Admission sodium level and prognosis in adult Guillain-Barré syndrome

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Abstract

**Purpose:** Guillain-Barré syndrome (GBS) varies in severity and outcome. Hyponatraemia predicts poor outcome but previous studies have used divergent methodology and (pseudo)hyponatraemia caused by IVIG administration may confound analysis. We studied if the plasma sodium level at admission was associated with GBS outcome.

**Methods:** All 69 patients at least 16 years of age treated for GBS in Turku University Hospital in 2004-2013 were included in the study. Clinical information was obtained from patient charts.

**Results:** Women had lower sodium levels at admission (138; IQR 135, 140) compared to men (140; IQR 138, 142; p=0.0116) but no association of sodium levels with demographics, pre-hospital variables or basic GBS characteristics was found. Multivariate analyses showed lower admission sodium levels to be associated with worse functional status at one year from disease onset (OR 1.37; 95% CI 1.07-1.76; p=0.0136) and probability of being discharged to another care facility from the hospital (OR 1.31; 95% CI 1.05-1.64; p=0.0180) but not associated with need of ICU care (p=0.09) or mechanical ventilation (p=0.45), length of hospital stay (p=0.48) or functional status at six months (p=0.07).

**Conclusions:** Low plasma sodium level at admission is associated with a more severe disease course and a worse outcome in GBS independently of previously identified prognostic factors. Hyponatraemia does not, however, appear to be caused by disease-specific factors.
Introduction

Guillain-Barré syndrome (GBS) is an acute, monophasic inflammatory polyradiculitis usually triggered by infection [1,2]. The disease is immune-mediated but the exact pathophysiological mechanism is still unknown [3]. Symptoms usually start from the lower extremities and progress in cranial direction reaching their nadir in four weeks from symptom onset. The clinical presentation may be slightly variable and the diagnosis is reached by combining patient history, clinical neurological examination, cerebrospinal fluid (CSF) analysis and electrophysiological studies [4]. Patients usually recover well, but healing may take years [5] and mortality is 5% even with modern treatment [6]. Plasma exchange (PE) [7] and intravenous immunoglobulin (IVIG) [8] treatments have been shown to be efficacious.

Several attempts have been made at creating a reliable rating scale for GBS which could also predict outcomes. Higher age, preceding diarrhoea, greater disability/weaker muscles at admission, short interval between symptom-onset and admission, mechanical ventilation and absent/low amplitude compound muscle action potentials have been consistently shown to be negative predictors of outcome. [5,9] Need of mechanical ventilation, in turn, has been shown to be predicted by time from onset of weakness to admission, Medical Research Council (MRC) sum score, and presence of facial and/or bulbar weakness. [10] Many of these, however, are yet unknown at the time of admission and thus cannot be used in contemplating the measures probably needed during the stay.

Hyponatraemia at some stage of illness, usually attributed to Syndrome of Inappropriate secretion of Antidiuretic Hormone (SIADH), is a documented feature in some patients with GBS [11-13] and has been reported even as the initial symptom [14]. Low plasma sodium level at some point of disease has been associated with mortality [11,12]. The assessment of serum sodium concentrations may nevertheless be confounded by (pseudo)hyponatraemia caused
by IVIG administration [15,16] Studies investigating hyponatraemia in GBS have used divergent methodologies of timing of measurement as well as different cut-off values to define hyponatraemia itself and risked confounding by treatment [13]. Since plasma sodium levels at admission have been shown to be prognostic factor in many other diseases [17], are clearly definable and free from bias of iatrogenic hyponatraemia, we sought to establish whether plasma sodium concentration at admission to hospital predicted clinical course and outcomes of GBS without using cut-off values.

Materials and methods

Study design and patients

The methods of ascertainment and basic clinical features of the patients have been reported earlier [2]. In brief, we searched the Turku University Hospital (TYKS) discharge records for all adult patients (over 16 years of age) treated for GBS in 2004-2013 and found 69 persons with a diagnosis that was valid according to the slightly modified Swiss Neurological Society criteria for GBS [2]. The diagnosis was confirmed and data gathered by chart review. Previously identified outcome predictors were analyzed in the following manner: age as a continuous variable, GBS trigger as a dichotomous variable (gastroenteritis versus other/unknown), muscle weakness by the ability to walk (unaided versus only with aid/unable), interval between symptom onset and admission as a continuous variable. The following variables were used to assess disease course and outcome: need of care in the Intensive Care Unit (ICU) as a dichotomous variable (yes versus no), need of mechanical ventilation as a dichotomous variable (yes versus no), mode of discharge as a dichotomous variable (home versus any other care facility) and length of hospital stay as a continuous variable. Functional status was assessed at six months and one year from disease onset using the modified Rankin scale (mRS). As this was a retrospective study involving no contact with
patients review by an ethics board was not mandated but the study was reviewed and approved by the Clinical Research Center of TYKS.

