prior to encephalitis. Nine patients had learning or motor disability before the onset of encephalitis. Eight children were born prematurely (<37 gestational weeks), two of them very prematurely (<32 gestational weeks). None of the patients had epilepsy before the encephalitis.

A total of 15 patients had obvious neurological sequelae caused by encephalitis (disability or death). Twenty-four patients (9 with learning or motor disability and 15 with obvious sequelae) were ineligible to participate in Study III. Figure 3 shows Study III's exclusion criteria. The subjects participating were younger at the time of encephalitis (median, 5.0; IQR, 0.3–10.1 years) compared to subjects not participating (median, 10.9 years; IQR, 4.8–13.9 years) (p=0.03). The groups did not differ from each other by other variables studied.

Table 4 shows the most common neurological symptoms at the onset of acute encephalitis. EEG was abnormal in 71 of 88 children studied. CRP was slightly elevated (>8 mg/L) in 72 (83%) patients, but >40 mg/L only in eight (8%) children. Fifty-five (56%) children were treated in the ICU, 14 (14%) needed mechanical ventilation and 30 (31%) needed AEDs for seizure control. Length of hospitalization varied from 1 to 152 days (median, 8; IQR, 6–12 days). Twelve patients (12%) were readmitted to the hospital after discharge due to relapsing or worsening symptoms.

Seven children were diagnosed with autoimmune encephalitis based on autoimmune encephalitis-related symptoms (e.g., acute movement disorder, neuropsychiatric symptoms and/or autonomic dysfunction), together with elevated CSF IgG-index and/or oligoclonal banding. One child also had positive autoantibodies in serum. Ten children had ADEM, three had ANE, eight had cerebellitis with or without a confirmed microbial causative agent, three had FIRES, 41 had encephalitis without a confirmed microbial causative agent, and 25 had encephalitis with a confirmed microbial causative agent. The diagnoses of infection-related syndromes (ANE due to RANBP mutation and FIRES syndrome) were confirmed later during clinical follow-up.

5.2 Diagnostics

5.2.1 Neuroimaging (I, III, IV)

A brain MRI was performed at the acute phase (<2 months from symptom onset) of the disease on 88 children included in Study IV. The MRI was normal (complexity

category 1, see 4.6.1) in 39 (44%) and abnormal in 49 (56%) children. The prevalence of abnormal findings was divided into complexity categories: category 2) meningeal or cranial nerve enhancement and/or focal T2-hyperintense lesion in 14 (26%); category 3) multifocal T2-hyperintense lesions in 18 (20%); category 4) confluent T2-hyperintense lesions in 4 (5%); and category 5) T2-hyperintense lesions plus diffusion restriction, hemorrhage, or hydrocephalus in 13 (15%) children. Neuroimaging was performed in five patients with a normal MRI during the first two days after the onset of symptoms without control imaging later. **Figure 4** shows examples of the brain MRI findings of different complexity categories.

An MRI was performed at the acute phase for 38 of 42 children in the cohort participating in the Touwen neurological examination and cognitive assessment, and there was an encephalitis-related pathology in 21 (55%) patients.

An MRI of the brain was performed for 22 of 94 children with facial palsy, and it was abnormal in 12 children (Study I). A brain CT was done for two children. The facial nerve palsy-related neuroimaging findings consisted of facial nerve enhancement in five children, enhancement of several cranial nerves in two children and mastoiditis in three children. Other findings were a small chronic lesion in the thalamus and a small aneurysm in an internal carotid artery. Neuroimaging was usually performed due to suspicion of shunt dysfunction, previous trauma or coexisting neurological symptoms.

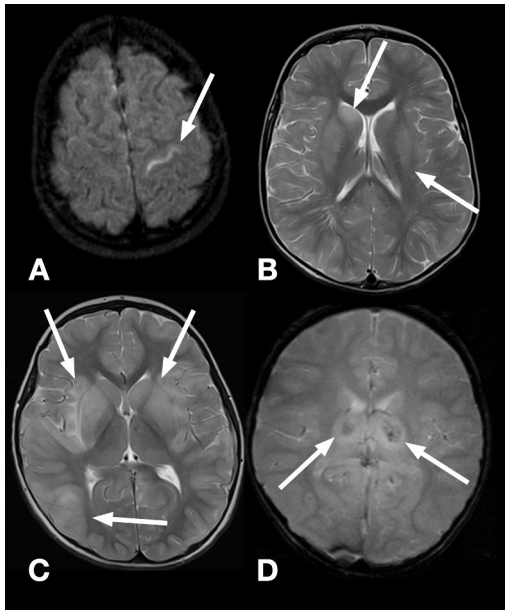

Figure 4. Examples of the abnormal brain MRI findings in acute encephalitis: A) meningeal enhancement (category 2), B) multiple focal brain lesions (category 3), C) confluent brain lesions (category 4), D) hemorrhagic brain lesions (category 5). Image by Mikko Nyman.

5.2.2 CSF analyses (I, III, IV)

A lumbar puncture was performed for 84 children with facial palsy (I) and for 96 children with encephalitis (III, IV). CSF pleocytosis was a common finding in children with facial palsy and encephalitis (**Table 4**). The median CSF leucocyte count was 14 (range 0–635) in children with encephalitis and 6 (range, 1–605) in children with facial palsy. An elevated CSF protein level was detected in 36 (43%) of 84 children with facial palsy and in 30 (31%) children with encephalitis. The CXCL13 level was determined in a CSF sample of 28 patients, including 12 patients with and 16 without neuroborreliosis (see 5.2.5 for details).

Table 4. Characteristics, clinical features and treatment of children with facial palsy and encephalitis.

	Facial palsy, n=94	**Encephalitis, n=98**
Age, median, years (Q1, Q3)	8.7 (5.5, 12.9)	6.8 (3.0, 11.5)
Gender, male, n (%)	46 (49)	59 (60)
CSF pleocytosis (%)	42/84 (50)	65/96 (68)
Symptoms		
Abnormal consciousness or alertness, n (%)	0 (0)	75 (75)
Fever, n (%)	24 (26)	58 (59)
Gastrointestinal symptoms, n (%)	10 (11)	56 (57)
Headache, n (%)	26 (28)	44 (46)
Seizures, n (%)	1 (1)	37 (38)
Difficulties in balance, n (%)	3 (3)	31 (32)
Respiratory symptoms, n (%)	25 (27)	30 (31)
Motor paresis, n (%)	6 (6)[1]	23 (24)
Difficulties in speech, n (%)	1 (1)	22 (23)
Psychiatric symptoms, n (%)	0 (0)	12 (12)
Movement disorder, n (%)	0 (0)	8 (8)
Neck stiffness, n (%)	3 (3)	8 (8)
Treatment		
Doxycycline, n (%)	76 (81)	90 (92)
Ceftriaxone, n (%)	25 (27)	25 (25)
Acyclovir, n (%)	14 (15)	83 (85)
Corticosteroid, n (%)	21 (22)[2]	25 (26)[3]
Intravenous immunoglobulin, n (%)	1 (1)[4]	20 (20)

[1] Oftalmoplegia or limb weakness
[2] Prednisolon 1-2 mg/kg/day
[3] High-dose methylprednisolon
[4] For treatment of Guillan Barré syndrome

5.2.3 Microbiologic diagnosis

A microbial diagnosis was confirmed in 38 of 98 (39%) children with encephalitis. The confirmed causative agents were HHV 6 or 7 in ten, *M. pneumoniae* in seven, HSV in four, *B. burgdorferi* in four, enterovirus in three and TBE virus in three children. Parainfluenza virus, rhinovirus, adenovirus, EBV, VZV, CMV and *S. pneumoniae*, each in one child, were also confirmed as causative agents. One child had two confirmed causative agents for encephalitis: positive HHV 7 PCR in CSF and positive TBE virus antibodies in CSF and serum. The confirmed microbial diagnosis was found in 15 of 42 (36%) subjects in the cohort of subjects participating in Study III's Touwen neurological examination and cognitive assessment. Microbial etiology other than *B. burgdorferi* was not routinely searched for facial palsy in Study I.

5.2.4 Neuroborreliosis in children with facial palsy (I)

A two-step test for *B. burgdorferi* antibodies was performed in the sera of all 94 patients included in the facial palsy study. A CSF sample was analyzed for *B. burgdorferi* by antibody measurements in all 84 patients with a lumbar puncture performed and by PCR in 26 of them. Neuroborreliosis was documented in 34 (36%) of 94 patients with facial palsy, in 33 (39%) of 84 with a lumbar puncture performed, and in one of ten patients with no lumbar puncture. Later serum and CSF specimens were unavailable for repeated measurements of *B. burgdorferi* antibodies.

Of 33 subjects with neuroborreliosis and a lumbar puncture performed, the diagnosis was confirmed by both serum and CSF analysis in 7 (21%), only by serology of serum in 17 (52%), and only by CSF analysis in 9 (27%). An intrathecal antibody index was positive in all 16, and a PCR in 3 of 16 patients, with a diagnosis of neuroborreliosis confirmed by CSF analysis. The PCR test was performed for 9 of these 16 children with neuroborreliosis confirmed by CSF analysis and altogether for 26 of 98 patients with facial palsy.

5.2.5 Sensitivity, specificity and predictive values of CSF analyses for neuroborreliosis in children with facial palsy (I)

Borreliosis was confirmed in 29 (69%) of 42 children with CSF pleocytosis and in four (10%) of 42 with a normal CSF leucocyte count. Of these four patients, one had an elevated protein level in their CSF. Thirteen (31%) of 42 subjects with pleocytosis had negative results for borreliosis in their serum and CSF samples. The sensitivity and specificity of CSF pleocytosis for borreliosis were 88% (95% CI, 78–98%) and

71% (58–84%), respectively, and the positive and negative predictive values were 69% (55–83%) and 90% (81–99%), respectively. The sensitivity but not the specificity of abnormal CSF, defined as pleocytosis or an elevated protein level, was slightly higher than that of pleocytosis only.

CXCL13 was elevated (range, 162–1230 ng/L) in 8 and low (< 7.8 ng/L) in 4 of 12 patients with borreliosis (sensitivity 67%; 95% CI, 51–83%). The intrathecal antibody index was negative in all four CXCL13 negative cases in the neuroborreliosis group, and the diagnosis of *Borrelia* infection was based on positive serology in serum (in one patient, also on a positive *B. burgdorferi* PCR in CSF). The CXCL13 level was low (< 7.8 ng/L) in all 16 children (specificity 100%) with facial palsy without borreliosis.

5.3 Dental findings after doxycycline treatment (II)

At the time of dental examination, 24 subjects (63%) were at the permanent dentition phase and fourteen subjects (37%) were at the mixed dentition phase. Neither tetracycline-like dental staining nor enamel hypoplasia was seen in the patients' permanent teeth in the clinical examination or in the photographs.

Figure 5 shows the teeth photograph of one study subject, and **Table 5** shows the details of the doxycycline treatment and dental findings.

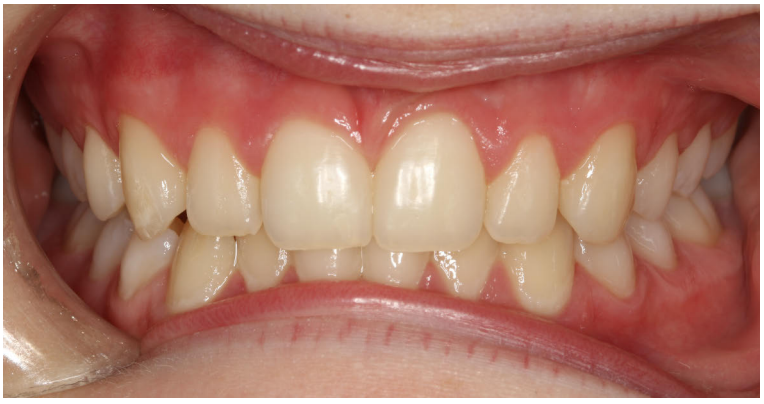

Figure 5. Teeth photograph of a study subject who had received a doxycycline course at 2 years of age. Dental examination was done at 12 years of age. Photograph by Mirka Nurmi.

Table 5. The details of doxycycline treatment and dental findings of 38 children with 39 doxycycline courses.

Age at treatment (years)	Diagnosis	Length of treatment (days)	Age at dental examination (years)	Enamel findings of teeth	Dentition
0.6	HHV6 encephalitis	11	9.4	-	Late mixed
0.8 and 6.9	Encephalitis	10 and 5	11.5	-	Late mixed
1.2	HHV6 encephalitis	16	15.3	-	Late mixed
1.4	Encephalitis	2	13.0	Fluorosis like hypomineralization	Permanent
1.6	ICH, sinus thrombosis	16	11.6	-	Late mixed
1.7	Cerebellitis	10	9.2	Fluorosis like hypomineralization	Late mixed
2.0	HHV6 encephalitis	7	12.6	Mild hypomineralization (d. 13)	Permanent
2.4	Rasmussen encephalitis	21	12.1	Molar incisor hypomineralization (dd. 16, 26, 23)	Late mixed
3.2	Neuroborreliosis	8	11.3	-	Late mixed
3.6	Cerebellitis/ ADEM	14	14.2	Molar incisor hypomineralization (d. 11)	Permanent
3.7	Encephalitis	10	15.8	-	Permanent
3.8	Encephalitis	14	8.3	-	Early mixed
4.0	Neuroborreliosis	7	11.2	-	Late mixed
4.2	Encephalitis	2	11.5	-	Late mixed
4.5	Enterovirus meningitis	2	17.8	Hypomineralization	Permanent
4.6	Encephalitis	10	11.8	-	Late mixed
4.6	Encephalitis	10	18.4	Molar incisor hypomineralization (d. 11, 21)	Permanent
4.7	Encephalitis	21	20.0	-	Permanent
4.9	Encephalitis	14	10.8	-	Late mixed
5.5	Neuroborreliosis	7	8.8	-	Late mixed
5.6	Encephalitis	12	16.9	Fluorosis like hypomineralization	Permanent
5.9	Encephalitis	16	17.5	-	Permanent
5.9	Stroke	14	13.3	Fluorosis like hypomineralization	Permanent
6.1	Meningitis viralis	14	15.1	Caries, history of orthodontic treatments	Permanent
6.3	Neuroborreliosis	21	19.5	-	Permanent
6.3	Epileptic seizure, ataxia	3	11.0	-	Permanent
6.5	Lyme borreliosis	28	15.0	Hypomineralization (dd. 37–35)	Permanent
6.8	Facial palsy	10	18.5	-	Permanent
6.8	Status epilepticus, neuroborreliosis	8	15.0	-	Permanent
6.9	Meningitis	10	19.5	Mild hypomineralization (dd. 15, 27)	Permanent
7.1	Encephalitis	16	22.6	Molar incisor hypomineralization (dd. 11, 21, 16, 26)	Permanent
7.2	Lyme borreliosis	14	15.9	Molar incisor hypomineralization	Permanent
7.4	Neuroborreliosis	21	17.6	-	Permanent
7.5	Neuroborreliosis	14	14.2	-	Permanent
7.8	Borrelia uveitis	21	20.9	Molar incisor hypomineralization (dd. 31, 36, 46)	Permanent
7.9	Neuroborreliosis	21	14.0	-	Permanent

ADEM, acute disseminated encephalomyelitis; HHV, human herpesvirus; HSV, herpes simplex virus; ICH, intracranial hemorrhage

5.4 Outcomes

5.4.1 Facial palsy recovery (I)

The follow-up data on facial palsy recovery were available for 93 of 94 patients. The recovery was good in 90 (97%) and permanently poor in three (3%) children aged 4.6, 7.9 and 12.9 years at the onset of their symptoms. Two of them were male and one was female. The etiology of facial palsy in the three children with a poor recovery was borreliosis in one, structural (cyst in facial nerve) in one and unknown in one. Thus, there was no discernible difference in the recovery rates of facial palsy in children with or without neuroborreliosis. The factors predicting a poor recovery were not studied due to the small sample size.

The grade of facial palsy was at least moderate (H-B FNGS III–VI) during the first two months of clinical follow-up in 18 of 93 (19%) children with a good final recovery, and the recovery was completed only later.

The facial palsy recurred in five children. The etiology for recurrence remained unknown. The first episode was not associated with borreliosis in these children.

5.4.2 Outcome after encephalitis

5.4.2.1 Recovery assessed by Glasgow Outcome Scale (IV)

GOS was defined for all 98 encephalitis patients at discharge, for 91 patients at short-term follow-up and for 82 patients at long-term follow-up. The median follow-up time was 6.0 (IQR, 2.7–11.5) years for 82 patients with a long-term follow-up.

Short-term recovery was poor (GOS 2–5) in 29 of 91 (32%) children. Long-term recovery was poor in 24 of 82 (29%) children: Of them, 14 children had moderate disability, eight children had a severe disability and two children died. One child died during an acute illness at the hospital, and one died later due to an encephalitis relapse; thus, the total mortality was 2%. None of the children remained in a vegetative state. A total of 52 patients had a good recovery at discharge (GOS 1), but 7 (13%) of them had a moderate or a severe disability at long-term follow-up. However, 7 of 15 (47%) children with a severe disability at discharge had a good recovery at long-term follow-up. **Table 6** shows the details of children with a severe disability (GOS3) or death (GOS5).

Table 6. Children with a severe disability or death as outcome of encephalitis.

Sex and age at time of encephalitis	Subtype of encephalitis	Microbe finding	MRI complexity category	Outcome; age at outcome assessment
Girl, 0.1 years	Encephalitis with confirmed microbial causative agent	HSV PCR and serology positive in CSF, HSV serology positive in serum	5	Epilepsy, cognitive disability, tetraparesis; 3.6 years
Boy, 1.3 years	Encephalitis with confirmed microbial causative agent	HSV PCR positive in CSF, HSV serology positive in serum	5	Epilepsy, learning difficulties, neuropsychiatric disorder; 17.5 years
Girl, 2.8 years	Autoimmune encephalitis (suspected)	Rhinovirus PCR positive in nasopharyngeal sample	5	Death; 4.8 years
Boy, 3.6 years	Encephalitis without confirmed microbial causative agent	Coronavirus PCR positive in nasopharyngeal sample	4	Learning difficulties, neuropsychiatric disorder; 8.3 years
Boy, 6.7 years	Encephalitis without confirmed microbial causative agent	Negative	4	Death; 6.7 years
Boy, 6.8 years	FIRES	*Chlamydia pneumoniae* serology positive in serum	2	Learning disability, severe epilepsy; 21.4 years
Boy, 7.0 years	Encephalitis without confirmed microbial causative agent	Adenovirus, enterovirus and parainfluenza virus PCR positive in nasopharyngeal sample	1	Behavioral problems, epilepsy, motor and speech problems; 8.0 years
Boy, 7.1 years	Encephalitis without confirmed microbial causative agent	Negative	3	Memory problems, learning difficulties, personality change; 24.5 years
Boy, 7.3 years	FIRES	Negative	2	Epilepsy, behavioral problems, learning difficulties; 12.8 years
Boy, 10.8 years	FIRES	*M. pneumoniae* serology positive in serum, rhinovirus PCR positive in nasopharyngeal sample	1	Epilepsy, behavioral and psychiatric problems, cognitive disability; 18.9 years

FIRES, febrile infection-related epilepsy syndrome; PCR, polymerase chain reaction

5.4.2.2 Rate of minor neurological dysfunction (III)

The Touwen neurological examination was performed on 41 of 42 children in Study III. The median follow-up time from acute encephalitis to the Touwen examination was 6.0 (range, 0.4–22.6) years. The examination was normal in 12 (29%). MND was detected in 29 participants, (71%), sMND in 16 participants, (39%) and cMND in 13 (32%) participants.

