AUTHOR(S)
Sipilä, J. O. T.

TITLE
Adult-Onset Encephalitis over Twelve Years in Easternmost Finland

YEAR
2024

DOI
https://doi.org/10.1159/000538020

CITATION
Sipilä, J. O. T. (2024). Adult-Onset Encephalitis over Twelve Years in Easternmost Finland. *Neuroepidemiology*, 58(4), 276–283. https://doi.org/10.1159/000538020

VERSION
Accepted Manuscript

Research Article

Adult-onset encephalitis over two decades in easternmost Finland

Jussi O.T. Sipilä

Department of Neurology, North Karelia Central Hospital, Siun Sote, Joensuu, Finland and Clinical Neurosciences, University of Turku, Turku, Finland.

Short Title: Adult encephalitis in eastern Finland

Corresponding Author:

Dr. Jussi Sipilä, Department of Neurology, North Karelia Central Hospital, Tikkamäentie 16, FI-80521 Joensuu, Finland

Keywords: autoimmune, encephalitis, epidemiology, incidence, virus

Abstract

Introduction: The epidemiology of encephalitis varies by region and time. Available Finnish data are outdated and there are no data from eastern parts of the country nor concerning the occurrence autoimmune encephalitides.

Material and methods: Patients with encephalitis were identified from mandatory administrative registries in North Karelia Central Hospital. The diagnoses were verified, and data extracted by reviewing the patient records. Study period was 2010-2021. Only patients >16 years of age were included.

Results: 51 patients with a clinical encephalitis were identified (55 % men) identified with a median age of 65 years [interquartile range (IQR) 45, 73; total age range 16-88 years] indicating a crude incidence of 3.1/100,000 person-years for the entire study period. A specific aetiology could be identified in 31 cases (61 %) with Tick-borne encephalitis (TBE) being the most common one (20 % of all 51 cases), followed by Herpes simplex virus type 1 (HSV-1, 16 %) and Varicella Zoster virus (VZV, 14 %). Autoimmune aetiology was confirmed in 10 %. TBE was most often found in the youngest age group (16-52 years of age) and the herpes viruses in the oldest group (71 years or older). A specific cause was most often identified in the oldest patients (78 %). TBE patients were younger than patients with VZV (p=0.0009) or HSV-1 (p=0.0057) but there was no difference when they were compared to patients with autoimmune (p=0.27) or unknown (p=0.074) aetiology.

At presentation, there were differences in the occurrence of some clinical signs and symptoms between aetiologies but nothing specific. Eight patients (16 %) were immunosuppressed. Inpatient seizures occurred in 10 patients (20 %). In these cases, the etiology was HSV-1 in 50 % and TBE or VZV in none. A full recovery was observed in 51 % of all patients while three patients (6 %) had died of the encephalitis while in hospital or shortly after discharge.

Conclusions: Adult-onset encephalitis was more common and the patients older in easternmost Finland than previously reported in other parts of the country. TBE, HSV-1 and VZV are the most commonly identified specific aetiologies whereas a fifth of the cases are probably caused by autoimmunity. Prognosis depended on aetiology but was very good in the majority of cases

Introduction

Globally, encephalitis causes as much years lived with disability as Multiple Sclerosis or melanoma and leukemia combined [1]. However, its burden varies at regional and national levels and appears to be constantly changing, probably because of changes in population structures and the climate. Nevertheless, the disability burden caused by encephalitis has remained stable between 1990 and 2019 in Western Europe [2]. The increase in arthropod-borne viruses, such as tick-borne encephalitis (TBE), has therefore either not occurred or at least not led to considerable increase in disability. Proven efficacy of the vaccines available against TBE may have contributed to this [3]. Alternatively, disability caused by other etiologies may have decreased. Increased knowledge about autoimmune encephalitides and how to treat them during the last 20 years may have contributed to this [4]. These disorders appear to be as common as infectious encephalitides and they often respond to immunotherapy which improves outcomes, especially when started early.

Previous Finnish data have documented the shift from TBE in the early 1960's to Herpes Simplex Virus type 1 (HSV-1) as the most often identified etiology of encephalitis from late 1960's at least up to 1991 in the southern part of the country [5, 6]. Moreover, TBE had virtually disappeared as a cause of encephalitis [6]. On the other hand, in national data from 1995-1996 Varicella Zoster Virus (VZV) was by far the most common identified cause of encephalitis with a threefold number of cases compared to HSV-1 [7]. VZV was the most common identified cause (12 %) also in 1999-2003 data from southwestern Finland, but HSV-1 and TBE were nearly as common (both 9 %) [8]. No data are available after that, except for a paper in Finnish reporting on TBE in 2010-2012, which showed a marked increase of annual cases nationally when comparing the situation to that of two decades earlier [9].