**Statistical analyses**

Categorical variables are presented as frequencies and proportions (percentages) while continuous variables are presented as means and standard deviations or as medians and interquartile ranges (IQR) due to their skewed distributions which were tested against normal distribution using Shapiro-Wilk’s test of normality. Differences of continuous variables between groups were tested with Wilcoxon’s Rank Sum test. Categorical variables as a response were modeled using univariate logistic regression. Model fit was evaluated with Likelihood Ratio test and raw residuals, if the assumptions were not satisfied, Wilcoxon Rank Sum test or Pearson’s Chi-Squared test were applied for continuous and categorical independent variables, respectively. Further on, multivariable logistic regression and multivariable linear regression models were fitted for categorical and continuous responses respectively in order to adjust for principal variables which were sodium level, time from symptom onset, age, gender, GBS trigger and inability to walk unassisted. Continuous response variables were log-transformed in order to attain normality for linear regression fitting. Linear regression fit was evaluated with scaled Pearson Chi-Square fit statistic and raw residuals. Estimates are presented as Odds Ratios (OR) for logistic regression models or mean rates (geometric means) for linear regression models due to back-transformations from the log-transformed scales. P-values less than 0.05 are considered statistically significant. All p-values from multiple comparisons were Bonferroni corrected.

All analyses were conducted with SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

**Results**
Plasma sodium levels at admission (table 1)

Admission plasma samples were obtained on median 5 days (IQR 2-9) after the onset of symptoms with a median sodium concentration of 139 mmol/l (IQR 137-141). The concentration was not associated with time from trigger factor to symptom onset (p=0.52), time from symptom onset to admission (p=0.55) or age (p=0.26). Women had lower sodium levels than men (p=0.0116; Wilcoxon Rank Sum test) but no differences were found between types of GBS (p=0.21; Wilcoxon Rank Sum test) or trigger (p=0.99; Wilcoxon Rank Sum test) or results of diagnostic tests. On admission, 10 patients used medication that could affect sodium levels and their sodium levels did not differ from the levels of those who did not use such medication (139.5 vs. 139; p=0.61; Wilcoxon Rank Sum test). During the course of their disease, 53 patients were treated with IVIG (five patients received two courses) and 8 patients with PE (five of them had received IVIG prior to PE treatment) but no patient had received either of these treatments before the evaluation of admission sodium levels.

Univariate analyses of sodium levels and prognosis (figure)

In univariate analyses plasma sodium levels on admission were lower in the 11 patients who were eventually admitted to the Intensive Care Unit (ICU) compared those who were not (Wilcoxon Rank Sum test) and in those 29 who were eventually discharged at least initially to another care facility when compared to those who could be discharged straight home from the hospital (logistic regression; one patient had a very mild disease and was treated as an outpatient). Mean duration of hospital admission was 19.1 ± 16.3 days (range 0-68) and the 39 patients who were discharged straight home also had shorter hospitalizations [11.0 (IQR 6, 15) vs. 22 (IQR 12, 42); p=0.0006, Wilcoxon Rank-Sum test]. Plasma sodium on admission did not correlate with the duration of stay (p=0.21, linear regression) but no association was found with need of mechanical
ventilation, required by 10 patients (Wilcoxon Rank Sum test). Lower plasma sodium levels at admission were associated with worse functional status both at six months (N=42, OR=0.80 (95% CI 0.67-0.97), p=0.0206) and one year (N=33, OR=0.81 (95% CI 0.67-0.99), p=0.0361) from disease onset (logistic regression).

**Multivariate analyses of sodium levels and prognosis (table 2)**

In multivariate analyses sodium levels on admission were found to have negative effect to functional status at one year from disease onset (multivariable logistic regression) and probability of being discharged to another care facility from the hospital (multivariable logistic regression). Short duration from symptom onset to admission, advanced age and any other or unknown type of GBS trigger as opposed to gastroenteritis were also found to be negative predictors of more severe disease course whereas advanced age and male gender were associated with worse long-term prognosis. The patients with gastroenteritis as a trigger did not differ from those with other triggers regarding discharge destination (p=0.15, Pearson’s Chi-Squared test).

**Discussion**

In this retrospective cohort study, low plasma sodium concentration at admission was associated with a more severe clinical course and worse prognosis even when previously established prognostic parameters were taken into account.