5.4.2.3 Rate of cognitive problems (III)

The cognitive assessment was performed on 38 of 42 participants in Study III. The median follow-up time from acute encephalitis to cognitive assessment was 4.1 (range, 0.4–28.9) years. The median full-scale IQ was 100 (range, 52–106). The full-scale IQ was ≥85 in 33 (87%) and <85 in 5 (13%) of the participants and <70 (52 and 59) in two (5%) participants. Both were born full term and suffered encephalitis at an early age, one at 5 months and the other at 7 months. The cognitive assessment was performed for one at 7.1 years and for the other at 10.9 years of age.

Gender, CRP value >40 mg/l, CSF pleocytosis, abnormal MRI, abnormal EEG, seizures, need for the ICU, length of hospital stay or duration of symptoms were not associated with full-scale IQ <85. The median full-scale IQ was lower in participants with MND (simple or complex) compared to participants with a normal Touwen neurological examination (98; range, 52–112; and 110; range, 88–126, respectively; p=0.02). The results remained consistent when two participants with full-scale IQ <70 were excluded.

5.4.2.4 Daily performance and schooling (III)

Forty-two subjects in Study III returned the Encephalitis study questionnaire. Five (12%) subjects reported difficulties in motor skills, with no significant difference in rates between subjects with a normal Touwen examination and subjects with MND. A total of 22 participants (52%) reported playing sports actively during leisure-time, with a clear overrepresentation in subjects with MND compared to subjects with a normal Touwen examination (70 vs. 18%, p=0.04). Difficulties in the activities of daily living were reported by ten (24%) subjects and were more common in subjects with full-scale IQ<85 compared to subjects with full-scale IQ≥85 (60 vs. 18%, p=0.008).

Twenty-seven (64%) participants attended primary school or preschool at the time of the follow-up. Of 15 participants who had finished primary school by age 15, 14 (93%) were presently studying or had completed their studies. Twelve (29%) participants reported the need for special support at preschool or at school, and the need for support was more common in subjects with lower full-scale IQ (80 vs. 22%, p=0.02).

5.4.3 Neuroimaging predicting outcome (III, IV)

The categories of the two most complex MRI findings (categories 4 and 5) showed that 8 of 17 (47%) children needed ventilatory therapy, 10 of 15 (67%) had poor long-term recovery (GOS 2–5) and 3 of 16 (19%) had a severe disability (GOS 3), while only 3 of 39 children (8%) in the category of a normal MRI needed ventilatory

therapy, 7 of 30 (23%) had poor long-term recovery and 2 of 30 (7%) had a severe disability. The increasing complexity of MRI findings was associated with the need for ventilator therapy at the acute phase of encephalitis (p=0.01), poor long-term recovery (p=0.04) and degree of disability (p=0.01).

An abnormal MRI was unrelated to MND or full-scale IQ <85 in the 42 subjects studied. The association of location, extent or type of MRI lesions with MND or low IQ was not studied due to the small sample size.

5.4.4 Other factors predicting outcome (III, IV)

The need for ventilator therapy was associated with poor long-term recovery (p=0.0005) and degree of long-term disability (p=0.01). The need for ventilator therapy had the strongest independent association with long-term disability. The need for ICU admission was associated with degree of disability (p=0.006) in 98 children with encephalitis (IV) but not with MND or lower full-scale IQ in the 42 subjects participating in the study visits (III). The need for AEDs was associated with poor long-term recovery (p=0.0006) (IV) but not with MND or lower full-scale IQ (III).

The encephalitis subtype was associated with a poor recovery (p=0.008) and a severe disability (p=0.0003). The prognosis of FIRES was adverse, with a poor recovery and a severe disability in all three children. A poor recovery was detected in two of three children with ANE, but none had a severe disability. Four of seven (57%) children with autoimmune encephalitis had a poor recovery (GOS 2–5), but a severe disability (GOS 3) was only seen in one child. A poor recovery was detected in all eight cerebellitis patients at discharge but in only three of seven (43%) at long-term follow-up. Encephalitis with a confirmed microbial causative agent had the most favorable outcome, because a poor outcome was detected in only 16% of children.

The median age at acute encephalitis was significantly lower in participants with full-scale IQ <85 at follow-up compared to the participants with full-scale IQ ≥85 (1.8 and 5.3 years, respectively, p=0.03) (III). However, age was not associated with MND (III), a poor long-term recovery or the degree of disability (IV). Gender, length of hospital stay or microbial etiology were unrelated to poor long-term recovery, degree of disability (IV), MND or lower full-scale IQ (III). Prematurity or developmental delay before encephalitis were also not associated with a poor long-term recovery or the degree of disability (IV); and CRP >40 mg/l, CSF pleocytosis, abnormal EEG, seizures, or duration of symptoms were not associated with MND or a lower full-scale IQ (III).

6 Discussion

6.1 Diagnostics of neuroborreliosis in children with facial palsy

Neuroborreliosis was detected in one third of children with facial palsy in this study. The rate of *Borrelia* infection in our study is in line with previous Finnish studies (Kanerva et al., 2013; Peltomaa et al., 1998), as well as with some other studies performed in endemic areas for borreliosis (Munro et al., 2020).

Pleocytosis had a high sensitivity and positive predictive value for neuroborreliosis, whereas normal CSF leucocyte and protein levels had a high negative predictive value for this disorder. Other investigators have also noted the high predictive value of pleocytosis in adult and paediatric patients with facial palsy and in adult patients with erythema migrans and suspected neuroborreliosis (Bremell & Hagberg, 2011; Ogrinc et al., 2013).

The results of a CSF leucocyte count and protein concentration are ready in two hours, which makes CSF analysis a useful tool to guide antimicrobial treatment in clinical work. The high predictive values of CSF pleocytosis suggest that an antimicrobial treatment against neuroborreliosis can be initiated in endemic areas in Europe based on CSF pleocytosis or an elevated protein level even before antibody results are available.

The high negative predictive value of normal CSF parameters (leucocyte count and protein level) suggests that an antimicrobial treatment can be withheld in that case until serologic results are available and corticosteroid treatment for idiopathic facial palsy can be considered. Avoiding the routine CSF sample would avoid the inconvenience of a lumbar puncture, but this strategy could result in an unnecessary antibiotic treatment in those who do not have neuroborreliosis.

We found that CXCL13 analysis was a specific but not highly sensitive tool for detecting neuroborreliosis in children with facial palsy. This means that an elevated CXCL13 concentration indicates neuroborreliosis, but a low concentration does not rule it out. The sensitivity of CXCL13 for neuroborreliosis has also been good or acceptable in previous paediatric studies (Henningsson et al., 2018; Knudtzen et al., 2020). These studies have included a wider range of clinical manifestations of neuroborreliosis, whereas our study is the first to evaluate the accuracy of CXCL13

analysis in children with facial palsy. The point-of-care method for determining CXCL13 concentration, together with a CSF cell count and protein level, could enable a rapid and specific diagnosis of neuroborreliosis in children with facial palsy.

The borreliosis diagnosis could be confirmed only by CSF analysis in one quarter of the children. The serologic response appears slowly in neuroborreliosis, and it may not be seen at the onset of facial palsy (Wormser et al., 2006). Thus, measurement of the intrathecal antibody production provides added value only over serum serology, because the intrathecal humoral response may be seen before the serologic response. Our findings suggest that *Borrelia* serology in serum should be repeated after a few weeks in the case when the first serum sample and CSF sample, if available, are not diagnostic for borreliosis but the clinical suspicion of borreliosis as the cause of facial palsy is strong.

The important role of CSF analysis in determining the etiology of facial palsy has been noticed for a long time (Christen et al., 1990). However, its role has also been recently questioned by the authors of another study in which children with a lumbar puncture performed were prone to be hospitalized and have an intravenous antimicrobial treatment for suspected meningitis due to a detected pleocytosis (Paydar-Darian et al., 2016). Neuroborreliosis presenting as facial palsy can be treated with doxycycline (Mygland et al., 2010), allowing oral administration. A considerable number of children with facial palsy were treated with doxycycline in our clinic, and 86% were treated without inpatient care or were discharged after a short hospitalization, despite a high rate of CSF pleocytosis. Thus, detection of pleocytosis should not routinely lead to hospitalization and treatment with intravenous drugs.

Facial palsy and pleocytosis are common findings in neuroborreliosis and should not be confused with bacterial meningitis that presents with a high fever, meningeal symptoms (headache and stiff neck) and elevated CRP in a sick child. However, bacterial meningitis may cause facial palsy, and, especially in infants, present without meningeal signs (Jadavji et al., 1986; Mwaniki et al., 2011); in turn, some cases of neuroborreliosis with facial palsy present with fever and meningeal symptoms. Thus, a lumbar puncture may be needed to indicate or exclude purulent meningitis in these cases to obtain the optimal treatment.

The risk for severe complications (e.g., spontaneous haemorrhage) of a lumbar puncture even in trombocytopenic paediatric patients is ≤1.75% (Howard et al., 2000) and the risk for less severe complications (e.g., postpuncture headache) is clearly lower than in adults (Ebinger et al., 2004; Evans, 1998). Small children usually need sedation for a lumbar puncture, but the disadvantages of general anaesthesia can be avoided by using conscious sedation (Ljungman et al., 2001).

This study has limitations. Thirteen patients had CSF pleocytosis but negative *B. burgdorferi*-specific tests both in their CSF and their serum. Other possible microbial

etiologies for facial palsy were not systematically explored in these children. Additionally, paired serum samples of these children were unavailable. There were also changes in the diagnostic methods for borreliosis during the study period, because the diagnostics have evolved over the years and are currently more advanced than earlier.

In conclusion for Study I, CSF analyses have an important role in achieving the diagnosis of neuroborreliosis in the early phase of facial nerve palsy symptoms. The positive predictive value of pleocytosis for neuroborreliosis was high enough to suggest that an antimicrobial treatment against neuroborreliosis can be initiated based on CSF pleocytosis or an elevated protein level. The negative predictive value of a normal CSF leucocyte count and protein level was excellent, which suggests that an antimicrobial treatment can be withheld. However, the predictive values are dependent on the local prevalence of illness, so these results are not directly applicable to areas that are not endemic for borreliosis.

6.2 Dental safety of doxycycline treatment

We did not find staining of permanent teeth in any of 38 patients who had received a course of doxycycline before the age of eight years in this study. Together with three other studies assessing staining of permanent teeth (Lochary & Lockhart, 1998; Todd et al., 2015; Volovitz et al., 2007), the combined rate of dental staining was 0/137 children. Two other studies assessed dental staining only one year after doxycycline exposure, probably mainly evaluating the state of the deciduous teeth. These studies reported a combined discoloration rate of 6/282 (Forti & Benincori, 1969; Poloczek, 1975). Considering that permanent teeth show less tetracycline effects than primary teeth (Grossman et al., 1971), the data are still lacking on the possible staining of permanent teeth after doxycycline exposure. Other researchers have reported doxycycline-induced staining of adult permanent dentition during a 4–6 week doxycycline course administered in the summer (Ayaslioglu et al., 2005). However, this staining completely resolved following dental cleaning. This indicates a totally different mechanism of staining on the surface of the teeth compared to tetracycline-induced staining presenting as pigmentated bands deep in the crown (**Figure 1**).

One fifth of our study's subjects were under 2 years of age during doxycycline exposure, which is a time of calcification of the permanent incisor teeth. We did not observe any staining in these most visible teeth during later examinations. About one third of these children's permanent teeth were erupted at the time of their dental examination, and the rest were at the phase of mixed dentition. None of the participants was at the phase of deciduous dentition; thus, our study gives reliable information on the state of the permanent teeth.

A considerable number of subjects received doxycycline intravenously. Our study is the first to show that even intravenous administration of doxycycline does not cause dental staining. This is an important finding for clinicians planning treatments for children with neuroborreliosis or encephalitis: Though doxycycline is well absorbed enterally (Aupee et al., 2009), the intravenous administration might be necessary at the beginning of the treatment in small children who may have difficulty swallowing tablets and in children with lowered consciousness.

Furthermore, a long treatment duration did not cause any dental discoloration. Our patients' treatment duration was longer (up to 28 days, mean 13 days) and their doses were higher (first up to 10 mg/kg/day for 2–3 days and thereafter 5 mg/kg/day) compared to previous studies reporting the mean doses and length of treatment (up to 10 days, mean 7 and 10 days; mean dose 4 mg/kg/day) (Todd et al., 2015; Volovitz et al., 2007). A higher loading dose is often used to achieve sufficient doxycycline concentration from the beginning of the treatment (Cunha, 2003).

We found dental hypomineralization in about one third of our study subjects. Molar incisor hypomineralization is a developmental enamel defect that is clinically seen as white or yellow demarcated opacities. The prevalence of molar-incisor hypomineralization has varied regionally from 3 to 44%, e.g., acute otitis media and the use of macrolides, amoxicillin and penicillin during the first years of life are found to increase the risk for molar-incisor hypomineralization (Wuollet et al., 2016). Our study did not investigate the association of doxycycline exposure with dental hypomineralization, but the detection and reporting of this finding highlights the accuracy of the performance of dental examinations.

The dental examinations were performed by an experienced paediatric dentist, and the teeth photographs were independently evaluated by another experienced dentist with similar results, which also adds to the reliability of our results.

The indication for treatment in our study was encephalitis or neuroborreliosis in about two thirds of the children. However, there are also other important applications for doxycycline treatment. Doxycycline is the recommended drug of choice for Rocky Mountain spotted fever in America (Cale & McCarthy, 1997). It is also effective against *Streptococcus pneumoniae* and *M. pneumoniae* (Lung et al., 2013), which are both common bacterial causative agents of paediatric pneumonia. Doxycycline could be widely used due to its low price in developing countries where pneumonia is an important cause of mortality in children (Leung et al., 2018). However, additional studies of efficacy and safety would be needed before its wide use can be suggested for respiratory tract infections in young children.

The use of long, 14-day treatment courses are recommended for the treatment of neuroborreliosis (Mygland et al., 2010). Children treated with long intravenous courses of antimicrobial drugs usually need a peripherally inserted central catheter, which carries an increased risk of treatment complications (Thompson, A. et al.,

2012). The catheter complications can be avoided by favoring orally administered drugs in neuroborreliosis treatments. It has been shown that parents would choose doxycycline for their child even if children treated with ceftriaxone had a slightly faster resolution of symptoms (Garro et al., 2018).

The lack of a control group and examination of teeth without the use of UV fluorescence can be suggested as limitations of our study (Wormser et al., 2018). However, only effects in the visible teeth (discoloration and enamel hypoplasia) were evaluated because these findings were considered the most relevant. We also do not find that including a control group would change the fact that our study participants had no visible dental staining after doxycycline exposure. The absence of staining in posterior molars cannot be excluded, because the dental examination was performed at the phase of mixed dentition in almost half of the children. However, we see the possible discoloration of posterior molar teeth cosmetically less relevant because these teeth are only visible at dental examination.

According to this study, doxycycline can be safely used in small children. However, the safety of high loading doses, long or several courses and intravenous administration of doxycycline is not yet widely studied. The lack of a suitable pharmaceutical form of the drug may, however, restrict the possibility of using oral doxycycline in small children. Additionally, due to the scarcity of children under two years of age included in this or previous studies, we suggest that doxycycline should be started in this age group in a hospital environment only for suspicion of a severe infection such as neuroborreliosis or encephalitis. More studies are also needed to ensure the safety of doxycycline in children under two years age.

6.3 Outcome

6.3.1 Outcome of facial palsy

Almost all children in our study with facial palsy were recovered after one year of follow-up. A poor recovery was detected in a minority (3%) of children both with and without neuroborreliosis. A previous Finnish study reported that facial palsy recovery after a minimum follow-up of 13 months was poor (H-B FNGS III–VI) in 6% of children with and without neuroborreliosis, and in another Finnish study, a poor recovery from facial palsy, detected by H-B FNGS after two years from onset, was noted even in 20% of children (Kanerva et al., 2021; Peltomaa et al., 1998).

Facial palsy recovery was not completed in our data during the first two months of the clinical follow-up in a considerable number of children. Facial palsy recovery may continue for as long as 12 months (Biebl et al., 2013; Devriese et al, 1990; Peitersen, 2002; Tang et al., 2009; Ünüvar et al., 1999); thus, it should not be assessed earlier.

Risk factors for a poor recovery, and the impact of treatment on recovery were not possible to study due to the small sample size (only three patients with a poor recovery).

6.3.2 Outcome of encephalitis

A severe disability was found in a little less than one tenth of the children in this thesis. The rate of severe disability has been at the same level, 9–14%, in previous studies assessing outcomes by GOS (Chen & Liu, 2018; DuBray et al., 2013; Mailles et al., 2012). However, in a study from French Guiana, the rate of severe disability was higher, 17%, but this study only included children admitted to the ICU (Elenga et al., 2020).

None of the children in our study remained in the vegetative state. The rate of vegetative state after encephalitis has been even 2% in previous studies reporting disability by functional scales (Chen & Liu, 2018; DuBray et al., 2013; Granerod et al., 2010; Mailles et al., 2012; McGrath et al., 1997). The study population in those studies has included both children and adults, or the proportion of HSV etiology has been higher, which may increase the rate of vegetative state.

There were two encephalitis-related deaths in our study, meaning the mortality rate was 2%. This rate agrees with the mortality rate of a systematic review and meta-analysis of long-term outcomes of infective encephalitis in children, in which 934 children were included (Khandaker et al., 2016).

Encephalitis causes not only death and severe disability but also milder neurological sequelae. A considerable portion of the survivors suffered lowered neurological performance measured by MND in a Touwen neurological examination. The rate of MND after encephalitis (71%) is remarkably higher than the rate of MND in the general paediatric population (up to 30%) (Hadders-Algra, 2002; Peters et al., 2011).