In addition to this national paucity of data concerning the recent decades, there are no data available at all on encephalitis in easternmost parts of Finland. There are also no data on the epidemiology of autoimmune encephalitides in Finland. This study was devised to provide these data.

Methods

People admitted to or discharged from North Karelia Central Hospital, a non-academic facility that is the sole provider of acute neurological care in this area for circa 140,000 adults, with a diagnostic code indicating encephalitis (International Classification of Diseases, 10th version: A83.X A84.X, A85.X, A87.9, A92.2, G04.X, G05.X) in 2010-2021 were identified from the hospital registries (N=154). Clinical diagnosis of encephalitis was used as the inclusion criterion [10]. Electronic patient

charts were used to confirm the diagnoses and extract clinical data. Patients younger than 16 years of age were excluded. For age group analyses, the data were divided into three categories of equal size: 16-52 years of age, 55-70 years of age and those 71 or older. Recovery from encephalitis was evaluated with the Glasgow Outcome Scale (GOS) at the end of follow-up or when another chronic condition manifested, whichever took place first. The total person years at risk for this population was calculated using the annual numbers of persons at least 16 years of age living in the area according to the open database of Statistics Finland (https://statfin.stat.fi/PxWeb/pxweb/fi/StatFin/StatFin__vaerak/statfin_vaerak_pxt_11re.px/).

Shapiro-Wilk and Kolmogorov-Smirnov tests were used to analyse age distribution and unpaired t-test or Independent-Samples Mann-Whitney U Test utilized accordingly. Analyses were conducted using SPSS Statistics, version 29 and Graphpad Prism, version 10.0.3.

Results

Altogether 51 local persons (55 % men) with an encephalitis were identified with a median age of 65 years [interquartile range (IQR) 45, 73; total age range 16-88 years; p=0.20 for difference between sexes] indicating a crude incidence of 3.1/100,000 person-years for the entire 12-year study period (Fig. 1).

Aetiology was suspected to be infectious in 59 %, autoimmune in 21 % and remained totally unknown in 20 %. A specific aetiology could be identified in 31 cases (61 %) with TBE (20 % of all 51 cases, crude incidence 0.5/100,000) being the most common one, closely followed by HSV-1 (16 %, crude incidence 0.4/100,000) and VZV (14 %, crude incidence 0.6/100,000) (table 1). Autoimmune aetiology was confirmed in 10 % (one case each of NMDAR, LGI1 and SEZ6L2 encephalitis in addition to two cases of paraneoplastic encephalitis of which one manifested several autoantibodies and the other none that could be identified), yielding a crude incidence of 0.3/100,000. Syphilis was identified in one case and grouped as “other” along with the unidentified cases in Figure 1 and table 1.

	Age group			
Aetiology	**16-52 years**	**55-70 years**	**71-88 years**	**All**
TBE	35 %	19 %	6 %	20 %
HSV-1	6 %	6 %	33 %	16 %
VZV	0 %	13 %	28 %	14 %
Autoimmune	12 %	6 %	11 %	10 %
Other/unknown	47 %	56 %	22 %	41 %

Table 1. The proportions of specific aetiologies by age group. HSV-1, Herpes simplex virus type 1; TBE, Tick Borne Encephalitis virus; VZV, Varicella Zoster virus.

TBE was most often found in the youngest age group and the herpes viruses in the oldest group while autoimmune causes did not show any preference according to age (table 1). A specific cause was most often identified in the oldest patients (78 % of cases). TBE patients were younger than patients with VZV or HSV-1 (Fig, 2) but there was no difference when they were compared to patients with autoimmune (p=0.27) or unknown (p=0.074) aetiology.

At presentation, all TBE patients had a fever and the majority also a headache whereas lethargy and seizures were most common with HSV-1 and change in behaviour with VZV (table 2). In the patients whose aetiology remained unknown, a change in behaviour was the most often recorded clinical finding but it was still far less common than in VZV. Eight patients (16 %) were immunosuppressed (of which 63 % in the oldest age group) with HSV-1, VZV and paraneoplastic encephalitis each diagnosed in two cases and two remaining of unknown aetiology.

	GCS	**Fever**	**Headache**	**Lethargy**	**Seizure**	**Change in behaviour**	**Focal neurological findings**
TBE	15 (13.75, 15)	100 %	70 %	38 %	10 %	30 %	30 %
HSV1	14 (13, 15)	86 %	17 %	71 %	38 %	38 %	13 %

VZV	14 (14, 15)	71 %	14 %	43 %	0 %	100 %	29 %
Unknown	14 (13.25, 14)	35 %	25 %	40 %	16 %	53 %	25 %

Table 2. Clinical signs and symptoms recorded at presentation in the three most common specific aetiologies and in the cases in which the aetiology remained unknown. GCS is presented as median (interquartile range). EEG, electroencephalogram; GCS, Glasgow Coma Scale; HSV-1, Herpes simplex virus type 1; TBE, Tick Borne Encephalitis virus; VZV, Varicella Zoster virus.

Inpatient seizures occurred in 10 patients (20 %). In these cases, the etiology was HSV-1 in 50 % and TBE or VZV in none. A full recovery was observed in 51 % of all patients while three patients (6 %) had died of the encephalitis while in hospital or shortly after discharge (Fig. 3).

Discussion

This study showed that the incidence of adult-onset encephalitis was higher in the easternmost part of Finland than previously reported in southern and southwestern parts of the country. A specific aetiology could now be identified in almost two thirds of the patients with TBE common one, closely followed by HSV-1 and VZV. Moreover, TBE has been mostly detected in last years of the study period suggesting it is becoming more common. Autoimmune aetiologies account for a tenth of all enephalitides in the region, although they had also been detected mostly in the last years of the study period suggesting that improved diagnostic methods may uncover these diseases in the future. The most common aetiologies showed some distinct differences in presentation and the outcome, although usually favourable, also differed between them.

Data from the southern Helsinki area covering the years 1945-1963 reported that, in 108 clinical cases of encephalitis, a specific aetiology could be identified in 40 % with TBE and mumps being the most common ones (approximately 10 % each) [11]. However, in these data 45 % of the patients were <15 years of age. Shortly thereafter HSV replaced TBE as the most common identified aetiology and between 1967 and 1991 TBE virtually disappeared as a cause of encephalitis in the area with only

five identified cases during that period among 322 adult patients with encephalitis (an average 1967-1991 incidence of adult-onset acute encephalitis in Uusimaa region: 1.4/100,000) [5, 6]. During that period, the proportion of patients with an identified aetiology increased from 36 % to 59 % with HSV becoming the most commonly detected culprit (16% of all and 33% of the known etiologies) followed by VZV, mumps, influenza A, and enteroviruses. Interestingly, in that data the number of HSV cases was over three times that of VZV cases whereas in national data covering 1995-1996 VZV was three times as common as HSV [7]. However, the national data included patients of all ages. At the turn of the millennium, an adult-onset encephalitis incidence of 2.2/100,000 was reported for southwestern Finland [8]. In that study, a specific aetiology could be identified in 36 % of all 42 encephalitis cases with VZV being the most common one and closely followed by HSV-1 and TBE with a proportion of approximately 10 % of all cases each. National data also show that the number of TBE cases increased from 5-20/year in 1995-1999 to 25-45/year in 2008-2012 [9]. Moreover, in every year from 2005 onwards, the majority of cases had been diagnosed outside the traditional hotspot of Åland archipelago. These developments are not surprising considering that TBE has become more common at least in Europe and Asia and in Finland tick contact areas have expanded over the past 60 years with observations becoming more common also in in eastern Finland [12-15].The majority of previous studies have globally reported HSV as the most frequent viral pathogen, followed by VZV in several studies. However, regional differences have been reported, especially in case of vector-borne transmission [16]. It is apparent that the incidence and causes of encephalitis vary by time and region and seems possible that TBE is once again becoming the most common cause of encephalitis in Finland. However, comprehensive aetiological data from other areas are definitely needed before any firm conclusions can be made. Differences in population age structures probably also affect the proportions of different aetiologies, as was also evident in our data where TBE most commonly occurred in the youngest age group and herpes viruses were most often found in the eldest patients. Improved methods of diagnosing both herpes viruses and autoimmune aetiologies may also affect the results. However, these data suggest that in a great majority in Finland, adult-onset encephalitis is caused by infectious agents and the proportion of autoimmune aetiologies may be approximately one fifth. In the light of previous data, this allotment appears credible [10]. Interestingly, the current cohort was considerably older than the adult-onset cohorts previously reported from southern and southwestern Finland [6, 8].