The lower neurological performance was associated with lower cognitive performance because the median full-scale IQ was 12 points lower in subjects with MND compared to the subjects with a normal Touwen neurological examination. Thus, the vulnerability of subjects with MND to the cognitive deficits (Kikkert et al., 2011) also seems to be valid after paediatric encephalitis.

The prevalence of IQ <70 and <85 in the general normative population is 2% and 16%, respectively (Wechsler, 2005, 2007, 2009, 2010, 2012). The prevalence of full-scale IQ <85 in our cohort was not higher than in the general population, and the full-scale IQ <70 was noted in only two participants. Both children with full-scale IQ <70 suffered encephalitis at a very young age. It is not possible to determine if the early neurological development of these children was normal or abnormal before encephalitis due to their young age at encephalitis.

After paediatric encephalitis, the prevalence of full-scale IQ <70 and <85 has been higher than in the normative population, 13–22% and 18–31%, respectively (Khandaker et al., 2016; Michaeli et al., 2014). Our study concentrated on the initial encephalitis survivors´ prognosis and excluded children with premorbid learning disabilities and patients with a recorded evident encephalitis-related disability, which obviously influenced the rates of full-scale IQ <70 and <85.

Over one sixth of the patients with a good recovery at discharge in our series were found to have a disability later in the clinical follow-up. Even symptoms and signs causing a remarkable disability may remain undetectable at discharge. The symptoms of seriously ill patients may resolve remarkably fast considering how severe they were, which may lead clinicians to categorize these patients with a good recovery at discharge regardless of sometimes severe cognitive effects. Lack of an objective disability scale can lead to overestimates of outcomes after brain injury (Jennett & Bond, 1975). The use of standardized outcome assessment methods helps to weigh up the daily performance, which often correctly defines the handicap stage and the rehabilitation need.

It is known that milder cognitive defects or behavioral changes may become evident later in the follow-up and cannot be noted at the acute phase, especially in the youngest children (Fowler et al., 2013; Khandaker et al., 2016). These symptoms do not necessarily affect functioning until a child gets back to home, school and leisure-time hobbies. However, almost half of the children with a severe disability at discharge had a good recovery at their long-term follow-up. A remarkable proportion of encephalitis-related residual symptoms may resolve between 3 and 12 months after discharge (Fowler et al., 2010), and the recovery can continue for up to 18 months in anti-NMDAR encephalitis (Titulaer et al., 2013); thus, the assessment of neurological outcome should not be done too soon after discharge.

6.3.2.1 Factors predicting outcome of encephalitis

The most complex MRI findings were associated with the need for ICU admission and ventilator therapy, indicating that patients with the most complex MRI findings had a severe acute illness and a later neurological disability. Our findings support a previous study's findings that also reported the association between neuroimaging findings and disease severity (Bykowski et al., 2015).

Young age at encephalitis was a risk factor for lower full-scale IQ in the follow-up. This supports the previous knowledge of young age predicting a poor outcome after paediatric encephalitis (Iff et al., 1998; Rautonen et al., 1991; Rismanchi et al., 2015b; Ward et al., 2012). All the children with full-scale IQ <85 were younger than 2 years old at encephalitis, but because there was only five children in this group, we could not define any risk age for a poor outcome.

Other risk factors along with young age were not found for lower cognitive performance, possibly due to the small sample size (only five subjects with IQ <85)

Young age at encephalitis was a risk factor for lower cognitive performance but not for a severe disability observed by GOS. GOS measures functional performance in several regions of everyday life, not only cognitive performance, and also weighs a child´s premorbid status in the evaluation (Beers et al., 2012). The subjects participating in the cognitive assessment were also younger at the onset of illness compared to all our subjects with encephalitis, which also might have influenced our results.

Risk factors for MND were not found in our study, which supports the findings of other investigators reporting only less severe neurological sequelae after encephalitis (Fowler et al., 2013; Schmolck et al., 2005). Only subjects without evident disability were eligible to participate in our cohort, which may explain the lack of statistically significant risk factors for MND.

One-fifth of our patients with a normal, acute phase MRI had poor outcomes in their long-term follow-up. It remains unclear if later re-imaging had revealed encephalitis-related abnormalities in patients with a normal MRI performed early after symptom onset. This could possibly have also revealed the association between an abnormal MRI with MND. We suggest that repeated MRIs should be considered if a child continues to be symptomatic.

Encephalitis without a confirmed microbial etiology had the best long-term outcome in our study. This group was heterogenic, including a variety of cases who did not meet the criteria of ADEM, AIE, cerebellitis or FIRES, and no microbial causative agent was found.

All the cerebellitis patients had a poor recovery at discharge, but over half of them recovered well later. Cerebellitis also did not cause any severe disability in the long-term follow-up. Similar outcomes are reported in earlier studies (Kornreich et al., 2016; Yildirim et al., 2020). This may reflect the high prevalence of motor and coordination problems that are easily recognized even in the hospital environment before the discharge but that may resolve later (Yildirim et al., 2020), compared to cognitive defects that may become evident only later in everyday life.

The outcome of cerebellitis is not reported to be as good as postinfectious cerebellar ataxia (Yildirim et al., 2020). We did not differentiate these disorders from each other in this study. One child in our data had clinically diagnosed chickenpox four days before the onset of fever and cerebellar symptoms (atactic gate and dysarthria) and may have been classified as postinfectious cerebellar ataxia.

FIRES is classified as immunologic epilepsy syndrome, but the diagnosis is usually made later in the clinical follow-up. FIRES is often treated as encephalitis at its acute phase. There was pleocytosis in one child and encephalitis-related imaging abnormalities in two children in our data, meeting the inclusion criteria of our study.

One patient also had a confirmed microbial etiology (positive *M. pneumoniae* IgM antibodies in serum sample) in the acute phase of illness. The etiology of FIRES is not yet fully understood, so we included these patients in the study.

FIRES was related to the poorest long-term outcome with a severe disability in all three children. The poor prognosis of this disorder is also reported by other investigators (Hon et al., 2018; van Baalen et al., 2010). The rate of severe disability would be only slightly smaller (6% vs. 8%) with the exclusion of these three patients, and the overall rate of good recovery would not be remarkably higher (72% vs. 71%).

The encephalitis subtypes and MRI findings were not compared because the acute phase MRI findings affect the clinical diagnosis of encephalitis subtype. The microbial etiology was not associated with the neurological outcome, which may reflect the diverse etiology and the small sample size; only 38 of the encephalitis cases had a confirmed microbial etiology. The microbial etiology was also unrelated to the complexity of MRI findings, which is consistent with a previous study (Bykowski et al., 2015).

6.3.3 Methodological discussion of outcome studies

The original H-B FNGS was used to assess facial palsy recovery. The newer grading scales, such as FNGS 2.0 or the Sunnybrook Facial Grading System, may be more strict and sensitive for assessing differences between different grades of facial nerve function (Ross et al., 1996; Vrabec et al., 2009). However, the accuracy of the classic scale was adequate for our purpose in scoring the recovery in the two categories of good recovery (grades I–II) and poor recovery (grades III–VI). This classification made it possible to evaluate the outcome retrospectively from medical records without study visits.

Mild dysfunction, or normal facial symmetry and tone at rest, and a slight weakness notable only on close inspection, was included in the category of good recovery in our study. The classification of separate grades of poor recovery (grades III–VI) was found not valid due to the small sample size (only three subjects suffered from a poor recovery).

We also did not assess the possible psychosocial difficulties caused by mild facial palsy and cannot exclude, e.g., low mood and withdrawal from social activities among these subjects (Hotton et al., 2020).

The criteria for acute encephalitis in this study were strict: >24 hours of symptoms of encephalopathy together with CSF, MRI or EEG abnormality related to encephalitis were required. We wanted to exclude transient encephalopathy during febrile illness caused by factors such as hypoglycaemia, dehydration or febrile seizures. The high proportion of MRI abnormalities most probably reflects a true brain disorder. The strict inclusion criteria may have affected the sample size and

worsened the overall outcome of our study by excluding some milder encephalitis cases.

The use of variable methods for assessing outcomes makes comparison of separate studies difficult. Some outcome markers, such as activities of daily living, returning to school or work, or the ability to live in the home, may be misleading because several socioeconomic factors can affect them. It may also be challenging to distinguish between behaviors frequently found in typically developing children and those with brain injury when using symptom surveys from parental interviews (Beers et al., 2012; B Jennett et al., 1981). The strength of this thesis was the use of standardized methods to assess outcomes after paediatric encephalitis.

The GOS method was used to evaluate neurological disability after encephalitis. This method makes it possible to compare the variable symptoms reported by patients and enables investigators to define the functional impairment of these symptoms in everyday life. This method takes into account a child´s premorbid level of function, so it can also be used with patients with premorbid disability without obligation to exclude these patients from the study population.

We used GOS, not GOS-E, to assess outcomes after encephalitis. The extended scale may reveal the change of an individual patient´s function over time more definitely, compared to the original GOS (Jennett et al., 1981). This may be an important point of evaluation in some aspects when, e.g., assessing the effectiveness of rehabilitation or dividing subjects with the mildest symptoms into separate categories of upper and lower good recovery (see details in 2.5.2.2.1). Instead, we wanted to identify children with a more severe disability, so we found the original score sufficient for our purposes.

GOS has advantages over other outcome scores. PCPC has been developed to assess short-term disability after a life-threatening medical injury: It has not been validated for outcome assessment after discharge or on the larger scale of severity of injury (Beers et al., 2012; Fiser et al., 2000; Fiser, 1992). The use of LOS requires a structured parental interview, while GOS allows gathering the information by personal assessment, parental interview or medical records (Beers et al., 2012; Lewthwaite et al., 2010). The Modified Ranking Scale (mRS) was developed to assess neurological outcome after a stroke, highlighting the role of physical impairment and motor disability (van Swieten et al., 1988). Encephalitis, like other brain injuries, causes not only physical but also mental impairment, which may make mRS a less useful method for assessing encephalitis outcome.

This study is the first to assess MND after paediatric encephalitis. The complete protocol of the Touwen neurological examination's latest version was used to obtain detailed and reliable information. The examination was performed and scored by an experienced physician and assessed from video recording by two other experienced physicians to ensure the ratings' reliability. The reliability of the Touwen

examination in the assessment of MND has been shown to be excellent or good (Peters et al., 2008). The cognitive assessments were performed by an experienced psychologist working at the hospital's department of paediatric neurology.

Our focus was on long-term neurological outcomes instead of reporting sequelae at discharge or after short-term follow-up. There are only a few previous studies that evaluated long-term outcomes of paediatric encephalitis with standardized methods (Armangue et al., 2013; Chen & Liu, 2018; DuBray et al., 2013; Mailles et al., 2012; Pillai et al., 2015).

The questionnaire used in this study was designed for the purposes of the present study without validation. The use of a questionnaire is an important method for discovering patients' opinions of their residual symptoms. However, there is no standardized questionnaire developed for the follow-up after paediatric encephalitis. The questionnaires used in previous studies have limitations. The lack of one validated questionnaire often requires investigators to use several separate questionnaires, which may be laborious for children and their parents. The parent-rated Five-to-Fifteen Questionnaire and the parent- or teacher-rated Behaviour Rating Inventory of Executive Functioning (BRIEF) (Engman et al., 2012; Fowler et al., 2013) may possibly not differentiate between the cognitive and behavioral symptoms related to a child´s typical development or encephalitis. The Rivermead post-concussion symptoms questionnaire (RPQ) evaluates the presence of symptoms before and after a traumatic brain injury (Fowler et al., 2013). The Patient-Reported Outcomes Measurement Information System measures (PROMIS) capture patients' own experiences surrounding their physical, social, mental, and emotional health in several neurological or autoimmune disorders (Blum et al., 2020). Both of these two last-mentioned questionnaires might have potential to be developed and validated for encephalitis outcome assessment tools.

6.3.4 Limitations of outcome studies

Our study has some limitations. Part of the data were collected retrospectively from the medical record system, which is prone to human errors in diagnosis recording. It is possible that all cases of facial palsy or encephalitis were not found because of incorrect recording of the ICD-10 codes, although we suppose the risk for incorrect recording of facial palsy to be an infrequent possibility because facial palsy is a rather clear-cut clinical diagnosis. We included a wide range of CNS infection-related conditions during data collection to find all encephalitis cases.

The time between the encephalitis and outcome assessment was variable and more than 20 years for some subjects. A long time gap between acute encephalitis and outcome assessment makes differentiation of all environmental factors affecting the patients´ neurological outcome impossible.

The participants were at different ages and stages of development, so the deficits may affect their everyday life at different levels. Milder challenges can manifest more clearly at an older age; however, with age a person may develop compensatory mechanisms to manage minor deficits.

The differentiation of developmental disorders and encephalitis-related symptoms can be challenging in the youngest children, even though their development was normal before the acute illness. Two children in our study with a severe disability, and in total seven children with a poor outcome, were under 2 years old during their acute encephalitis. Still, the use of an instrument with standardized outcome measures increased the reliability of the evaluation even in these patients.

The cohort of patients participating in the Touwen neurological examination and the cognitive assessments were younger at encephalitis onset, which may have influenced the results by worsening the outcome assessed by their cognitive performance (Iff et al., 1998; Rautonen et al., 1991; Rismanchi et al., 2015b; Ward et al., 2012).

6.3.5 Conclusions of outcome studies

A remarkable portion of the children with encephalitis in this study suffered from poor long-term recovery. The increasing complexity of the MRI findings was associated with severe illness and poor long-term outcomes. However, it is important to note that a normal MRI does not exclude poor long-term outcome. The prevalence of MND was high in children with no evident disability after encephalitis. No acute phase risk factors for MND were found. The clinical follow-up by a paediatric neurologist and neuropsychologist should therefore be offered to all children after acute encephalitis and continued for at least 1-2 years to detect not only any severe disabilities but also any milder defects affecting everyday life. The youngest children and children with complex MRI findings should be followed up with special attention.

A moderate or severe disability after a brain injury is usually easily recognized. However, mild sequelae may remain unrecognized in a standard paediatric examination, leaving these patients with insufficient support. Mild symptoms may become evident with age and increasing environmental demands and cause problems affecting the individual's health, quality of life and independence in everyday life. Thus, standardized methods are needed to recognize patients with milder sequelae. The Touwen neurological examination can be useful in detecting non-evident neurological deficits and in establishing the need for cognitive assessment after childhood encephalitis.

6.4 Considerations for future research

In addition to CXCL13, cytokines induced by Th1, Th2, Th9, Th17 and Treg responses, and neopterin seem to be potential markers of neuroborreliosis (Hytönen et al., 2014; Pietikäinen et al., 2016). Interferon gamma and Th2 and Th17 cytokines, respectively, are frequently elevated in viral encephalitis and ADEM (Kothur et al., 2016), indicating that cytokine and chemokine profiling may provide a useful tool for diagnostics of neuroborreliosis and encephalitis and for monitoring the treatment response in these disorders.

The effect of corticosteroid treatment for facial palsy recovery in children and adolescents, possibly in different age groups, should be a consideration for future research. A research plan for a randomized, placebo-controlled, multi-center trial was recently published (Karlsson et al., 2021). The psychosocial difficulties caused by mild facial palsy could also be an interesting focus of research.

The major problem after paediatric encephalitis is not only the lower IQ but also the problems in specific cognitive functions like executive function and working memory (Fowler et al., 2013). Personality changes, headache, fatigue, and irritability may also affect their performance in everyday life (Fowler et al., 2010). Thus, it would be interesting to study specific cognitive functions and behavioral problems more widely, especially in patients with difficulties in motor performance.

7 Summary

The following results considering the diagnostics of neuroborreliosis, safety of doxycycline treatment and outcome of encephalitis and facial palsy were obtained in this thesis:

- The positive and negative predictive values for CSF pleocytosis to predict neuroborreliosis in children with facial palsy were 69% and 92%, respectively.
- The sensitivity and specificity of elevated CXCL13 chemokine level in CSF to predict neuroborreliosis in children with facial palsy were 67% and 100%, respectively.
- Tetracycline-like discoloration of permanent teeth was not found in 38 subjects with doxycycline-exposure before the age of eight years.
- A total of 97% of subjects with facial palsy had good long-term outcomes.
- A poor long-term recovery was detected in 29% and a severe disability in 8% of subjects after paediatric encephalitis. The increasing complexity of MRI findings predicted a severe acute illness and a poor long-term recovery.
- MND was found in 71% of subjects without an obvious encephalitis-related disability. MND associated with a lower IQ. Young age at encephalitis was a risk factor for lower cognitive performance.

In conclusion, CSF analyses have an important role in supporting the diagnosis of neuroborreliosis in children with facial palsy. Antimicrobial treatment can be initiated or withheld based on this result due to the good predictive value of CSF pleocytosis. Doxycycline can be safely used in children for treatment of severe CNS infections such as neuroborreliosis and encephalitis. Paediatric encephalitis causes neurological disability in a remarkable proportion of survivors. Most children with milder sequelae also suffer from MND, which can affect their everyday life and indicate cognitive difficulties. The clinical follow-up should be offered to all children after encephalitis. The youngest children and the children with complex

MRI findings should be followed up with special attention. Standardized methods to assess less severe deficits in neurological performance, such as the Touwen neurological examination, should be used.

Acknowledgements

This work was done at the Departments of Paediatric Neurology, and Pediatrics and Adolescent Medicine at the University of Turku and Turku University Hospital. This work was supported by Arvo and Lea Ylppö Foundation, Finnish Pediatric Neurology Association, Finnish-Norwegian Research Foundation for Medicine, Foundation for Pediatric Research, Juhani Aho Foundation for Medical Research, Maire Taponen Foundation, Orion Research Foundation, Päivikki and Sakari Sohlberg Foundation, The Finnish Cultural Foundation, The Finnish Medical Foundation, The Paolo Foundation, Turku University Foundation and Turku University Hospital Research Foundation.

There are plenty of people to whom I wish to express my gratitude. First, I want to thank my supervisors, Docent Tuire Lähdesmäki and Professor Ville Peltola, for their guidance and support throughout the whole process. Tuire, I admire your ability to turn every obstacle into an opportunity. You inspired me to enter the field of paediatric neurology, and acted as a tutor and a role model for me. Ville, I respect your knowledge in research and expertise in scientific writing. I have learned a lot from you.

I want to thank the reviewers of this thesis, Docent Päivi Vieira and Docent Tuula Pelkonen, for their valuable comments on my thesis, and the members of my follow-up committee, Professor Leena Haataja and Doctor Lauri Ivaska, for their interest in my study over all these years. I warmly thank my co-authors, Mirka Nurmi, Olli Ruuskanen, Satu Alaluusua, Jukka Hytönen, Sirkku Setänen, Nea Isaksson, Anna Nyman, Mikko Nyman, and Eliisa Löyttyniemi for collaboration. A special thanks for Mirka, Nea and Sirkku for all their work with clinical examinations. Also, I want to thank my great colleague, Annika Tihveräinen, for her valuable help with language revision. Importantly, I want to thank all the children and their families who participated in our study visits. Without them, these studies would not exist.