Some clinical signs and symptoms were more common in some aetiologies compared to others but no constellation specific to any aetiology emerged. Specific diagnosis therefore still relies on laboratory studies, which fortunately are increasingly available. At the beginning of the study period, diagnostic methods available for aetiological diagnosis at our institution were serological testing from

serum and cerebrospinal fluid (CSF). During the study period, polymerase chain reaction (PCR) testing for infectious pathogens from the CSF became available and increasingly comprehensive with, for example, generic PCR for herpes viruses or bacteriae available at the end of the period. Consequently, serological testing was abandoned during the study period because its results were not deemed to have consequences for clinical care.

Testing for autoimmune antibodies in serum and CSF also became available during the period with comprehensive panels clinically routinely utilized during the last years of the period. Specific autoimmune aetiologies were probably therefore identified mostly in 2018-2021 and the current results concerning the epidemiology of specific autoantibodies should therefore be regarded as preliminary. Indeed, autoimmune aetiology had been confirmed in only 10 % of the current cases but suspected in 21 %, which would have yielded a crude incidence of 0.6/100,000 if all had been confirmed. However, this remains a far cry from the 1.2/100,000 reported for Olmsted county, MN, USA figures [17]. On the other hand, those data showed a four-fold incidence of autoimmune encephalitis among African-Americans compared to Caucasians. Considering that the population of North Karelia is nearly entirely Caucasian, this difference in ethnic backgrounds might explain the difference in incidence. Indeed, recent data from Sweden suggest an annual incidence of 0.3/100,000 person-years for autoimmune encephalitis and paraneoplastic neurological syndrome with a tendency to increase during the study period (2015-2019) [18]. Recent data from Denmark show an incidence of 0.17/100,000 for NMDAR encephalitis alone [19], suggesting that 0.3 certainly is too low and 0.6/100,000 is more likely to reflect true occurrence rate.

In the current data, the majority of patients had an excellent prognosis. Mortality was within the limits considered currently normal [10]. Interestingly, these proportions were nearly identical to those reported for the 1967-1991 Uusimaa data [6]. This probably not only reflects the lack of advances in treating infectious encephalitis in the intervening decades but also the difference in age structures of the cohorts: median age in the previous cohort was in the 25-34 years age group vs. 65 in the current data. Interestingly, none of the fatal cases in the current data had HSV-1, suggesting that our low threshold for using acyclovir in suspected encephalitis is justifiable. The impact of acyclovir was evident also in the previous data from Uusimaa [6]. Nevertheless, it must be remembered that in rare cases acyclovir and valacyclovir can be neurotoxic [20].

Prognosis was worst with VZV suggesting that acyclovir does not benefit these patients as much as those with HSV-1. Best outcomes were observed in the youngest aetiological group, those with TBE, in which only 20 % had residual symptoms (mild to moderate). This appears a much better prognosis compared to that recently reported from Germany [21]. This probably primarily reflects the fact that

prognosis in TBE clearly worsens with increasing age and in the German study 66 % of the included adult patients were >50 years of age whereas 60 % of the TBE cases in the current cohort were <44 years of age. However, the retrospective nature of the current study must also be acknowledged when comparing the results. Outcomes in the three non-paraneoplastic cases with autoantibodies were fair to moderate with all patients responding to therapy, even when SEZ6L2 was the culprit [22].

The main strength of the study is the complete coverage in the area. 9oweverr, the retrospective nature and long time period of the study mean that not only diagnostic methods but also the workflows and resources available to care have changed during the period. The work-up has changed to focus on treatable causes and dwindling resources could be seen to, for example, influence the personnel available to admit the patient and the data available in the clinical notes. Naturally, clinicians also differ in how they appraise and record these, leading to some variability in data quality. Clinical needs also dictated what investigations, and when, had been performed on each patient. Data on CSF and electroencephalogram results were therefore not analysed. Relying on retrospective chart review also increases the possibility of under diagnosis.

In conclusion, adult-onset encephalitis was more common and the patients older in easternmost Finland than previously reported in other parts of the country. TBE, HSV-1 and VZV are the most commonly identified specific aetiologies whereas a fifth of the cases are probably caused by autoimmunity. Prognosis depended on aetiology but was very good in the majority of cases.

Statement of Ethics

Please address the following aspects in your Statement of Ethics.