I am grateful to both the former and current head of the Department of Paediatric and Adolescent Medicine, Professor Jussi Mertsola and Docent Heikki Lukkarinen for creating a science-friendly working atmosphere. Also, I am grateful to both former and current head of Tutkari, Professor Olli Ruuskanen and Doctor Minna Lukkarinen, for the opportunity to do my scientific work in Tutkari. I want to thank

my science friends for lunch and coffee breaks and refreshing talks. Specifically, I want to thank Minna S., Minna V., and Vilhelmiina for their friendship and support during all these years, as well as Antti, Kjell and Olli for their unselfish help in all those times when I got stuck with computer problems.

I want to thank all my workmates at Turku University Hospital. I thank the talented teams of paediatric neurology and paediatric ward UB5/MJ2. I owe my most hearty thanks to my dear paediatric neurologist colleagues Anna K., Anna P., Erika S., Harri A., Milla and Nina, for their friendship and support during these years. I also thank Tiina Mariella and Janna-Maija for our excellent teamwork; Tiina, I admire the warmth and empathy you show for all your patients and people around you; and Janna-Maija, I really respect your skills as a clinician and as a leader. I also want to thank Anu for her tutorship during my residence studies of paediatrics, and Anis for her continuous support and guidance. I express my gratitude to all my talented colleagues at Seinäjoki Central Hospital where I started my career. A special thanks to Tarja for her tutorship, to Kirsi, Mervi and Riitta for their wise life instructions, and Anne for her long lasting friendship.

I want to thank my "old" friends Heli, Pia, Anniina, Julia, Anna O., Anna Aho, Ulpu and Anna Aromaa for staying in my life and supporting me for all these years. I thank my dearest friend Laura for keeping me from going insane, and for all talks, walks and journeys we did together. I am thankful for my closest cousin Johanna; you have always been like a big sister for me, believed in me and supported me throughout my life.

Finally, I want to thank my family. My parents Armi and Kalle, you have always believed in me, prayed for me and been ready to help immediately when needed. You are just perfect grandparents for my children. I thank my sister Katri, her husband Markus, and their adorable children Olivia and Daniel, as well as my little brother Miikka and his delightful wife Iina-Sofia just for being in my life. My parents-in-law, Päivi and Reino, I appreciate your endless support, and help with children. I thank my brother-in-law Markus, his wife Marianne and sons Miko and Sulo, for all the unforgettable moments you spent with us.

Most importantly, I want to thank "my boys" Mikko, Eelis and Eino. Mikko, there are no words to express my gratitude for our last 20 years together. You have always stayed by me, and even moved with me to Seinäjoki to care for our children when I started my residence studies. Thank you for loving me as I am. I thank my sons Eelis and Eino, just for being you. You always remind me what really matters in life.

February, 2022
Heidi Pöyhönen

References

Absoud, M., Parslow, R., Wassmer, E., Hemingway, C., Duncan, H., Cummins, C., & Lim, M. (2011). Severe acute disseminated encephalomyelitis: a paediatric intensive care population-based study. *Multiple Sclerosis Journal*, *17*(10), 1258–1261.

Agwuh, K. N., & MacGowan, A. (2006). Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. *The Journal of Antimicrobial Chemotherapy*, *58*(2), 256–265.

Albisetti, M., Schaer, G., Good, M., Boltshauser, E., & Nadal, D. (1997). Diagnostic value of cerebrospinal fluid examination in children with peripheral facial palsy and suspected Lyme borreliosis. *Neurology*, *49*(3), 817–824.

Amin, R., Ford-Jones, E., Richardson, S. E., MacGregor, D., Tellier, R., Heurter, H., Fearon M., & Bitnun, A. (2008). Acute Childhood Encephalitis and Encephalopathy Associated With Influenza. *Pediatric Infectious Disease Journal*, *27*(5), 390–395.

Arican, P., Dundar, N. O., Gencpinar, P., & Cavusoglu, D. (2017). Efficacy of Low-Dose Corticosteroid Therapy Versus High-Dose Corticosteroid Therapy in Bell's Palsy in Children. *Journal of Child Neurology*, *32*(1), 72–75.

Armangue, T., Titulaer, M. J., Málaga, I., Bataller, L., Gabilondo, I., Graus, F., & Dalmau, J. (2013). Pediatric Anti-N-methyl-D-Aspartate Receptor Encephalitis – Clinical Analysis and Novel Findings in a Series of 20 Patients. *The Journal of Pediatrics*, *162*(4), 850–856.

Arnason, S., Hultcrantz, M., Nilsson, A., & Laestadius, Å. (2020). Peripheral facial nerve palsy in children in a Borrelia high-endemic area, a retrospective follow-up study. *Acta Paediatrica*, *109*(6), 1229–1235.

Arnaud, C., Daubisse-Marliac, L., White-Koning, M., Pierrat, V., Larroque, B., Grandjean, H., Alberge, C., Marret, S., Burguet, A., Ancel, P-Y., Supernant, K., & Kaminski, M. (2007). Prevalence and Associated Factors of Minor Neuromotor Dysfunctions at Age 5 Years in Prematurely Born Children. *Archives of Pediatrics & Adolescent Medicine*, *161*(11), 1053–1061.

Artunduaga, M., Liu, C. A., Morin, C. E., Serai, S. D., & Udayasankar, U. (2021). Minisymposium: Pediatric MRI Quality and Safety. Safety challenges related to the use of sedation and general anesthesia in pediatric patients undergoing magnetic resonance imaging examinations. *Pediatric Radiology*, *51*(5), 724–735.

Aupee, O., Almeras, D., Le Garlantezec, P., & Bohand, X. (2009). Doxycycline . *La Doxycycline*, *69*(6), 556–558.

Ayaslioglu, E., Erkek, E., Oba, A. A., & Cebecioğlu, E. (2005). Doxycycline-induced staining of permanent adult dentition. *Australian Dental Journal*, *50*(4), 273–275.

Aydoğdu, İ., Ataç, E., Saltürk, Z., Atar, Y., Özdemir, E., Uyar, Y., Arslanoglu, A., & Berkiten, G. (2015). Pediatric Ramsay Hunt Syndrome: Analysis of Three Cases. *Case Reports in Otolaryngology*, *971249* (Epub).

Aygun, A. D., Kabakuş, N., Çelik, İ., Turgut, M., Yoldaş, T., Gök, Ü., & Güler, R. (2001). Long-term Neurological Outcome of Acute Encephalitis. *Journal of Tropical Pediatrics*, *47*(4), 243–247.

Backman, K., & Skogman, B. H. (2018). Occurrence of erythema migrans in children with Lyme neuroborreliosis and the association with clinical characteristics and outcome – a prospective cohort study. *BMC Pediatrics*, *18*(1), 189.

Bagger-Sjöbäck, D., Remahl, S., & Ericsson, M. (2005). Long-Term Outcome of Facial Palsy in Neuroborreliosis. *Otology & Neurotology*, *26*(4), 790–795.

Barstad, B., Tveitnes, D., Dalen, I., Noraas, S., Ask, I. S., Bosse, F. J., & Øymar, K. (2019). The B-lymphocyte chemokine CXCL13 in the cerebrospinal fluid of children with Lyme neuroborreliosis: associations with clinical and laboratory variables. *Infectious Diseases*, *51*(11–12), 856–863.

Baumann, M., Hennes, E.-M., Schanda, K., Karenfort, M., Kornek, B., Seidl, R., Diepoldt, K., Lauffer, H., Marquardt, I., Strautmanis, I., Syrbe, S., Vieker, S., Höftberger, R., Reindl, M., & Rostásy, K. (2016). Children with multiphasic disseminated encephalomyelitis and antibodies to the myelin oligodendrocyte glycoprotein (MOG): Extending the spectrum of MOG antibody positive diseases. *Multiple Sclerosis Journal*, *22*(14), 1821–1829.

Beattie, G. C., Glaser, C. A., Sheriff, H., Messenger, S., Preas, C. P., Shahkarami, M., & Venkatesan, A. (2013). Encephalitis with thalamic and basal ganglia abnormalities: Etiologies, neuroimaging, and potential role of respiratory viruses. *Clinical Infectious Diseases*, *56*(6), 825–832.

Benaim, J., Amar, O., Alliez, A., & Bertrand, B. (2015). The interest of electroneuromyography in peripheral facial palsy. *Annales de Chirurgie Plastique Esthétique, 60*(5), 374–376.

Beers, S. R., Wisniewski, S. R., Garcia-Filion, P., Tian, Y., Hahner, T., Berger, R. P., Bell, M., & Adelson, P. D. (2012). Validity of a pediatric version of the glasgow outcome scale-extended. *Journal of Neurotrauma*, *29*(6), 1126–1139.

Belman, A. L., Reynolds, L., Preston, T., Postels, D., Grimson, R., & Coyle, P. K. (1997). Cerebrospinal Fluid Findings in Children With Lyme Disease-Associated Facial Nerve Palsy. *Archives of Pediatrics & Adolescent Medicine*, *151*(12), 1224–1228.

Benavides, S., & Nahata, M. C. (2002). Anthrax: safe treatment for children. *The Annals of Pharmacotherapy*, *36*(2), 334–337.

Berglund, J., Eitrem, R., Ornstein, K., Lindberg, A., Ringnér, Å., Elmrud, H., Carlsson, M., Runehagen, A., Svanborg, C., & Norrby, R. (1995). An Epidemiologic Study of Lyme Disease in Southern Sweden. *New England Journal of Medicine*, *333*(20), 1319–1327.

Biebl, A., Lechner, E., Hroncek, K., Preisinger, A., Eisenkölbl, A., Schmitt, K., & Furthner, D. (2013). Facial nerve paralysis in children: Is it as benign as supposed? *Pediatric Neurology*, *49*(3), 178–181.

Bingham, P. M., Galetta, S. L., Athreya, B., & Sladky, J. (1995). Neurologic manifestations in children with Lyme disease. *Pediatrics*, *96*(6), 1053–1056.

Blum, R. A., Tomlinson, A. R., Jetté, N., Kwon, C.-S., Easton, A., & Yeshokumar, A. K. (2020). Assessment of long-term psychosocial outcomes in anti-NMDA receptor encephalitis. *Epilepsy & Behavior*, *108*(107088).

Boast, A., Curtis, N., & Gwee, A. (2016). Question 1: Teething issues: can doxycycline be safely used in young children? *Archives of Disease in Childhood*, *101*(8), 772–774.

Boulloche, J., Slim, S., Le Luyer, B., Mallet, E., Tron, P., Le Roux, P., Lienhardt, P., & Coudray, C. (1993). Isolated acute peripheral facial paralysis in children. Etiological and prognostic study. *Archives Francaises de Pediatrie*, *50*(5), 387–389.

Bozzola, E., Bozzola, M., Tozzi, A. E., Calcaterra, V., Longo, D., Krzystofiak, A., & Villani, A. (2014). Acute cerebellitis in varicella: a ten year case series and systematic review of the literature. *Italian Joural of Pediatrics*, *40*(57), 1–5.

Bremell, D., & Hagberg, L. (2011). Clinical characteristics and cerebrospinal fluid parameters in patients with peripheral facial palsy caused by Lyme neuroborreliosis compared with facial palsy of unknown origin (Bell's palsy). *BMC Infectious Diseases*, *1*(11), 215.

Britton, P. N., Eastwood, K., Paterson, B., Durrheim, D. N., Dale, R. C., Cheng, A. C., Kenedi, C., Brew, B. J., Burrow, J., Nagree, Y., Leman, P., Smith, D. W., Read, K., Booy, R., & Jones, C. A. (2015). Consensus guidelines for the investigation and management of encephalitis in adults and children in Australia and New Zealand. *Internal Medicine Journal*, *45*(5), 563–576.

Britton, P. N., Blyth, C. C., Macartney, K., Dale, R. C., Li-Kim-Moy, J., Khandaker, G., Crawford, N. W., Marshall, H., Clark, J. E., Elliot, E. J., Booy, R., Cheng, A. C., & Jones, C. A. (2017). The Spectrum and Burden of Influenza-Associated Neurological Disease in Children: Combined Encephalitis and Influenza Sentinel Site Surveillance From Australia, 2013–2015. *Clinical Infectious Diseases*, *65*(4), 653–660.

Britton, P. N, Dale, R. C., Blyth, C. C., Clark, J. E., Crawford, N., Marshall, H., Elliot, E. J., Macartney, K., Booy, R., & Jones, C. A. (2020). Causes and Clinical Features of Childhood Encephalitis: A Multicenter, Prospective Cohort Study. *Clinical Infectious Diseases*, *70*(12), 2517–2526.

Broström, L., Vollmer, B., Bolk, J., Eklöf, E., & Ådén, U. (2018). Minor neurological dysfunction and associations with motor function, general cognitive abilities, and behaviour in children born extremely preterm. *Developmental Medicine & Child Neurology*, *60*(8), 826–832.

Burres, S., & Fisch, U. (1986). The Comparison of Facial Grading Systems. *Archives of Otolaryngology – Head and Neck Surgery*, *112*(7), 755–758.

Bykowski, J., Kruk, P., Gold, J. J., Glaser, C. A., Sheriff, H., & Crawford, J. R. (2015). Acute Pediatric Encephalitis Neuroimaging: Single-Institution Series as Part of the California Encephalitis Project. *Pediatric Neurology*, *52*(6), 606–614.

Cale, D. F., & McCarthy, M. W. (1997). Treatment of Rocky Mountain spotted fever in children. *The Annals of Pharmacotherapy*, *31*(4), 492–494.

Cameron, P. D., Wallace, S. J., & Munro, J. (1992). Herpes simplex virus encephalitis: problems in diagnosis. *Developmental Medicine & Child Neurology*, *34*(2), 134–140.

Cellucci, T., Van Mater, H., Graus, F., Muscal, E., Gallentine, W., Klein-Gitelman, M. S., Benseler, S. M., Frankovich, J., Gorman, M. P., Van Haren, K., Dalmau, J., & Dale, R. C. (2020). Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. *Neurology – Neuroimmunology Neuroinflammation*, *7*(2), e663.

Cha, C. Il, Hong, C. K., Park, M. S., & Yeo, S. G. (2008). Comparison of facial nerve paralysis in adults and children. *Yonsei Medical Journal*, *49*(5), 725–735.

Chang, L., Huang, L., Gau, S., Wu, Y., Hsia, S., Fan, T., Lin, K., Huang, Y., Lu, C., & Lin, T. (2007). Neurodevelopment and Cognition in Children After Enterovirus 71 Infection. *The New England Journal of Medicine*, *356*(12), 1226–1234.

Chen, T., & Liu, G. (2018). Long-term outcome of acute central nervous system infection in children. *Pediatric Investigation*, *2*(3), 155–163.

Chen, W.-X., & Wong, V. (2005). Prognosis of Bell's palsy in children – analysis of 29 cases. *Brain and Development*, *27*(7), 504–508.

Christen, H. J., Bartlau, N., Hanefeld, F., Eiffert, H., & Thomssen, R. (1990). Peripheral facial palsy in childhood – Lyme borreliosis to be suspected unless proven otherwise. *Acta Paediatrica Scandinavica*, *79*(12), 1219–1224.

Christen, Hans-Jurgen. (1996). Lyme Neuroborreliosis in Children. *Annals of Medicine*, *28*(3), 235–240.

Christie, L. J., Honarmand, S., Talkington, D. F., Gavali, S. S., Preas, C., Pan, C., Yagi, S., & Glaser, C. A. (2007). Pediatric encephalitis: what is the role of Mycoplasma pneumoniae? *Pediatrics*, *120*(2), 305–313.

Clarke, M., Newton, R. W., Klapper, P. E., Sutcliffe, H., Laing, I., & Wallace, G. (2006). Childhood encephalopathy: Viruses, immune response, and outcome. *Developmental Medicine and Child Neurology*, *48*(4), 294–399.

Committee on Infectious Diseases; American Academy of Pediatrics. (2015). *Red Book, 30th Edition (2015): 2015 Report of the Committee on Infectious Diseases*. (D. W. Kimberlin, M. T. Brady, J. M. A, & S. S. Long, Eds.), *Redbook* (30th ed.). American Academy of Pediatrics.

Committee on Infectious Diseases; American Academy of Pediatrics. (2018). *Red Book, 31st Edition (2018): 2018 Report of the Committee on Infectious Diseases*. (Kimberlin D, Brady M, A J, & Long S, Eds.) (31st Edition). American Academy of Pediatrics.

Committee on Infectious Diseases; American Academy of Pediatrics. (2021). *Red Book, 32nd Edition (2021): 2021 Report of the Committee on Infectious Diseases*.

Conchie, J. M., Munroe, J. D., & Anderson, D. O. (1970). The incidence of staining of permanent teeth by the tetracyclines. *Canadian Medical Association Journal*, *103*(4), 351–356.

Crawford, J. R., Anderson, V., Rankin, P. M., & MacDonald, J. (2010). An index-based short-form of the WISC-IV with accompanying analysis of the reliability and abnormality of differences. *British Journal of Clinical Psychology*, *49*, 235–258.

Cross, R., Ling, C., Day, N. P. J., McGready, R., & Paris, D. H. (2016). Revisiting doxycycline in pregnancy and early childhood - time to rebuild its reputation? *Expert Opinion on Drug Safety*, 1–16.

Cunha, B A, Sibley, C. M., & Ristuccia, A. M. (1982). Doxycycline. *Therapeutic Drug Monitoring*, *4*(2), 115–135.

Cunha, Burke A. (2003). Doxycycline for Community Acquired Pneumonia. *Clinical Infectious Diseases*, *37*(6), 870.

Dalmau, J., & Graus, F. (2018). Antibody-Mediated Encephalitis. *New England Journal of Medicine*, *378*(9), 840–851.

Daxboeck, F., Blacky, A., Seidl, R., Krause, R., & Assadian, O. (2004). Diagnosis, treatment, and prognosis of Mycoplasma pneumoniae childhood encephalitis: systematic review of 58 cases. *Journal of Child Neurology*, *19*(11), 865–871.

De Jong, M., Punt, M., De Groot, E., Minderaa, R. B., & Hadders-Algra, M. (2011). Minor neurological dysfunction in children with autism spectrum disorder. *Developmental Medicine & Child Neurology*, *53*(7), 641–646.

De Tiège, X., Rozenberg, F., & Héron, B. (2008). The spectrum of herpes simplex encephalitis in children. *European Journal of Paediatric Neurology*, *12*(2), 72–81.