Study approval statement: This study was approved by the regional registry keeper Siun Sote (). This was a retrospective register study, and thus no ethical board review or informed consent was required, and the participants were not contacted. The legal basis for processing personal data is public interest and scientific research (EU General Data Protection Regulation 2016/679, Article 6(1)€ and Article 9(2)(j); Data Protection Act, Sections 4 and 6).

Consent to participate statement: According to Finnish law, written informed consent was not required because the patients were not contacted.

Conflict of Interest Statement

Jussi Sipilä has received honoraria (Terveystalo/Novartis), consultancy fees (Medaffcon/gmp-orphan, Sandoz), travel grants and congress sponsorship (Lundbeck) and holds shares (Orion Corporation).

Funding Sources

This study was not supported by any sponsor or funder.

Data Availability Statement

The author is not permitted to disclose data to third parties. Requests to access the data set may be sent to Siun Sote.

References

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1789-1858.
2. Wang H, Zhao S, Wang S, Zheng Y, Wang S, Chen H, et al. Global magnitude of encephalitis burden and its evolving pattern over the past 30 years. *J Infect*. 2022;84:777-787.
3. Miazga W, Wnuk K, Tatara T, Świtalski J, Matera A, Religioni U, et al. The long-term efficacy of tick-borne encephalitis vaccines available in Euro–e - a systematic review. *BMC Infect Dis*. 2023;23:621.
4. Uy CE, Binks S, Irani SR. Autoimmune encephalitis: clinical spectrum and management. *Pract Neurol*. 2021;21:412-423.
5. Koskiniemi ML, Vaheri A. Acute encephalitis of viral origin. *Scand J Infect Dis*. 1982;14:181-187.
6. Rantalaiho T, Färkkilä M, Vaheri A, Koskiniemi M. Acute encephalitis from 1967 to 1991. *J Neurol Sci*. 2001;184:169-177.
7. Koskiniemi M, Rantalaiho T, Piiparinen H, von Bonsdorff CH, Färkkilä M, Järvinen A, et al. Infections of the central nervous system of suspected viral origin: a collaborative study from Finland. *J Neurovirol*. 2001;7:400-408.
8. Etiology of aseptic meningitis and encephalitis in an adult population. Etiology of aseptic meningitis and encephalitis in an adult population. *Neurology.* 2006;66:75–80
9. Metsi J, Vuorela M, Kantele A, Kuusi M, Oksi J. [Tick-borne encephalitis in Finland from 2010 to 2012]. *Duodecim*. 2015;131:1367–1375
10. Venkatesan A, Michael BD, Probasco JC, Geocadin RG, Solomon T. Acute encephalitis in immunocompetent adults. *Lancet*. 2019;393:702-716.

11. Klemola E, Kääriäinen L, Ollila O, Pettersson T, Jansson E, Haapanen L, et al. Studies on Viral Encephalitis. *Acta Med Scand*. 1965;177:707-716.
12. Sormunen JJ, Sääksjärvi IE, Vesterinen EJ, Klemola T. Crowdsourced tick observation data from across 60 years reveals major increases and northwards shifts in tick contact areas in Finland. Sci Rep. 2023;13:21274.
13. Sormunen JJ, Andersson T, Aspi J, Bäck J, Cederberg T, Haavisto N, et al. Monitoring of ticks and tick-borne pathogens through a nationwide research station network in Finland. Ticks Tick Borne Dis. 2020;11:101449.
14. Kwasnik M, Rola J, Rozek W. Tick-Borne Encephalitis—Review of the Current Status. J. Clin. Med. 2023, 12(20), 6603.
15. Ohira M, Yoshii K, Aso Y, Nakajima H, Yamashita T, Takahashi-Iwata I, et al. First evidence of tick-borne encephalitis (TBE) outside of Hokkaido Island in Japan. Emerg Microbes Infect. 2023 Dec;12(2):2278898.
16. Boucher A, Herrmann JL, Morand P, Buzelé R, Crabol Y, Stahl JP, et al. Epidemiology of infectious encephalitis causes in 2016. Med Mal Infect. 2017;47:221-235.
17. Dubey D, Pittock SJ, Kelly CR, McKeon A, Lopez-Chiriboga AS, Lennon VA, et al. Autoimmune Encephalitis Epidemiology and a comparison to Infectious Encephalitis. Ann Neurol. 2018;83:166-177.
18. Kosek S, Persson B, Rodrigues R, Malmeström C, Punga AR, Burman J. Antibody-Positive Autoimmune Encephalitis and Paraneoplastic Neurological Syndrome: Epidemiology and Outcome of Neuronal Antibody Testing in Sweden. Acta Neurol Scand. 2023: 6993615
19. Nissen MS, Ørvik MS, Nilsson AC, Ryding M, Lydolph M, Blaabjerg M. NMDA-receptor encephalitis in Denmark from 2009 to 2019: a national cohort study. J Neurol. 2022;269:1618-1630.