Demers, P., & Fraser, D. (1968). Effects of Tetracyclines on Skeletal Growth and Dentition : A Report by the Nutrition Committee of the Canadian Paediatric Society. *Canadian Medical Association Journal*, *99*(17), 849–854.

Devriese, P. P., Schumacher, T., Scheide, A., Jongh, R. H., & Houtkooper, J. M. (1990). Incidence, prognosis and recovery of Bell's palsy A survey of about 1000 patients (1974-1983). *Clinical Otolaryngology*, *15*(1), 15–27.

Dhiravibulya, K. (2002). Outcome of Bell's palsy in children. *Journal of the Medical Association of Thailand = Chotmaihet Thangphaet*, *85*(3), 334–339.

Ding, D., & Zhen Hong, S.-J. Z. (2007). Long-term disability from acute childhood Japanese encephalitis in Shanghai, China. *American Journal of Tropical Medicine and Hygiene*, *77*(3), 528–533.

Dotevall, L., & Hagberg, L. (1989). Penetration of doxycycline into cerebrospinal fluid in patients treated for suspected Lyme neuroborreliosis. *Antimicrobial Agents and Chemotherapy*, *33*(7), 1078–1080.

Dotevall, L., & Hagberg, L. (1999). Successful oral doxycycline treatment of Lyme disease-associated facial palsy and meningitis. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *28*(3), 569–574.

Drack, F. D., & Weissert, M. (2013). Outcome of peripheral facial palsy in children – A catamnestic study. *European Journal of Paediatric Neurology*, *17*(2), 185–191.

DuBray, K., Anglemyer, A., LaBeaud, a D., Flori, H., Bloch, K., Joaquin, K. S., Preas, C., Sheriff, H. & Glaser, C. (2013). Epidemiology, outcomes and predictors of recovery in childhood encephalitis: a hospital-based study. *The Pediatric Infectious Disease Journal*, *32*(8), 839–844.

Dutta, A., Hunter, J., & Vallejo, J. (2021). Bannwarth syndrome: a rare manifestation of pediatric Lyme neuroborreliosis. *The Pediatric Infectious Disease Journal*, *40*(1), e442–e444.

Ebaugh, F. G. (2007). Neuropsychiatric Sequelae of Acute Epidemic Encephalitis in Children. *Journal of Attention Disorders*, *11*(3), 336–338.

Ebinger, F., Kosel, C., Pietz, J., & Rating, D. (2004). Headache and backache after lumbar puncture in children and adolescents: a prospective study. *Pediatrics*, *113*(6), 1588–1592.

Eckman, M. H., Steere, a C., Kalish, R. a, & Pauker, S. G. (1997). Cost effectiveness of oral as compared with intravenous antibiotic therapy for patients with early Lyme disease or Lyme arthritis. *The New England Journal of Medicine*, *337*(5), 357–363.

Elbers, J. M., Bitnun, A., Richardson, S. E., Ford-Jones, E. L., Tellier, R., Wald, R. M., Petric, M., Kolski, H., Heurter, H., & MacGregor, D. (2007). A 12-year prospective study of childhood herpes simplex encephalitis: Is there a broader spectrum of disease? *Pediatrics*, *119*(2), e399–e497.

Elenga, N., Roux, A., Cuadro-Alvarez, E., Martin, E., Kallel, H., & Defo, A. (2020). Etiology and prognosis of encephalitis in French Guianese children: a retrospective record-based study. *Journal of Infection and Public Health*, *13*(7), 1051–1053.

Ellefsen, B., & Bonding, P. (1996). Facial palsy in acute otitis media. *Clinical Otolaryngology and Allied Sciences*, *21*(5), 393–395.

Ellul, M., & Solomon, T. (2018). Acute encephalitis - diagnosis and management. *Journal of Clinical Medicine*, *18*(2), 155–159.

Engervall, K., Carlsson-Nordlander, B., Hederstedt, B., Berggren, D., Bjerkhoel, A., Carlborg, A., Grenner, J., Hanner, P., Högmo, A., & Ödkvist, L. (1995). Borreliosis as a Cause of Peripheral Facial Palsy: A Multi-Center Study. *Journal of Oto-Hino-Laryngology and Its Related Specialities*, *57*(4), 202–206.

Engman, M.-L., Lindström, K., Sallamba, M., Hertz, C., Sundberg, B., Hansson, M. E. A., Lindquist, L., Orvell, C., Lidefelt, C. J., & Sundin, M. (2012). One-year Follow-up of Tick-borne Central Nervous System Infections in Childhood. *Pediatric Infectious Disease Journal*, *31*(6), 570–574.

Esposito, S., Di Pietro, G. M., Madini, B., Mastrolia, M. V., & Rigante, D. (2015). A spectrum of inflammation and demyelination in acute disseminated encephalomyelitis (ADEM) of children. *Autoimmunity Reviews*, *14*(10), 923–929.

Evans, A. K., Licameli, G., Brietzke, S., Whittemore, K., & Kenna, M. (2005). Pediatric facial nerve paralysis: Patients, management and outcomes. *International Journal of Pediatric Otorhinolaryngology*, *69*(11), 1521–1528.

Evans, R. W. (1998). Complications of lumbar puncture. *Neurologic Clinics*, *16*(1), 83–105.

Ferrari, F., Gallo, C., Pugliese, M., Guidotti, I., Gavioli, S., Coccolini, E., Zagni, P., Casa, E. D., Rossi, C., Lugli, L., Todeschini, A., Luca, O., & Bertoncelli, N. (2012). Preterm birth and developmental problems in the preschool age. Part I: minor motor problems. *The Journal of Maternal-Fetal & Neonatal Medicine*, *25*(11), 2154–2159.

Fiser, D. H., Long, N., Roberson, P. K., Hefley, G., Zolten, K., & Brodie-Fowler, M. (2000). Relationship of Pediatric Overall Performance Category and Pediatric Cerebral Performance Category scores at pediatric intensive care unit discharge with outcome measures collected at hospital discharge and 1- and 6-month follow-up assessments. *Critical Care Medicine*, *28*(7), 2616–2620.

Fiser, D. H. (1992). Assessing the outcome of pediatric intensive care. *The Journal of Pediatrics*, *121*(1), 68–74.

Forti, G., & Benincori, C. (1969). Doxycycline and the teeth. *Lancet*, *1*(7598), 782.

Fowler, A., Stodberg, T., Eriksson, M., & Wickstrom, R. (2010). Long-term outcomes of acute encephalitis in childhood. *Pediatrics*, *126*(4), e828–35.

Fowler, Å, Stödberg, T., Eriksson, M., & Wickström, R. (2008). Childhood encephalitis in Sweden: Etiology, clinical presentation and outcome. *European Journal of Paediatric Neurology*, *12*(6), 484–490.

Fowler, Åsa, Forsman, L., Eriksson, M., & Wickström, R. (2013). Tick-borne encephalitis carries a high risk of incomplete recovery in children. *Journal of Pediatrics*, *163*(2), 555–560.

Fowler, Åsa, Ygberg, S., Svensson, E., Bergman, K., Cooray, G., & Wickström, R. (2020). Prospective Evaluation of Childhood Encephalitis. *Pediatric Infectious Disease Journal*.

Gable, M. S., Sheriff, H., Dalmau, J., Tilley, D. H., & Glaser, C. A. (2012). The Frequency of Autoimmune N-Methyl-D-Aspartate Receptor Encephalitis Surpasses That of Individual Viral Etiologies in Young Individuals Enrolled in the California Encephalitis Project. *Clinical Infectious Diseases*, *54*(7).

Galanakis, E., Tzoufi, M., Katragkou, A., Nakou, I., & Roilides, E. (2009). A prospective multicenter study of childhood encephalitis in Greece. *Pediatric Infectious Disease Journal*, *28*(8), 740–742.

Gantz, B. J., Rubinstein, J. T., Gidley, P., & Woodworth, G. G. (1999). Surgical Management of Bell's Palsy. *The Laryngoscope*, *109*(8), 1177–1178.

Garro, A., Koster, M., LaRue, M., Hipolito, E., Congdon, E., Burnett, K., Cullen, N., & Nigrovic, L. E. (2018). Would Parents Consent to a Comparative Effectiveness Trial of Oral Doxycycline Versus Intravenous Ceftriaxone for the Treatment of Children with Lyme Meningitis? *The Pediatric Infectious Disease Journal*, *37*(5), e140–e142.

Genizi, J., Golan-Shany, O., Tarazov, T., Pechter, S., Assaf, N., Segal, I., Srugo, I., & Bamberger, E. (2019). Does Herpes 6 Infection have a Role in Bell's Palsy Among Children and Adolescents? *The Pediatric Infectious Disease Journal*, *38*(5), 481–483.

Glaser, C. A., Gilliam, S., Schnurr, D., Forghani, B., Honarmand, S., Khetsuriani, N., & Anderson, L. J. California Encephalitis Project, 1998-2000. (2003). In Search of Encephalitis Etiologies: Diagnostic Challenges in the California Encephalitis Project, 1998–2000. *Clinical Infectious Diseases*, *36*(6), 731–742.

Granerod, J., Ambrose, H. E., Davies, N. W., Clewley, J. P., Walsh, A. L., Morgan, D., Cunningham, R., Zuckerman, M., Mutton, K. J., Solomon, T., Ward, C. N., Lunn, M. P., Irani, S., R., Vincent, A., Brown, D. W., & Crowcroft, N. S. UK Health Protection Agency. Aetiology of Encephalitis Study Group. (2010). Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *The Lancet Infectious Diseases*, *10*(12), 835–844.

Gronseth, G. S., & Paduga, R. (2012). Evidence-based guideline update: Steroids and antivirals for Bell palsy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*, *79*(22).

Grossman, E. R., Walchek, A., & Freedman, H. (1971). Tetracyclines and permanent teeth: the relation between dose and tooth color. *Pediatrics*, *47*(3), 567–570.

Grundfast, K. M., Guarisco, J. L., Thomsen, J. R., & Koch, B. (1990). Diverse etiologies of facial paralysis in children. *International Journal of Pediatric Otorhinolaryngology*, *19*(3), 223–239.

Guggenheimer J. (1984). Tetracyclines and the human dentition. *Compendium of Continuing Education in Dentistry*, *5*(3), 251–252.

Hacohen, Y., Wright, S., Waters, P., Agrawal, S., Carr, L., Cross, H., De Sousa, C., Devile, C., Fallon, P., Gupta, R., Hedderly, T., Hughes, E., Kerr, T., Lascelles, K., Lin J.-P., Philip, S., Pohl, K., Prabahkar, P., Smith, M., Williams, R., Clarke, A., Hemingway, C., Wassmer, E., Vincent, A., & Lim, M. J. (2013). Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens. *Journal of Neurology, Neurosurgery & Psychiatry*, *84*(7), 748–755.

Hacohen, Y., Yi Wong, Y., Lechner, C., Jurynczyk, M., Wright, S., Konuskan, B., Kalser, J., Poulat, A., Maurey E., Ganelin-Cohen, E., Wassmer, E., Hemingway, C., Forsyth, R., Hennes, E., Leite, M., Ciccarelli, O., Anlar, B., Hintzen, R., Marignier, R., Palace, J., Baumann, M., Rostásy, K., Neuteboom, R., Deiva, K., & Lim, M. (2018). Disease Course and Treatment Responses in Children With Relapsing Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease Supplemental content. *JAMA Neurol*, *75*(4), 478–487.

Hadders-Algra, M. (2002). Two distinct forms of minor neurological dysfunction: Perspectives emerging from a review of data of the Groningen Perinatal Project. *Developmental Medicine and Child Neurology*.

Hadders-Algra, M. (2010). *Neurological Examination of the Child with Minor Neurological Dysfunction*. (H. M. Hart, Ed.) (Third Edit). London.

Hall, A. (1925). Mental Sequelae of Epidemic Encephalitis in Children. *British Medical Journal*, *17*.

Hamp S E. (1967). The tetracyclines and their effect on teeth A clinical study. *Odontologisk Tidskrift*, *75*(1), 33–49.

Hansen, K., & Lebech, A.-M. (1992). The clinical and epidemiological profile of Lyme neuroborreliosis in Denmark 1985–1990. A prospective study of 187 patients with Borrelia burgdorferi specific intrathecal antibody production. *Brain*, *115*(2), 399–423.

Hatachi, T., Michihata, N., Inata, Y., Takeuchi, M., Matsui, H., Fushimi, K., & Yasunaga, H. (2021). Prognostic factors among children with acute encephalitis/encephalopathy associated with viral and other pathogens. *Clinical Infectious Diseases76*, *73*(1), 76–82.

Hausler, M., Schaade, L., Schaade, L., Kemeny, S., Scheizer, K., Schoenmackers, C., & Ramaekers, V. (2002). Encephalitis related to primary varicella-zoster virus infection in immunocompetent children. *Journal of The Neurological Sciences, 195*(2), 111–116.

Hébert, J., Gros, P., Lapointe, S., Amtashar, F. S., Steriade, C., Maurice, C., Wennberg, R., Day, G., & Tang-Wai, D. F. (2020). Searching for autoimmune encephalitis: Beware of normal CSF. *Journal of Neuroimmunology*, *345*.

Hennes, E., Zotter, S., Dorninger, L., Hartmann, H., Häusler, M., Huppke, P., Jacobs, J., Kraus, W., Makowski, C., Schlachter, K., Ulmer, H., van Baalen, A., Koch, J., Gotwald, T., & Rostasy, K. (2012). Long-term outcome of children with acute cerebellitis. *Neuropediatrics*, *43*(5), 240–248.

Henningsson, A. J., Lager, M., Bränström, R., Tjernberg, I., & Skogman, B. H. (2018). The chemokine CXCL13 in cerebrospinal fluid in children with Lyme neuroborreliosis. *European Journal of Clinical Microbiology & Infectious Diseases*, *37*(10), 1983–1991.

Hon, K. L. E., Tsang, Y. C. K., Chan, L. C. N., Tsang, H. W., Wong, K. Y. K., Wu, Y. H. G., Chan, P. K. S., Cheung, K. L., Ng, E. Y. K., & Totapally, B. R. (2016). Outcome of Encephalitis in Pediatric Intensive Care Unit. *Indian Journal of Pediatrics*, *83*(10), 1098–1103.

Hon, K. L., Leung, A. K. C., & Torres, A. R. (2018). Febrile Infection-Related Epilepsy Syndrome (FIRES): An Overview of Treatment and Recent Patents. *Recent Patents on Inflammation & Allergy Drug Discovery*, *12*(2), 128–135.

Hotton, M., Huggons, E., Hamlet, C., Shore, D., Johnson, D., Norris, J. H., Kilcoyne, S., & Dalton, L. (2020). The psychosocial impact of facial palsy: A systematic review. *British Journal of Health Psychology*, *25*(3), 695–727.

House, J. W., & Brackmann, D. E. (1985). Facial Nerve Grading System. *Otolaryngology-Head and Neck Surgery*, *93*(2), 146–147.

Howard, S. C., Gajjar, A., Ribeiro, R. C., Rivera, G. K., Rubnitz, J. E., Sandlund, J. T., Harrison, P. L., de Armendi, A., Dahl, G. V., & Pui, C.-H. (2000). Safety of Lumbar Puncture for Children With Acute Lymphoblastic Leukemia and Thrombocytopenia. *JAMA*, *284*(17), 2222–2224.

Howarth, R. A., Vova, J., & Blackwell, L. S. (2019). Early Functional Outcomes for Pediatric Patients Diagnosed with Anti-N-Methyl-D-Aspartate Receptor Encephalitis during Inpatient Rehabilitation. *American Journal of Physical Medicine & Rehabilitation*, *98*(7), 529–535.

Huang, C.-C., Liu, C.-C., Chang, Y.-C., Chen, C.-Y., Wang, S.-T., & Yeh, T.-F. (1999). Neurologic Complications in Children with Enterovirus 71 Infection. *New England Journal of Medicine*, *341*(13), 936–942.

Huang, M.-C., Wang, S.-M., Hsu, Y.-W., Lin, H.-C., Chi, C.-Y., & Liu, C.-C. (2006). Long-term Cognitive and Motor Deficits After Enterovirus 71 Brainstem Encephalitis in Children. *Pediatrics*, *118*(6), 1785–1788.

Huisman, T. A. G. M., Wohlrab, G., Nadal, D., Boltshauser, E., & Martin, E. (1999). Unusual Presentations of Neuroborreliosis (Lyme Disease) in Childhood. *Journal of Computer Assisted Tomography*, *23*(1), 39–42.

Hytönen, J., Kortela, E., Waris, M., Puustinen, J., Salo, J., & Oksi, J. (2014). CXCL13 and neopterin concentrations in cerebrospinal fluid of patients with Lyme neuroborreliosis and other diseases that cause neuroinflammation. *Journal of Neuroinflammation*, *11*(103), 103.

Iff, T., Donati, F., Vassella, F., Schaad, U. B., & Bianchetti, M. G. (1998). Acute encephalitis in Swiss children: Aetiology and outcome. *European Journal of Paediatric Neurology*, *2*(5), 233–237.

Ilias, A., Galanakis, E., Raissaki, M., & Kalmanti, M. (2006). Childhood encephalitis in Crete, Greece. *Journal of Child Neurology*, *21*(10), 910–912.

Inamura, H., Aoyagi, M., Tojima, H., Kohsyu, H., & Koike, Y. (1994). Facial Nerve Palsy in Children: Clinical Aspects of Diagnosis and Treatment. *Acta Oto-Laryngologica*, *114*(sup511), 150–152.

Iro, M. A., Martin, N. G., Absoud, M., & Pollard, A. J. (2017). Intravenous immunoglobulin for the treatment of childhood encephalitis. *Cochrane Database of Systematic Reviews*, *10*(10).

Ivacic, L., Reed, K. D., Mitchell, P. D., & Ghebranious, N. (2007). A LightCycler TaqMan assay for detection of Borrelia burgdorferi sensu lato in clinical samples. *Diagnostic Microbiology and Infectious Disease*, *57*(2), 137–143.

Jadavji, T., Biggar, W., Gold, R., & Prober, C. (1986). Sequelae of acute bacterial meningitis in children older than one month: Clinical features and diagnosis. *Pediatrics, 78*(1), 21.

Jenke, A. C., Stoek, L. M., Zilbauer, M., Wirth, S., & Borusiak, P. (2011). Facial palsy: Etiology, outcome and management in children. *European Journal of Paediatric Neurology*, *15*(3), 209–213.

Jennett, B., Snoek, J., Bond, M. R., & Brooks, N. (1981). Disability after severe head injury: observations on the use of the Glasgow Outcome Scale. *Journal of Neurology, Neurosurgery & Psychiatry*, *44*(4), 285–293.

Jennett, B., & Bond, M. (1975). Assessment of outcome after severe brain damage. *The Lancet*, *1*(7905), 480–484.