20. Brandariz-Nuñez D, Correas-Sanahuja M, Maya-Gallego S, Martín Herranz I. Neurotoxicity associated with acyclovir and valacyclovir: A systematic review of cases. J Clin Pharm Ther. 2021;46:918-926.
21. Nygren TM, Pilic A, Böhmer MM, Wagner-Wiening C, Wichmann O, Hellenbrand W. Recovery and sequelae in 523 adults and children with tick-borne encephalitis in Germany. *Infection.* 2023;51:1503–1511
22. Mehdiyeva A, Hietaharju A, Sipilä J. SEZ6L2 Antibody-Associated Cerebellar Ataxia Responsive to Sequential Immunotherapy. *Neurol Neuroimmunol Neuroinflamm*. 2022;9:e1131.

Figure Legends

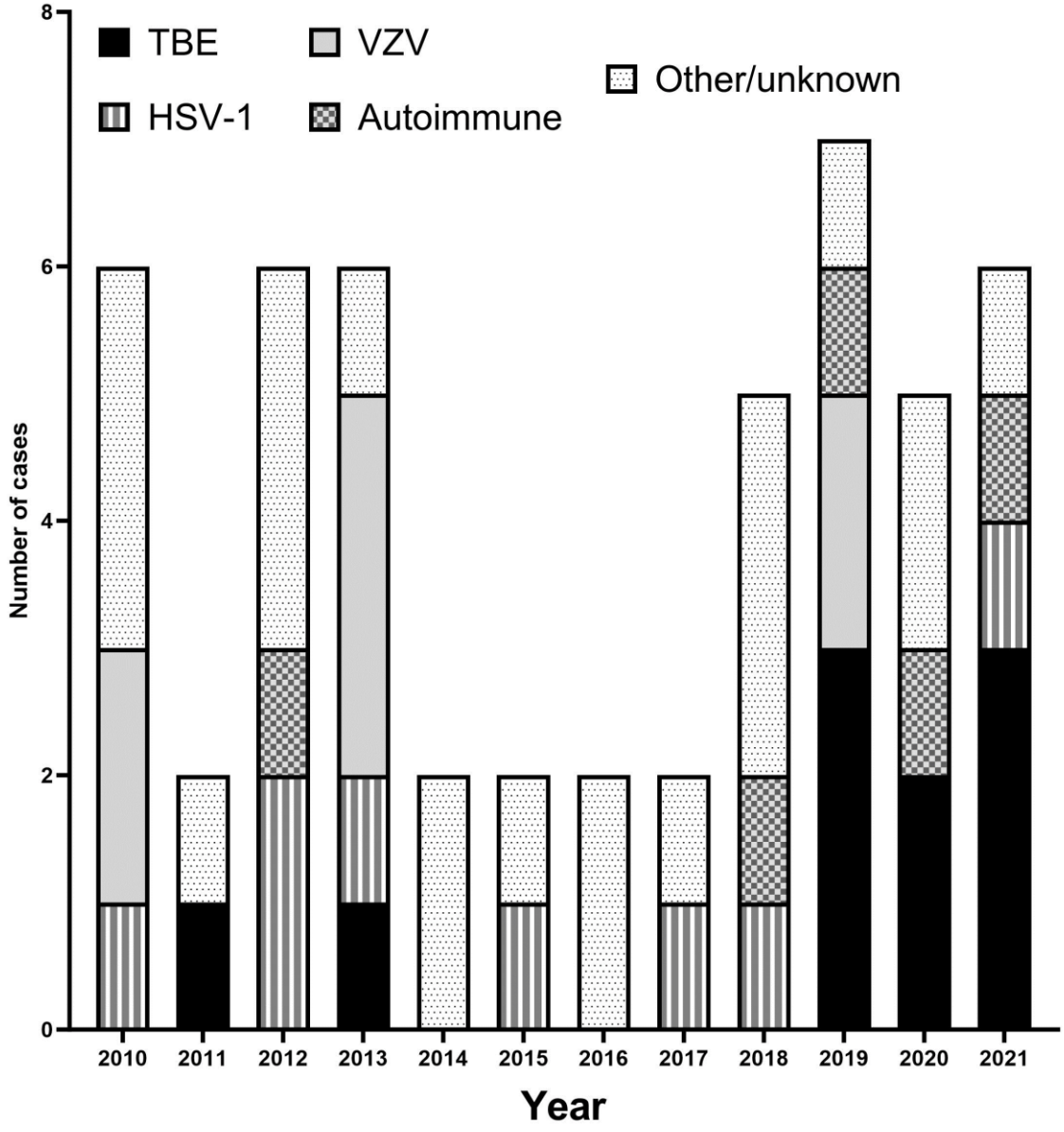

Fig. 1. The number of cases per specific aetiology according to year of admission. HSV-1, Herpes simplex virus type 1; TBE, Tick Borne Encephalitis virus; VZV, Varicella Zoster virus.

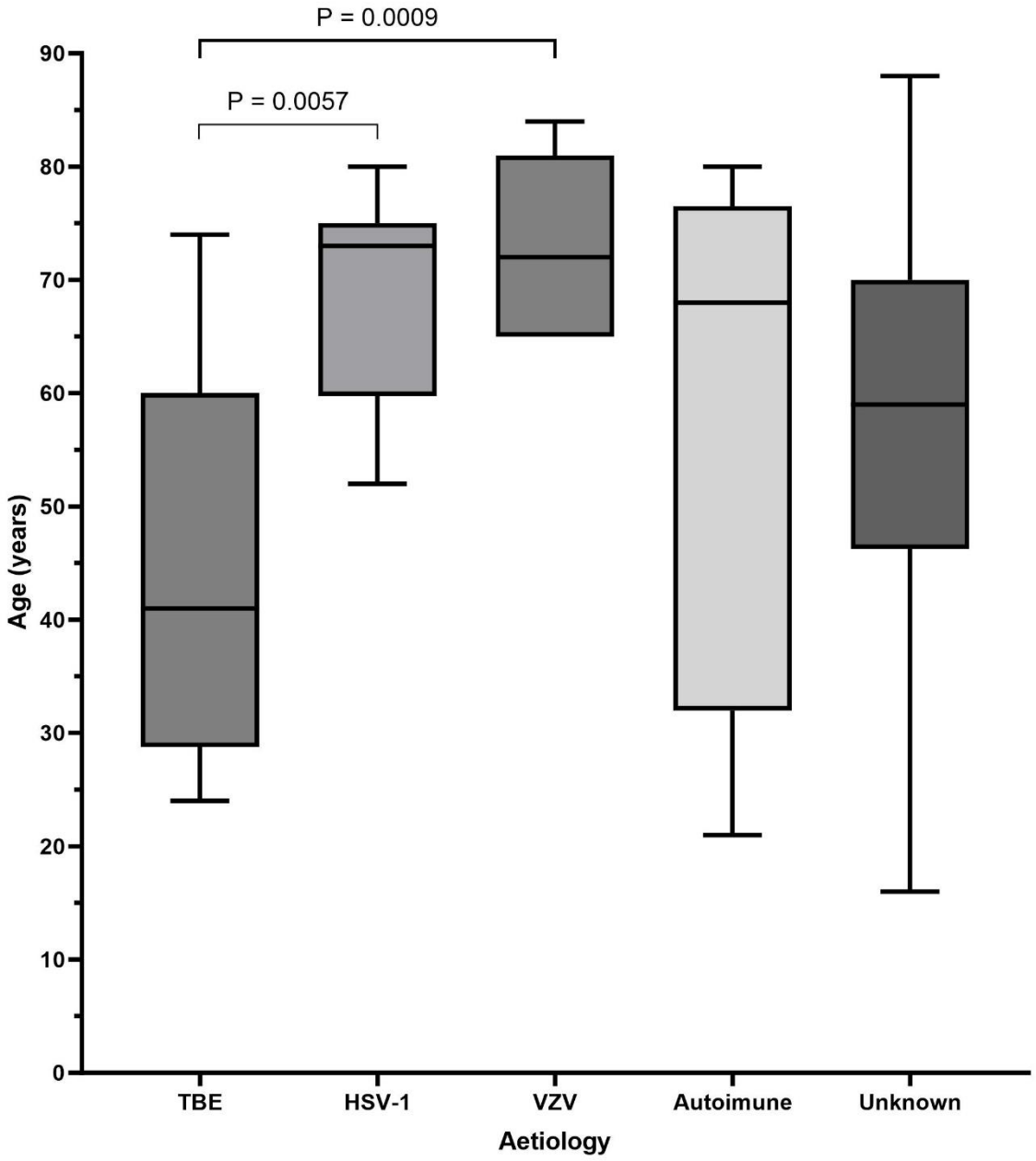

Fig. 2. Patient age according to encephalitis aetiology.

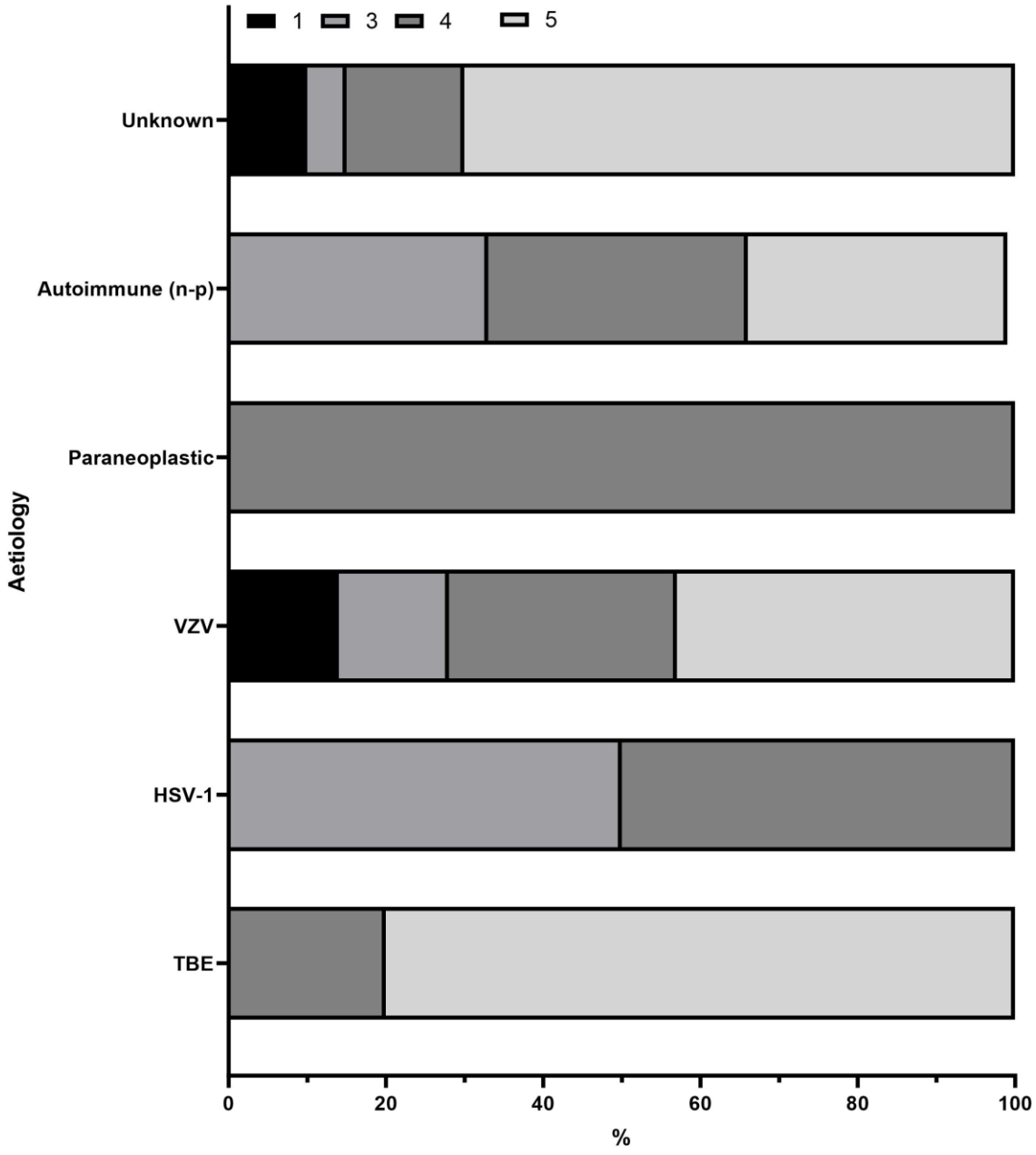

Fig. 3. Outcomes according to aetiology as Glasgow Outcome Scale scores. HSV-1, Herpes simplex virus type 1; n-p, non-paraneoplastic; TBE, Tick Borne Encephalitis virus; VZV, Varicella Zoster virus.