Johnson, R. (1998). Acute encephalitis. *Infectious Diseases, 23*(2), 219–224.

Kaga, K., Kaga, M., Tamai, F., & Shindo, M. (2003). Auditory agnosia in children after herpes encephalitis. *Acta Otolaryngologica, 123*(2), 232–235.

Kahlmann, V., Roodbol, J., van Leeuwen, N., Ramakers, C. R. B., van Pelt, D., Neuteboom, R. F., Catsman-Berrevoets., C. E., de Wit, M. C. Y., & Jacobs, B. C. (2017). Validated age-specific reference values for CSF total protein levels in children. *European Journal of Paediatric Neurology*, *21*(4), 654–660.

Kahn, J. B., Gliklich, R. E., Boyev, K. P., Stewart, M. G., Metson, R. B., & McKenna, M. J. (2001). Validation of a Patient-Graded Instrument for Facial Nerve Paralysis: The FaCE Scale. *The Laryngoscope*, *111*(3), 387–398.

Kalita, J., Mani, V. E., Bhoi, S. K., & Misra, U. K. (2017). Spectrum and outcome of acute infectious encephalitis/encephalopathy in an intensive care unit from India. *QJM*, *110*(3), 141–148.

Kamei, S. (2005). Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. *Journal of Neurology, Neurosurgery & Psychiatry*, *76*(11), 1544–1549.

Kanerva, M., Liikanen, H., & Pitkäranta, A. (2021). Facial palsy in children: long-term outcome assessed face-to-face and follow-up revealing high recurrence rate. *European Archives of Oto-Rhino-Laryngology*, *278*(6), 2081–2091.

Kanerva, M., Nissinen, J., Moilanen, K., Mäki, M., Lahdenne, P., & Pitkäranta, A. (2013). Microbiologic Findings in Acute Facial Palsy in Children. *Otology & Neurotology*, *34*(7), e82–e87.

Karalok, Z. S., Taskin, B. D., Ozturk, Z., Gurkas, E., Koc, T. B., & Guven, A. (2018). Childhood peripheral facial palsy. *Child's Nervous System* , *34*(5), 911–917.

Karatoprak, E., & Yilmaz, S. (2019). Prognostic Factors Associated With Recovery in Children With Bell's Palsy. *Journal of Child Neurology*, *34*(14), 891–896.

Karlsson, M., Hammers-Berggren, S., Lindquist, L., Stiernstedt, G., & Svenungsson, B. (1994). Comparison of intravenous penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis. *Neurology*, *44*(7), 1203–1207.

Karlsson, M., Hammers, S., Nilsson-Ehle, I., Malmborg, A. S., & Wretlind, B. (1996). Concentrations of doxycycline and penicillin G in sera and cerebrospinal fluid of patients treated for neuroborreliosis. *Antimicrobial Agents and Chemotherapy*, *40*(5), 1104–1107.

Karlsson, S., Arnason, S., Hadziosmanovic, N., Laestadius, Å., Hultcrantz, M., Marsk, E., & Skogman, B. H. (2021). The facial nerve palsy and cortisone evaluation (FACE) study in children: protocol for a randomized, placebo-controlled, multicenter trial, in a Borrelia burgdorferi endemic area. *BMC Pediatrics*, *21*(1), 220.

Kennedy, C. R., Duffy, S. W., & Smith, R. (1987). Clinical predictors of outcome in encephalitis. *Archives of Disease in Childhood*, *62*(11), 1156–1162.

Ketelslegers, I., Visser, I., Neuteboom, R., Boon, M., Catsman-Berrevoets, C., & Hintzen, R. (2011). Disease course and outcome of acute disseminated encephalomyelitis is more severe in adults than in children. *Multiple Sclerosis Journal*, *17*(4), 441–448.

Khandaker, G., Jung, J., Britton, P. N., King, C., Yin, J. K., & Jones, C. A. (2016). Long-term outcomes of infective encephalitis in children: a systematic review and meta-analysis. *Developmental Medicine & Child Neurology*, *58*(11), 1108–1115.

Kikkert, H. K., De Jong, C., & Hadders-Algra, M. (2011). Minor neurological dysfunction and IQ in 9-year-old children born at term. *Developmental Medicine and Child Neurology*, *53*(4), e16-25.

Kimura H, Aso H, & Kuzushima K. (1992). Relapse of herpes encephalitis in children. *Pediatrics*, *89*(5 Pt 1), 891–894.

Klein, S. K., Hom, D. L., Anderson, M. R., Latrizza, A. T., & Toltzis, P. (1994). Predictive factors of short-term neurologic outcome in children with encephalitis. *Pediatric Neurology*, *11*(4), 308–312.

Kneen, R., Michael, B. D., Menson, E., Mehta, B., Easton, A., Hemingway, C., Klapper, P. E., Vincent, A., Lim, M., Carrol, E., & Solomon, T. National Encephalitis Guidelines Development and Stekeholder Groups. (2012). Management of suspected viral encephalitis in children – Association of British Neurologists and British Paediatric Allergy, Immunology and Infection Group National Guidelines. *Journal of Infection*, *64*(5), 449–477.

Knudtzen, F. C., Andersen, N. S., Jensen, T. G., & Skarphédinsson, S. (2017). Characteristics and Clinical Outcome of Lyme Neuroborreliosis in a High Endemic Area, 1995-2014: A Retrospective Cohort Study in Denmark. *Clinical Infectious Diseases*, *65*(9), 1489–1495.

Knudtzen, F. C., Nilsson, A. C., Hovius, J. W., & Skarphedinsson, S. (2020). The predictive value of CXCL13 in suspected Lyme neuroborreliosis: a retrospective cross-sectional study. *European Journal of Clinical Microbiology & Infectious Diseases*, *39*(8), 1461–1470.

Koelfen, W., Freund, M., Gückel, F., Rohr, H., & Schultze, C. (1996). MRI of encephalitis in children: Comparison of CT and MRI in the acute stage with long-term follow-up. *Neuroradiology*, *38*(1), 73–79.

Kolski, H., Ford-Jones, E. L., Richardson, S., Petric, M., Nelson, S., Jamieson, F., Blaser, S., Gold, R., Otsubo, H., Heurter, H., & MacGregor, D. (1998). Etiology of acute childhood encephalitis at the hospital for sick children, Toronto, 1994-1995. *Clinical Infectious Diseases*, *26*(2), 398–409.

Kornreich, L., Shkalim-Zemer, V., Levinsky, Y., Abdallah, W., Ganelin-Cohen, E., & Straussberg, R. (2016). Acute Cerebellitis in Children: A Many-Faceted Disease. *Journal of Child Neurology*, *31*(8), 991–997.

Koskiniemi, M, Rantalaiho, T., Piiparinen, H., von Bonsdorff, C. H., Färkkilä, M., Järvinen, A., Kinnunen, E., Koskiniemi, S., Mannonen, L., Muttilainen, M., Linnavuori, K., Porras, J., Puolakkainen, M., Räihä, M., Salonen, E. M., Ukkonen, P., Vaheri, A., & Valtonen, V. Study Group. (2001). Infections of the central nervous system of suspected viral origin: a collaborative study from Finland. *Journal of Neurovirology*, *7*(5), 400–408.

Koskiniemi, M., Korppi, M., Mustonen, K., Rantala, H., Muttilainen, M., Herrgård, E., Ukkonen P. & Vaheri A. (1997). Epidemiology of encephalitis in children. A prospective multicentre study. *European Journal of Pediatrics, 156*(7), 541–545.

Koskiniemi, M., Rautonen, J., Lehtokoski-Lehtiniemi, E., & Vaheri, A. (1991). Epidemiology of encephalitis in children: A 20-Year survey. *Annals of Neurology*, *29*(5), 492–497.

Kothur, K., Wienholt, L., Brilot, F., & Dale, R. C. (2016). CSF cytokines/chemokines as biomarkers in neuroinflammatory CNS disorders: A systematic review. *Cytokine*, *77*, 227–237.

Kramer, U., Chi, Y.-S., Lin, Z.-L., Specchio, X., Sahin, M., Olson, H., Nabbout, R., Gluger, K., Lin, J.-J., & van Baalen, A. (2011). Febrile infection-related epilepsy syndrome (FIRES): Pathogenesis, treatment, and outcome A multicenter study on 77 children. *Epilepsia*, *52*(11), 1956–1965.

Kraus, B. S. (1959). Calcification of the human deciduous teeth. *The Journal of the American Dental Association*, *59*(6), 1128–1136.

Krbkova, L., & Stanek, G. (1996). Therapy of Lyme borreliosis in children. *Infection*, *24*(2), 170–173.

Lahat, E., Barr, J., Barkai, G., Paret, G., Brand, N., & Barzilai, A. (1999). Long term neurological outcome of herpes encephalitis. *Archives of Disease in Childhood*, *80*(1), 69–71.

Lai, C.-W., & Gragasin, M. E. (1988). Electroencephalography in Herpes Simplex Encephalitis. *Journal of Clinical Neurophysiology*, *5*(1).

Lancella, L., Esposito, S., Galli, M. L., Bozzola, E., Labalestra, V., Boccuzzi, E., Krzystofiak, A., Cursi, L., Gattinara, G. C., Mirante, N., Buonsenso, D., Tagliabue, C., Castellazzi, L., Montagnani, C., Tersigni, C., Valentini, P., Capozza, M., Pata, D., Di Gangi, M., Dones, P., Garazzino, S., Baroero, L., Verrotti, A., Melzi, M. L., Sacco, M., Germano, M., Greco, F., Uga, E., Crichiutti, G., & Villani, A. (2017). Acute cerebellitis in children: an eleven year retrospective multicentre study in Italy. *Italian Journal of Pediatrics, 43*(1), 54.

Lantos, P., Rumbaugh, J., Bockenstedt, L., Falck-Ytter, Y., Aguero-Rosenfeld, M., Auwaerter, P., Baldwin, K., Bannuru, R., Belani, K., Bowie, W., Branda, J., Clifford, D., DiMario, F., Halperin, J., Krause, P., Lavergne, V., Liang, M., Cody Meissner, H., Nigrovic, L., Nocton, J., Osani, M., Pruitt, A., Rips, J., Rosenfeld, L., Savoy, M., Sood, S., Steere, A., Strle, F., Sundel, R., Tsao, J., Vaysbrot, E., Wormser, G., & Zemel, L. (2021). Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. *Arthritis & Rheumatolog*y, 73(1), 12-20.

Lazarini, E., Mitre, E., Takati, E. & Tidei, R., (2006). Graphic-visual adaptation of House-Brackmann facial nerve grading for peripheral facial palsy. *Clinical Otolaryngology, 31(3)*, 192–197.

Lazzarini, M., Martin, S., Mitkovski, M., Vozari, R. R., Stühmer, W., & Bel, E. Del. (2013). Doxycycline restrains glia and confers neuroprotection in a 6-OHDA Parkinson model. *Glia*, *61*(7), 1084–1100.

Lee, W. T., Yu, T. W., Chang, W. C., & Shau, W. Y. (2007). Risk factors for postencephalitic epilepsy in children: A hospital-based study in Taiwan. *European Journal of Paediatric Neurology*, *11*(5), 302–309.

Lee, Y.-J., Hwang, S.-K., & Kwon, S. (2019). Acute Necrotizing Encephalopathy in Children: a Long Way to Go. *Journal of Korean Medical Science*, *34*(19), e143.

Lehtokoski-Lehtiniemi, E., & Koskiniemi, M. L. (1989). Mycoplasma pneumoniae encephalitis: A severe entity in children. *Pediatric Infectious Disease Journal*, *8*(9), 651–653.

Leonard, J. R., Moran, C. J., Cross, D. W. T., Wippold, F. J., Schlesinger, Y., & Storch, G. A. (2000). MR imaging of herpes simplex type I encephalitis in infants and young children: A separate pattern of findings. *American Journal of Roentgenology*, *174*(6), 1651–1655.

Leung, A. K. C., Wong, A. H. C., & Hon, K. L. (2018). Community-Acquired Pneumonia in Children. *Recent Patents on Inflammation & Allergy Drug Discovery*, *12*(2), 136–144.

Levine, J. M., Ahsan, N., Ho, E., & Santoro, J. D. (2020). Genetic Acute Necrotizing Encephalopathy Associated with RANBP2: Clinical and Therapeutic Implications in Pediatrics. *Multiple Sclerosis and Related Disorders*, *43*(102194), 102194.

Lewthwaite, P., Begum, A., Ooi, M. H., Faragher, B., Lai, B. F., Sandaradura, I., Mohan, A., Mandhan, G., Meharwade, P., Subhashini, P., Abhishek, Penkulinti, S., Shankar, M. V., Ravikumar, R., Young, C., Cardosa, M. J., Ravi, V., Wong, S. C., Kneen, R., & Solomon, T. (2010). Disability after encephalitis: development and validation of a new outcome score. *Bulletin of the World Health Organization*, *88*(8), 584–592.

Ley, D., Laurin, J., Bjerre, I., & Marsal, K. (1996). Abnormal fetal aortic velocity waveform and minor neurological dysfunction at 7 years of age. *Ultrasound in Obstetrics and Gynecology*, *8*(3), 152–159.

Leypoldt, F., Höftberger, R., Titulaer, M. J., Armangue, T., Gresa-Arribas, N., Jahn, H., Rostásy, K., Schlumbrger, W., Meyer, T., Wandinger, K.-P., Rosenfelt, M. R., Graus, F., & Dalmau, J. (2015). Investigations on CXCL13 in anti-N-methyl-D-aspartate receptor encephalitis: a potential biomarker of treatment response. *JAMA Neurology*, *72*(2), 180–186.

Ljøstad, U., Skogvoll, E., Eikeland, R., Midgard, R., Skarpaas, T., Berg, Å., & Mygland, Å. (2008). Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blind, randomised trial. *The Lancet Neurology*, *7*(8), 690–695.

Ljungman, G., Gordh, T., Sörensen, S., & Kreuger, A. (2001). Lumbar puncture in pediatric oncology: Conscious sedation vs. general anesthesia. *Medical and Pediatric Oncology*, *36*(3), 372–379.

Lochary, M., & Lockhart, P. (1998). Doxycycline and staining of permanent teeth. *Pediatric Infectious Diseases Journal*, *17*(5), 429–431.

Lung, D. C., Yip, E. K. T., Lam, D. S. Y., & Que, T. L. (2013). Rapid defervescence after doxycycline treatment of macrolide-resistant Mycoplasma pneumoniae-associated community-acquired pneumonia in children. *The Pediatric Infectious Disease Journal*, *32*(12), 1396–1399.

Ma, J., & Jiang, L. (2013). Outcome of children with Japanese encephalitis and predictors of outcome in southwestern China. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, *107*(10), 660–665.

Mailles, A., De Broucker, T., Costanzo, P., Martinez-Almoyna, L., Vaillant, V., & Stahl, J. P. (2012). Long-term outcome of patients presenting with acute infectious encephalitis of various causes in France. *Clinical Infectious Diseases*, *54*(10), 1455–1464.

Mantsopoulos, K., Psillas, G., Psychogios, G., Brase, C., Iro, H., & Constantinidis, J. (2011). Predicting the Long-Term Outcome After Idiopathic Facial Nerve Paralysis. *Otology & Neurotology*, *32*(5), 848–851.

May, M., Fria, T. J., Blumenthal, F., & Curtin, H. (1981). Facial Paralysis in Children: Differential Diagnosis. *Otolaryngology–Head and Neck Surgery*, *89*(5), 841–848.

Meli, D., Coimbra, R., Erhart, D., Loquet, G., Bellac, C., Täuber, M., Neumann, U., & Leib, S. (2006). Doxycycline reduces mortality and to the brain and to cochlea in experimantal pneumococcal meningitis. *Infection and Immunity, 74*(7), 3890–3896.

McGrath, N., Anderson, N. E., Croxson, M. C., & Powell, K. F. (1997). Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. *Journal of Neurology, Neurosurgery & Psychiatry*, *63*(3), 321–326.

McNamara, R., Doyle, J., Mc Kay, M., Keenan, P., & Babl, F. E. (2013). Medium term outcome in Bell's palsy in children: Table 1. *Emergency Medicine Journal*, *30*(6), 444–446.

Mehta, R. P., WernickRobinson, M., & Hadlock, T. A. (2007). Validation of the Synkinesis Assessment Questionnaire. *The Laryngoscope*, *117*(5), 923–926.

Meier-Gallati, V., Scriba, H., & Fisch, U. (1998). Objective scaling of facial nerve function based on area analysis (OSCAR). *Otolaryngology–Head and Neck Surgery*, *118*(4), 545–550.

Messacar, K., Fischer, M., Dominguez, S. R., Tyler, K. L., & Abzug, M. J. (2018). Encephalitis in US Children. *Infectious Disease Clinics of North America, 32*(1), 145-162.

Meyer, H. M., Johnson, R. T., Crawford, I. P., Dascomb, H. E., & Rogers, N. G. (1960). Central nervous system syndromes of "viral" etiology. *The American Journal of Medicine*, *29*(2), 334–347.

Michaeli, O., Kassis, I., Shachor-Meyouhas, Y., Shahar, E., & Ravid, S. (2014). Long-term motor and cognitive outcome of acute encephalitis. *Pediatrics*, *133*(3), e546-52.

Micheli R, Telesca C, Gitti F, Giordano L, & Perini A. (1996). Bell´s palsy: diagnostic and therapeutic trial in childhood. *Minerva Pediatrics*, *48*(6), 245–250.

Moffitt, J. M., Cooley, R. O., Olsen, N. H., & Hefferren, J. J. (1974). Prediction of tetracycline-induced tooth discoloration. *The Journal of the American Dental Association*, *88*(3), 547–552.

Mohammad, S. S., Jones, H., Hong, M., Nosadini, M., Sharpe, C., Pillai, S. C., Brilot, F., & Dale, R. C. (2016). Symptomatic treatment of children with anti-NMDAR encephalitis. *Developmental Medicine & Child Neurology*, *58*(4), 376–384.

Mohammad, S. S., Soe, S. M., Pillai, S. C., Nosadini, M., Barnes, E. H., Gill, D., & Dale, R. C. (2016). Etiological associations and outcome predictors of acute electroencephalography in childhood encephalitis. *Clinical Neurophysiology*, *127*(10), 3217–3224.

Müllegger, R. R., Millner, M. M., Spork, K. D., & Stanek, G. (1991). Penicillin G sodium and ceftriaxone in the treatment of neuroborreliosis in children – A prospective study. *Infection*, *19*(4), 279–283.

Munro, A. P. S., Dorey, R. B., Owens, D. R., Steed, D. J., Petridou, C., Herdman, T., Jones, C. E., Patel, S. V., Pryde, K., & Faust, S. N. (2020). High frequency of paediatric facial nerve palsy due to Lyme disease in a geographically endemic region. *International Journal of Pediatric Otorhinolaryngology*, *132*(109905).

Murty, G. E., Diver, J. P., Kelly, P. J., O'Donoghue, G. M., & Bradley, P. J. (1994). The Nottingham System: Objective Assessment of Facial Nerve Function in the Clinic. *Otolaryngology–Head and Neck Surgery*, *110*(2), 156–161.

Mwaniki, M., Talbert, A., Njuguna, P., English, M., Were, E., Lowe, B., Newton, C., & Berkley, J. Clinical indicators of bacterial meningitis among neonates and young infants in rural Kenya. (2011). *BMC Infectious Diseases, 11*, 301.

Mygland, Å., Ljøstad, U., Fingerle, V., Rupprecht, T., Schmutzhard, E., Steiner, I., & European Federation of Neurological Societies. (2010). EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. *European Journal of Neurology*, *17*(1), 8–16.

Neilson, D. E., Adams, M. D., Orr, C. M. D., Schelling, D. K., Eiben, R. M., Kerr, D. S., Anderson, J., Bassuk, A., Bye, A. M., Childs, A. M., Clarke, A., Crow, Y. J., Di Rocco, M., Dohna-Schwake, C, Dueckers, D., Fasano, A. E., Gika, A. D., Gionnis, D., Gorman, M. P., Grattan-Smith, P. J., Hackenberg, A., Kuster, A., Lentschig, M. G., Lopez-Laso, E., Marco, E. J., Mastroyianni, S., Perrier, J., Schmitt-Mechelke, T., Servidei, S., Skardoutsou, A., Uldall, P., van der Knaap, Goglin, K. C., Tefft, D. L., Aubin, C., de Jager, P., Hafler, D., & M. S., Warman, M. L. (2009). Infection-Triggered Familial or Recurrent Cases of Acute Necrotizing Encephalopathy Caused by Mutations in a Component of the Nuclear Pore, RANBP2. *The American Journal of Human Genetics*, *84*(1), 44–51.

Nigrovic, L. E., Thompson, A. D., Fine, A. M., & Kimia, A. (2008). Clinical Predictors of Lyme Disease Among Children With a Peripheral Facial Palsy at an Emergency Department in a Lyme Disease-Endemic Area. *Pediatrics*, *122*(5), e1080–e1085.

Ogrinc, K., Lotrič-Furlan, S., Maraspin, V., Lusa, L., Cerar, T., Ružič-Sabljič, E., & Strle, F. (2013). Suspected early Lyme neuroborreliosis in patients with erythema migrans. *Clinical Infectious Diseases*, *57*, 501–509.

Okada, T., Morozumi, M., Tajima, T., Hasegawa, M., Sakata, H., Ohnari, S., Chiba, M., Iwata, S, & Ubukata, K. (2012). Rapid effectiveness of minocycline or doxycycline against macrolide-resistant mycoplasma pneumoniae infection in a 2011 outbreak among Japanese children. *Clinical Infectious Diseases*, *55*(12), 1642–1649.

Okumura, A., Mizuguchi, M., Kidokoro, H., Tanaka, M., Abe, S., Hosoya, M., Aiba, H., Maegaki, Y., Yamamoto, H., Tanabe, T., Noda, E., Imakata, G., & Kurahashi, H. (2009). Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin. *Brain and Development*, *31*(3), 221–227.

Özkale, Y., Erol, I., Saygi, S., & Yilmaz, I. (2015). Overview of pediatric peripheral facial nerve paralysis: Analysis of 40 patients. *Journal of Child Neurology*.

Paolilo, R. B., Deiva, K., Neuteboom, R., Rostásy, K., & Lim, M. (2020). children Acute Disseminated Encephalomyelitis: Current Perspectives. *Children*, *7*(11), 210.

Papan, C., Kremp, L., Weiß, C., Petzold, A., Schroten, H., & Tenenbaum, T. (2019). Infectious causes of peripheral facial nerve palsy in children – a retrospective cohort study with long-term follow-up. *European Journal of Clinical Microbiology & Infectious Diseases*, *38*(11), 2177–2184.

Pavlou, E., Gkampeta, A., & Arampatzi, M. (2011). Facial nerve palsy in childhood. *Brain and Development*, *33*(8), 644–650.

Paydar-Darian, N., Kimia, A. A., Lantos, P. M., Fine, A. M., Gordon, C. D., Gordon, C. R., Landschaft, A., & Nigrovic, L. E. (2016). Diagnostic Lumbar Puncture Among Children With Facial Palsy in a Lyme Disease Endemic Area. *Journal of the Pediatric Infectious Diseases Society*, *6*(2), 205–208.

Peitersen E. (2002). Bell´s palsy: the spontaneous course of 2,500 peripheral facial nerve palsies of different etiologies. *Acta Oto-Laryngologica. Supplementum.*, (549), 4–30.

Peltomaa, M., Saxen, H., Seppälä, I., Viljanen, M., & Pyykkö, I. (1998). Paediatric Facial Paralysis caused by Lyme borreliosis: A Prospective and Retrospective Analysis. *Scandinavian Journal of Infectious Diseases*, *30*(3), 269–275.

Pereira, L. M., Obara, K., Dias, J. M., Menacho, M. O., Lavado, E. L., Cardoso, J. R., & Cardoso, J. R. (2011). Facial exercise therapy for facial palsy: systematic review and meta-analysis. *Clinical Rehabilitation*, *25*(7), 649–658.

Peters, L. H. J., Maathuis, C. G. B., & Hadders-Algra, M. (2011). Limited motor performance and minor neurological dysfunction at school age. *Acta Paediatrica, International Journal of Paediatrics*, *100*(2), 271–278.

Peters, L. H. J., Maathuis, K. G. B., Kouw, E., Hamming, M., & Hadders-Algra, M. (2008). Test-retest, inter-assessor and intra-assessor reliability of the modified Touwen examination. *European Journal of Paediatric Neurology*, *12*(4), 328–333.

Pietikäinen, A., Maksimow, M., Kauko, T., Hurme, S., Salmi, M., & Hytönen, J. (2016). Cerebrospinal fluid cytokines in Lyme neuroborreliosis. *Journal of Neuroinflammation*, *13*(1), 273.

Pietikäinen, A., Oksi, J., & Hytönen, J. (2018). Point-of-care testing for CXCL13 in Lyme neuroborreliosis. *Diagnostic Microbiology and Infectious Disease*, *91*(3), 226–228.

Pillai, S. C., Hacohen, Y., Tantsis, E., Prelog, K., Merheb, V., Kesson, A., Barnes, E., Gill, D., Webster, R., Menezes, M., Ardern-Holmes, S., Gupta, S., Procopis, P., Troedson, C., Antony, J., Ouvrier, R. A., Polfrit, Y., Davies, N. W. S., Waters, P., Lang, B., Lim, M. J., Brilot, F., Vincent, A., Dale, R. C. (2015). Infectious and autoantibody-associated encephalitis: clinical features and long-term outcome. *Pediatrics*, *135*(4), e974–e984.

Poloczek, S. (1975). Possibility of tooth discoloration after doxycycline therapy in infants and small children from the view point of the residential pediatrist. *Zeitschrift Für Allgemeinmedizin*, *51*(11), 549–550.

Punt, M., De Jong, M., DEe Groot, E., & Hadders-Algra, M. (2010). Minor neurological dysfunction in children with dyslexia. *Developmental Medicine & Child Neurology*, *52*(12), 1127–1132.

Ramanuj, P. P., Granerød, J., Davies, N. W. S., Conti, S., Brown, D. W. G., & Crowcroft, N. S. (2014). Quality of life and associated socio-clinical factors after encephalitis in children and adults in England: A population-based, prospective cohort study. *PLoS ONE*, *9*(7), e103496.

Rantala, H., Uhari, M., Saukkonen, A., & Sorri, M. (1991). Outcome after childhood encephalitis. *Developmental Medicine and Child Neurology*, *33*, 858–867.

Rao, S., Elkon, B., Flett, K. B., Moss, A. F. D., Bernard, T. J., Stroud, B., & Wilson, K. M. (2017). Long-Term Outcomes and Risk Factors Associated With Acute Encephalitis in Children. *Journal of the Pediatric Infectious Diseases Society*, *6*(1), 20–27.

Raschilas, F., Wolff, M., Delatour, F., Chaffaut, C., De Broucker, T., Chevret, S., Lebon, B., Canton, P., & Rozenberg, F. (2002). Outcome of and Prognostic Factors for Herpes Simplex Encephalitis in Adult Patients: Results of a Multicenter Study. *Clinical Infectious Diseases*, *35*(3), 254–260.

Rautonen, J., Koskiniemi, M., & Vaheri, A. (1991). Prognostic factors in childhood acute encephalitis. *The Pediatric Infectious Disease Journal*, *10*(6), 441–446.

Remy, M. M., Schöbi, N., Kottanattu, L., Pfister, S., Duppenthaler, A., & Suter-Riniker, F. (2017). Cerebrospinal fluid CXCL13 as a diagnostic marker of neuroborreliosis in children: a retrospective case-control study. *Journal of Neuroinflammation*, *14*(1), 173.

Rismanchi, N., Gold, J. J., Sattar, S., Glaser, C. A., Sheriff, H., M., Proudfoot, J., Mower, A., Crawford, J. R., Nespeca, M., & Wang, S. G. (2015a). Epilepsy After Resolution of Presumed Childhood Encephalitis. *Pediatric Neurology*, *53*(1), 65–72.

Rismanchi, N., Gold, J. J., Sattar, S., Glaser, C. A., Sheriff, H. M., Proudfoot, J., Mower, A., Nespeca, M., Crawford, J. R., & Wang, S. G. (2015b). Neurological outcomes after presumed childhood encephalitis. *Pediatric Neurology*, *53*(3), 200–206.

Ross, B., Fradet, G., & Nedzelski, J. (1996). Development of a sensitive clinical facial grading system. *Otolaryngology - Head and Neck Surgery*, *114*(3), 370–386.

Rupprecht, T. A., Koedel, U., Fingerle, V., & Pfister, H.-W. (2008). The pathogenesis of lyme neuroborreliosis: from infection to inflammation. *Molecular Medicine (Cambridge, Mass.)*, *14*(3–4), 205–212.

Salanitri, S., & Seow, W. (2013). Developmental enamel defects in the primary dentition: aetiology and clinical management. *Australian Dental Journal*, *58*(2), 133–140.

Sánchez, A. R., Rogers, R. S., & Sheridan, P. J. (2004). Tetracycline and other tetracycline-derivated staining of the teeth and oral cavity. *International Journal of Dermatology*, *43*(10), 709–715.

Sanchez, E., Vannier, E., Wormser, G. P., & Hu, L. T. (2016). Diagnosis, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis. *JAMA*, *315*(16), 1767–1777.

Sasaki, J., Chegondi, M., Raszynski, A., & Totapally, B. R. (2014). Outcome of Children With Acute Encephalitis and Refractory Status Epilepticus. *Journal of Child Neurology*, *29*(12), 1638–1644.

Schleede, L., Bueter, W., Baumgartner-Sigl, S., Opladen, T., Weigt-Usinger, K., Stephan, S., Kaiser, O., Kraus, V., van Baalen, A., Skopnik, H., Hartmann, H., Rostasy, K., Lücke, T., Schara, U., & Häusler, M. (2013). Pediatric Herpes Simplex Virus Encephalitis. *Journal of Child Neurology*, *28*(3), 321–331.

Schlesinger, Y., Buller, R. S., Brunstrom, J. E., Moran, C. J., & Storch, G. A. (1995). Expanded spectrum of herpes simplex encephalitis in childhood. *The Journal of Pediatrics*, *126*(2), 234–241.

Schmidt, B. L. (1997). PCR in laboratory diagnosis of human Borrelia burgdorferi infections. *Clinical Microbiology Reviews*, *10*(1), 185–201.

Schmolck, H., Maritz, E., Kletzin, I., & Korinthenberg, R. (2005). Neurologic, neuropsychologic, and electroencephalographic findings after European tick-borne encephalitis in children. *Journal of Child Neurology*, *20*(6), 500–508.

Sells, C. J., Carpenter, R. L., & Ray, C. G. (1975). Sequelae of central-nervous-system enterovirus infections. *The New England Journal of Medicine*, *293*(1), 1–4.

Seow, W. (1991). Enamel hypoplasia in the primary dentition: a review. *ASDC Journal of Dentistry for Children*, *58*(6), 441–452.

Setänen, S., Lehtonen, L., Parkkola, R., Aho, K., & Haataja, L. (2016). Prediction of neuromotor outcome in infants born preterm at 11 years of age using volumetric neonatal magnetic resonance imaging and neurological examinations. *Developmental Medicine & Child Neurology*, *58*(7), 721–727.

Shaffer, D., Schonfeld, I., O'connor, P. A., Stokman, C., Trautman, P., Shafer, S., & Ng, S. (1985). Neurological Soft Signs: Their Relationship to Psychiatric Disorder and Intelligence in Childhood and Adolescence. *Archives of General Psychiatry*, *42*(2), 342–351.

Shargorodsky, J., Lin, H. W., & Gopen, Q. (2010). Facial nerve palsy in the pediatric population. *Clinical Pediatrics*, *49*(5), 411–417.

Shetty, A. K. (2002). Tetracyclines in Pediatrics Revisited. *Clinical Pediatrics*, *41*(4), 203–209.

Shih, W.-H., Tseng, F.-Y., Yeh, T.-H., Hsu, C.-J., & Chen, Y.-S. (2009). Outcomes of facial palsy in children. *Acta Oto-Laryngologica*, *129*(8), 915–920.

Shwachman, H., Fekete, E., Kulczycki, L. L., & Foley, G. E. (1958). The effect of long-term antibiotic therapy in patients with cystic fibrosis of the pancreas. *Antibiotics Annual*, *6*, 692–699.

Sillanpää, H., Skogman, B. H., Sarvas, H., Seppälä, I. J. T., & Lahdenne, P. (2013). Cerebrospinal fluid chemokine CXCL13 in the diagnosis of neuroborreliosis in children. *Scandinavian Journal of Infectious Diseases*, *45*(7), 526–530.

Skogman, B. H., Glimaker, K., Nordwall, M., Vrethem, M., Odkvist, L., & Forsberg, P. (2012). Long-term Clinical Outcome After Lyme Neuroborreliosis in Childhood. *Pediatrics*, *130*(2), 262–269.

Skogman, B. H., Sjöwall, J., & Lindgren, P.-E. (2015). The NeBoP score – a clinical prediction test for evaluation of children with Lyme Neuroborreliosis in Europe. *BMC Pediatrics*, *15*(1), 214.

Södermark, L., Sigurdsson, V., Näs, W., Wall, P., & Trollfors, B. (2017). Neuroborreliosis in Swedish Children: A Population-based Study on Incidence and Clinical Characteristics. *Pediatric Infectious Disease Journal*, *36*(11), 1052–1056.

Soorani-Lunsing, R. J., Hadders-Algra, M., Olinga, A. A., Huisjes, H. J., & Touwen, B. C. L. (1993). Is minor neurological dysfunction at 12 years related to behaviour and cognition? *Developmental Medicine & Child Neurology*, *35*(4), 321–330.

Stähelin-Massik, J., Zimmermann, H., & Gnehm, H. E. (2008). Tick-Borne Encephalitis in Swiss Children 2000–2004. *Pediatric Infectious Disease Journal*, *27*(6), 555–557.

Stahl, J. P., & Mailles, A. (2019). Herpes simplex virus encephalitis update. *Current Opinion in Infectious Diseases*, *32*(3), 239–243.

Steere, A. C., Berardi, V. P., Weeks, K. E., Logigian, E. L., & Ackermann, R. (1990). Evaluation of the Intrathecal Antibody Response to Borrelia burgdorferi as a Diagnostic Test for Lyme Neuroborreliosis. *Journal of Infectious Diseases*, *161*(6), 1203–1209.

Sullivan, F. M., Swan, I. R. C., Donnan, P. T., Morrison, J. M., Smith, B. H., Davenport, R. J., Vale, L. D., Clarkson, J. E., Hammersley, V., Hayavi, S., McAteer, A., Stewart, K., & Daly, F. (2007). Early Treatment with Prednisolone or Acyclovir in Bell's Palsy. *New England Journal of Medicine*, *357*(16), 1598–1607.

Tang, I., Lee, S., Shashinder, S., & Raman, R. (2009). Outcome of patients presenting with idiopathic facial nerve paralysis (Bell´s palsy) in at tertiary centre - a five years experience. *Medical Journal of Malaysia*, *64*(2), 155–158.

Teixeira, L. J., Valbuza, J. S., & Prado, G. F. (2011). Physical therapy for Bell's palsy (idiopathic facial paralysis). *Cochrane Database of Systematic Reviews*.

Thompson, A. D., Cohn, K. A., Shah, S. S., Lyons, T., Welsh, E. J., Hines, E. M., & Nigrovic, L. E. (2012). Treatment complications in children with lyme meningitis. *Pediatric Infectious Disease Journal*, *31*(10), 1032–1035.

Thompson, C., Kneen, R., Riordan, A., Kelly, D., & Pollard, A. J. (2012). Encephalitis in children. *Archives of Disease in Childhood*, *97*(2), 150–161.

Thorstrand, C., Belfrage, E., Bennet, R., Malmborg, P., & Eriksson, M. (2002). Successful treatment of neuroborreliosis with ten day regimens. *The Pediatric Infectious Disease Journal*, *21*(12), 1142–1145.

Titulaer, M. J., McCracken, L., Gabilondo, I., Armangué, T., Glaser, C., Iizuka, T., Honing, L. S., Benseler, S. M., Kawachi, I., Martinez-Hernandez, E., Aguilar, E., Gresa-Arribas, N., Ryan-Florence N., Torrents, A., Saiz, A., Rosenfeld, M. R., Balice-Gordon, R., Graus, F., & Dalmau, J. (2013). Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. *Lancet Neurology*, *12*(2), 157–165.

To, T. M., Soldatos, A., Sheriff, H., Schmid, D. S., Espinosa, N., Cosentino, G., Preas, C. P., & Glaser, C. A. (2014). Insights into pediatric herpes simplex encephalitis from a cohort of 21 children from the California encephalitis project, 1998–2011. *Pediatric Infectious Disease Journal*, *33*(12), 1287–1288.

Todd, S. R., Dahlgren, F. S., Traeger, M. S., Beltrán-Aguilar, E. D., Marianos, D. W., Hamilton, C., McQuiston, H. J., & Regan, J. J. (2015). No visible dental staining in children treated with

doxycycline for suspected Rocky Mountain Spotted Fever. *The Journal of Pediatrics*, *166*(5), 1246–1251.

Tunkel, A. R., Glaser, C. A., Bloch, K. C., Sejvar, J. J., Marra, C. M., Roos, K. L., Hartman, B. J., Kaplan, S. L., Scheld, W. M., & Whitley, R. J. (2008). The Management of Encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, *47*(3), 303–327.

Tveitnes, D., Øymar, K., & Natås, O. (2007). Acute facial nerve palsy in children: How often is it Lyme borreliosis? *Scandinavian Journal of Infectious Diseases*, *39*(5), 425–431.

Ünüvar, E., Oğuz, F., Sıdal, M., & Kılıç, A. (1999). Corticosteroid treatment of childhood Bell's palsy. *Pediatric Neurology*, *21*(5).

van Baalen, A., Häusler, M., Boor, R., Rohr, A., Sperner, J., Kurlemann, G., Panzer, A., Stepani, U. & Kluger, G. (2010). Febrile infection-related epilepsy syndrome (FIRES): A nonencephalitic encephalopathy in childhood. *Epilepsia*, *51*(7), 1323–1328.

van Baalen, A., Stephani, U., Kluger, G., Häusler, M., & Dulac, O. (2009). FIRES: febrile infection responsive epileptic (FIRE) encephalopathies of school age. *Brain & Development*, *31*(1), 92–93.

Van Swieten, J. C., Koudstaal, P. J., Visser, M. C., Schouten, H. J., & van Gijn, J. (1988). Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*, *19*(5), 604–607.

VanSwearingen, J. M., & Brach, J. S. (1996). The Facial Disability Index: Reliability and Validity of a Disability Assessment Instrument for Disorders of the Facial Neuromuscular System. *Physical Therapy*, *76*(12), 1298–1300.

Venkatesan, A., Tunkel, A. R., Bloch, K. C., Lauring, A. S., Sejvar, J., Bitnun, A., Stahl, J.-P., Mailler, A., Drebot, M., Rupprecht, C. E., Yoder, J., Cope, J. R., Wilson M. R., Whitley, R., J., Sullivan, J., Granerod, J., Jones, C., Eastwood, K., Ward, K. N., Durrheim, D. N., Solbrig, M. V., Guo-Dong, L., & Glaser, C. A. International Encephalitis Consortium. (2013). Case definitions, diagnostic algorithms, and priorities in encephalitis: Consensus statement of the international encephalitis consortium. *Clinical Infectious Diseases*, *57*(8), 1114–1128.

Venkatesan, A., & Geocadin, R. G. (2014). Diagnosis and management of acute encephalitis: A practical approach. *Neurology: Clinical Practice*, *4*(3), 206–215.

Viljanen, M. K., & Punnonen, J. (1989). The effect of storage of antigen-coated polystyrene microwells on the detection of antibodies against Borrelia burgdorferi by enzyme immunoassay (EIA). *Journal of Immunological Methods*, *124*(1989), 137–141.

Volovitz, B., Shkap, R., Amir, J., Calderon, S., Varsano, I., & Nussinovitch, M. (2007). Absence of tooth staining with doxycycline treatment in young children. *Clinical Pediatric*, *46*(2), 121–126.

von Stülpnagel, C., Winkler, P., Koch, J., Zeches-Kansy, C., Schöttler-Glas, A., Wolf, G., Hiller, H. H., Staudt, M., Kluger, G., & Rostasy, K. (2016). MRI-imaging and clinical findings of eleven children with tick-borne encephalitis and review of the literature. *European Journal of Paediatric Neurology*, *20*(1), 45–52.

Von Wittenau, S. (1968). Some Pharmacokinetic Aspects of Doxycycline Metabolism in Man. *Chemotherapy*, *13*(1), 41–50.

Vrabec, J. T., Backous, D. D., Djalilian, H. R., Gidley, P. W., Leonetti, J. P., Marzo, S. J., Morrison, D., Ng, M., Ramsey, M. J., Schaitkin, B. M., Smouha, E., Toh, E. H., Wax, M. K., Williamson, A., & Smith, E. O. B. Facial Nerve Disorders Committee. (2009). Facial Nerve Grading System 2.0. *Otolaryngology - Head and Neck Surgery*, *140*(4), 445–450.

Vukelic, D., Bozinovic, D., Morovic, M., Tesovic, G., Ruzic Sabljic, E., Barisic, N., & Knezovic, I. (2000). Opsoclonus-myoclonus syndrome in a child with neuroborreliosis. *Journal of Infection*, *40*(2).

Wang, D. D., Englot, D. J., Garcia, P. A., Lawton, M. T., & Young, W. L. (2012). Minocycline- and tetracycline-class antibiotics are protective against partial seizures in vivo. *Epilepsy & Behavior : E&B*, *24*(3), 314–318.

Wang, I. J., Lee, P. I., Huang, L. M., Chen, C. J., Chen, C. L., & Lee, W. T. (2007). The correlation between neurological evaluations and neurological outcome in acute encephalitis: A hospital-based study. *European Journal of Paediatric Neurology*, *11*(2), 63–69.

Ward, K. N., Ohrling, A., Bryant, N. J., Bowley, J. S., Ross, E. M., & Verity, C. M. (2012). Herpes simplex serious neurological disease in young children: Incidence and long-term outcome. *Archives of Disease in Childhood*, *97*(2), 162–165.

Wechsler, D. (2005). *Wechsler Preschool and Primary Scale of Intelligence – Third Edition*. Stockholm: NCS Pearson Inc.

Wechsler, D. (2007). *Wechsler Intelligence Scale for Children – Fourth Edition: Manual*. Stockholm: NCS Pearson Inc.

Wechsler, D. (2009). *Wechsler Preschool and Primary Scale of Intelligence – Third Edition: Manual*. Helsinki: Psykologien Kustannus Oy.

Wechsler, D. (2010). *Wechsler Intelligence Scale for Children – Fourth Edition: Manual.* Helsinki: Psykologien Kustannus Oy.

Wechsler, D. (2012). *Wechsler Adult Intelligence Scale – Fourth Edition: Manual*. Helsinki: Psykologien Kustannus Oy.

Weihua, Z., Changhong, R., Xiaohui, W., Jiuwei, L., Changhong, D., Tongli, H., Lv, J., Chen, C., Gong, S., Xiuwei, Z., Dai, L., Feng, W., Yang, X., Zhang, S., Zhou, J., Ren, H., Guan, H., Ren, X., & Fang, F. (2021). Age-dependent characteristics and prognostic factors of pediatric anti-N-methyl-d-aspartate receptor encephalitis in a Chinese single-center study. *European Journal of Paediatric Neurology*, *34*, 67–73.

Weng, W., Shin-forng Peng, S., Lee, W., Fan, P., Chien, Y., Du, J., Shen, Y. Acute disseminated encephalomyelitis in children: one medical center experience. (2006). *Acta paediatrica Taiwanica, 47*(2), 67–41.

Weyman, J. (1965). The Clinical Appearances of Tetracycline Staining of the Teeth. *British Dental Journal*, *118*, 281–291.

Widerøe, M., Havnes, M. B., Morken, T. S., Skranes, J., Goa, P.-E., & Brubakk, A.-M. (2012). Doxycycline treatment in a neonatal rat model of hypoxia-ischemia reduces cerebral tissue and white matter injury: a longitudinal magnetic resonance imaging study. *The European Journal of Neuroscience*, *36*(1), 2006–2016.

Wilke, M. (2000). Primarily chronic and cerebrovascular course of Lyme neuroborreliosis: case reports and literature review. *Archives of Disease in Childhood*, *83*(1), 67–71.

Wilske, B. (2003). Diagnosis of Lyme Borreliosis in Europe. *Vector-Borne and Zoonotic Diseases*, *3*(4), 215–227.

Wilske, B., Fingerle, V., & Schulte-Spechtel, U. (2007). Microbiological and serological diagnosis of Lyme borreliosis. *FEMS Immunology & Medical Microbiology*, *49*(1), 13–21.

Wolfovitz, A., Yehudai, N., & Luntz, M. (2017). Prognostic factors for facial nerve palsy in a pediatric population: A retrospective study and review. *The Laryngoscope*, *127*(5), 1175–1180.

Wormser, G. P., Dattwyler, R. J., Shapiro, E. D., Halperin, J. J., Steere, A. C., Klempner, M. S., Krause, P., Bakken, J. S., Strle, F., Stanek, G., Bockenstedt, L., Fish, D., Dumler, J. S., & Nadelman, R. B. (2006). The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clinical Infectious Diseases*, *43*(9), 1089–1134.

Wormser, G. P., Wormser, R. P., Myers, R., & Cunha, B. A. (2018). How safe is doxycycline for young children or for pregnant or breastfeeding women? *Diagnostic Microbiology and Infectious Disease Journals*, *93*(3), 238–242.

Wuollet, E., Laisi, S., Salmela, E., Ess, A., & Alaluusua, S. (2016). Molar-incisor hypomineralization and the association with childhood illnessess and antibiotics in a group of Finnish children. *Acta Odontologica Scandinavica, 74*(5), 416–412.

Yildirim, M., Gocmen, R., Konuskan, B., Parlak, S., Yalnizoglu, D., & Anlar, B. (2020). Acute Cerebellitis or Postinfectious Cerebellar Ataxia? Clinical and Imaging Features in Acute Cerebellitis. *Journal of Child Neurology*, *35*(6), 380–388.

Ylitalo, V., & Hagberg, B. A. (2009). Progressive ataxia in Swedish children: a re-evaluation study. *Acta Neurologica Scandinavica*, *89*(4), 299–302.

Yoo, H. W., Yoon, L., Kim, H. Y., Kwak, M. J., Park, K. H., Bae, M. H., Lee, Y., Nam, S. O., & Kim, Y. M. (2018). Comparison of conservative therapy and steroid therapy for Bell's palsy in children. *Korean Journal of Pediatrics*, *61*(10), 332–337.

Yuen, K., Inokuchi, I., Maeta, M., Kawakami, S., & Masuda, Y. (1997). Evaluation of facial palsy by moiré topography index. *Otolaryngology – Head and Neck Surgery*, *117*(5), 567–572.

Appendices

Appendix 1. The original questionnaire of Study II. The Finnish translation.

KYSELYLOMAKE TUTKITTAVALLE

Nimi ja henkilötunnus: _____

Yleisiä tietoja
Syntymämitat (pituus, paino ja päänympärys):_____
Syntynyt raskausviikolla:_____

Lähisuvun neurologiset sairaudet:
_____
_____
_____

Varhaislapsuuden kehitys
Opin kävelemään (ikä): _____
Sainko fysioterapiaa alle kouluiässä: 1. en 2. kyllä

Opin puhumaan (ikä)
- sanoja_____
- 2-3 sanan lauseita _____

Sainko puheterapiaa alle kouluiässä: 1. en 2. kyllä

Esikoulu ja koulu (ympyröi oikea vaihtoehto)
Olin esikoulussa 1. kyllä 2. en
Aloitin esikoulun samanaikaisesti ikätovereideni kanssa 1. kyllä 2. en; vuotta aiemmin 3. en; vuotta myöhemmin
Menestyminen esikoulussa ennen sairastumista 1. hyvä 2. kohtalainen 3. huono
Menestyminen esikoulussa keskushermostotulehduksen jälkeen 1. hyvä 2. kohtalainen 3. huono
Mahdolliset vaikeudet:
_____
_____

Aloitin koulun samanaikaisesti ikätovereideni kanssa 1. kyllä 2. en; vuotta aiemmin 3. en; vuotta myöhemmin
Olin 1. tavallisessa koulussa 2. erityiskoulussa
Tukimuoto: 1. yleinen tuki 2. tehostettu tuki 3. erityinen tuki
Menestyminen koulussa ennen sairastumista: 1. hyvä 2. kohtalainen 3. huono
Menestyminen koulussa keskushermostotulehduksen jälkeen 1. hyvä 2. kohtalainen 3. huono
Vaikeudet koulussa, tuen tarve:
_____
_____
_____

Opiskelu

Tämän hetkinen koulu-/opiskelumuoto (ympyröi) 1. peruskoulu: luokka-aste _____ 2. lukio
3. ammattikoulu: tutkintolinja _____
4. ammattikorkeakoulu: tutkintolinja _____
5. yliopisto: pääaine_____
Suoritetut tutkinnot (rastita):
Peruskoulu ____ päästötodistuksen keskiarvo: _____
Ylioppilastutkinto _____ ylioppilastutkinnon arvosanat: _____
lukiotodistuksen keskiarvo: _____
Ammattikoulututkinto: ____ mikä: _____
Ammattikorkeakoulututkinto: _____ mikä: _____
Ylempi korkeakoulututkinto: _____ mikä: _____

Työelämä (ympyröi oikea vaihtoehto)

1. en ole vielä työelämässä (koulu tai opinnot kesken)
2. teen sijaisuuksia
3. olen vakituisessa työssä: työnantaja ja toimenkuva _____
4. työtön
5. pitkäaikainen sairauslomat
6. työkyvyttömyyseläke

Yleinen terveydentila

Mahdolliset hammaslääkärin tai suuhygienistin toteamat hammasongelmat **ennen** keskushermostotulehdusta ja doksisykliinihoitoa:

_____
_____

Mahdolliset hammaslääkärin tai suuhygienistin toteamat hammasongelmat keskushermostotulehduksen ja doksisykliinihoidon **jälkeen**:

_____
_____

Pitkäaikaissairaudet ja säännölliset lääkehoidot **ennen** keskushermostotulehdusta ja doksisykliinihoitoa:

_____
_____

Pitkäaikaissairaudet ja säännölliset lääkehoidot keskushermostotulehduksen ja doksisykliinihoidon **jälkeen**:

_____
_____

Appendix 2. The original questionnaire of Study III. The Finnish translation.

KYSELYLOMAKE (Keskushermostotulehduksen seurantatutkimus)

Nimi ja syntymäaika/ henkilötunnus: _____

Ikä nyt: _____ Ikä keskushermostotulehduksen sairastamishetkellä: _____

Yleisiä tietoja

Syntymämitat (pituus, paino ja päänympärys):_____

Syntynyt raskausviikolla:_____

Lähisuvun neurologiset sairaudet (esim. kehitysvammaisuus, epilepsia, keskushermostotulehdukset):

_____

_____

_____

Varhaislapsuuden kehitys

Liikunnalliset taidot:

Kävelyn oppiminen (ikä): _____

Onko saanut fysioterapiaa (ympyröi): ei kyllä

Kesto ja tiheys: _____

Ongelmia arkiliikkumisessa (ympyröi): ei kyllä

seuraavissa toiminnoissa/tilanteissa: _____

_____

Kielellinen kehitys

Puhumaan oppimisen aikataulu:

- yksittäisiä sanoja (missä iässä): _____
- 2-3 sanan lauseita (missä iässä): _____

Puheterapian tarvetta nyt tai aiemmin: ei kyllä

Milloin/kesto/tiheys_____

Oppimisvaikeudet

Ennen kouluikää:

Mahdolliset vaikeudet päiväkodissa tai esikoulussa nyt tai aiemmin (esim. käyttäytymisessä, tarkkaavuudessa, sosiaalisissa suhteissa tai oppimisessa)_____

_____

_____

Jos keskushermostotulehdus sairastettiin päiväkoti- tai esikouluiässä, muuttuiko pärjääminen päiväkodissa keskushermostotulehduksen myötä? Ei kyllä

Jos kyllä, niin miten/ kuinka pitkäksi aikaa ym? _____

_____

_____

Peruskoulussa:

Tukimuoto (ympyröi): yleinen tuki tehostettu tuki erityinen tuki erityiskoulu

Mahdolliset vaikeudet koulussa (esim. ongelmat muistissa, tarkkaavuuden säätelyssä, sosiaalisissa suhteissa, käyttäytymisessä) tai tuen tarve nyt tai aiemmin:

_____

_____

_____

Jos keskushermostotulehdus sairastettiin kouluiässä, muuttuiko koulumenestys tai pärjääminen sosiaalisissa suhteissa keskushermostotulehduksen jälkeen? Ei kyllä

Jos kyllä, niin miten ja kuinka pitkäksi aikaa?

_____

_____

_____

Opiskelu

Tämän hetkinen koulu-/opiskelumuoto (ympyröi tai rastita):

Peruskoulu luokka-aste _____

lukio

ammattikoulu tutkintolinja_____

ammattikorkeakoulu tutkintolinja _____

yliopisto pääaine_____

Korkein suoritettu tutkinto (ympyröi tai rastita):

Peruskoulu päästötodistuksen keskiarvo: _____

Yo-tutkinto yo-kokeen arvosanat: _____ lukiotodistuksen keskiarvo: _____

Ammattikoulututkinto mikä: _____

Ammattikorkeakoulututkinto mikä: _____

Ylempi korkeakoulututkinto mikä: _____

Mahdolliset ongelmat opinnoissa peruskoulun jälkeen: _____

_____

_____

Työelämä

Valitse nykyistä tilannetta parhaiten kuvaava vaihtoehto seuraavista (ympyröi tai rastita):

ei vielä työelämässä (opinnot kesken tms.)

työtön

pitkäaikainen sairausloma

työkyvyttömyyseläke

työelämässä

Nykyinen ammatti ja työnantaja:

_____

Nykyinen työ on (ympyröi) vakituinen sijaisuus

Yleinen terveydentila

Pitkäaikaissairaudet ja säännölliset lääkehoidot **ennen** keskushermostotulehdusta:

_____

_____

Pitkäaikaissairaudet ja säännölliset lääkehoidot keskushermostotulehduksen **jälkeen**:

_____

_____

Arjen toimintakyky (rasti perään, jos pitää paikkansa):
Ongelmia päivittäistoiminnoissa (peseytyminen, pukeutuminens, syöminen ym.) ____
Ongelmia liikkumisessa kodin ulkopuolella itsenäisesti _____
Vaikeuksia siirtymätilanteissa _____
Vaikeuksia rahan arvon tai kellonajan hahmottamisessa _____
Avustajan/avustuksen tarve kodin ulkopuolella ____
Lisätietoja e.m. kohtiin liittyen:_____
_____

Muuttuiko arjen toimintakyky (esim. käyttäytyminen, itsenäinen selviytyminen arkitoiminnoissa ym. sairastetun keskushermostotulehduksen jälkeen? Ei kyllä
Jos kyllä, niin miten? _____
_____
_____

Harrastukset:_____
_____

Aiemmat tutkimukset
Psykologin tutkimuksia tehty muualla kuin TYKSissä kyllä ei
Jos kyllä,
missä ja milloin tehty:_____
psykologin nimi: _____

Kaavakkeen täyttäjä (ympyröi oikea vaihtoehto): tutkittava tutkittavan huoltaja
muu (suhde tutkittavaan)_____

Päiväys: _____
Allekirjoitus ja nimenselvennys: _____

TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Painosalama, Turku, Finland 2022

ISBN 978-951-29-8808-2 (PRINT)
ISBN 978-951-29-8809-9 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)