Hyponatraemia has been associated with many neuroimmunological disorders such as autoimmune encephalitis associated with antibodies against voltage-gated potassium channel (VGKC) complex [18,19] in which it also predict progression [20], Neuromyelitis Optica (NMO) [21] and Schmidt’s syndrome [22]. The mechanism of hyponatraemia in neuroimmunological disorders is usually attributed to SIADH [12,23] which has been connected to hypothalamic inflammation [24] but psychogenic polydipsia has also been described [25]. SIADH is the
mechanism most often proposed for hyponatraemia also in GBS [26-28], but and iatrogenic (pseudo)hyponatraemia caused by administration of IVIG has been documented [11,15,16] and renal salt wasting because of dysautonomia has also been suggested [29]. However, recent research suggests that hyponatraemia in GBS is not disease-specific [13] and the lack of association between sodium levels and factors such as GBS type, also reported earlier [12], and severe neuromuscular affection necessitating mechanical ventilation in our study support this view. It appears that hyponatraemia is rather an indicator of more severe disruption of homeostasis regardless of the disease [13,17].

Previous studies have consistently associated hyponatraemia with a worse prognosis in GBS. [11-13,30] They have, however, used divergent methodology and risked confounding by treatment, which is why we studied sodium levels before any treatment had been initiated. Our results confirm the association between intrinsic sodium level and prognosis in GBS with low plasma sodium levels at admission predicting more severe disease course and worse outcome. Considering our retrospective study design and modest cohort size, these results should be considered preliminary and, before clinical use is considered, their prognostic relevance needs to be further defined in a larger prospective study to find out whether admission sodium level gives also clinically relevant additional value. If so, it could be used to identify patients possibly needing ICU care and more close monitoring, as well as in discharge and follow-up planning. At the moment, admission sodium level should not be used as a predictor of disease course on individual level and should not affect patient care or information given beyond the point of necessary measures to rectify the patient’s electrolyte and fluid balance. However, considering the message hyponatraemia conveys about the patient’s general homeostasis, the attending physician would do well to take this into account on the general level.

This was a retrospective study and the data at our disposal was slightly varying and not optimal for a scientific assessment thus necessitating the use of outcome measures such as the
mRS. Also, clinical prediction scores developed for GBS, such as MRC sumscores, were unavailable. This is partly compensated for by the use of single expert (first author) chart review and the fact that all patients were assessed and treated in a single university hospital minimizing the effect of local practice procedures. There were no data available to assess the etiology of low serum sodium levels. The sodium levels were, however, assessed in a single university hospital laboratory, accredited by the Finnish Accreditation Service (FINAS) based on internationally agreed criteria, increasing their comparability. Our cohort size is modest but the results conform to those previously reported. Rarity of cranial nerve involvement at the time of presentation in such a limited cohort also made it impossible to analyze the significance of bulbar palsy as a mediator of admission of sodium levels.

In conclusion, low plasma sodium level at admission is associated with a more severe disease course of GBS and worse outcome independently of previously identified prognostic factors. Low plasma sodium levels, however, do not appear to be associated specifically with GBS but probably reflect a general dyshomeostatic state associated with severe disease.
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Declaration of interests

Jussi Sipilä has attended conferences at the cost of a pharmaceutical company (Orion Corporation, Lundbeck, Sanquin, Merck Serono), received lecture fees (Boehringer Ingelheim, scientific medical society Duodecim) and holds shares (Orion Corporation)

Tommi Kauko has no conflicts of interest

Merja Soilu-Hänninen has attended conferences at the cost of pharmaceutical companies and got lecture, consulting and investigator fees from pharmaceutical companies (Astra-Tech, Bayer, Biogen-Idec, Eisai, Genzyme, GSK, Lundbeck, Merck, Novartis, Orion, Sanofi-Aventis, UCB).
REFERENCES


14. Kloesel B, Hickson LJ. Severe hyponatremia as the initial sign preceding Guillain-Barré 
syndrome, an acute inflammatory demyelinating neuropathy: a case report. Case Rep Neurol 

15. Nguyen MK, Rastogi A, Kurtz I. True hyponatremia secondary to intravenous 

16. Steinberger BA, Ford SM, Coleman TA. Intravenous immunoglobulin therapy results in 
post-infusional hyperproteinemia, increased serum viscosity, and pseudohyponatremia. Am 

17. Assadolahi K, Hastings IM, Beeching NJ, Gill GV. Laboratory risk factors for hospital 
mortality in acutely admitted patients. QJM. 2007;100:501-507.

gated potassium channel autoimmunity mimicking Creutzfeldt-Jacob disease. Arch Neurol. 
2008;65:1341-6.


neuromyelitis optica presenting with syndrome of inappropriate antidiuretic hormone 


Figure. Differences in plasma sodium levels at admission analyzed with reference to eventual need of care in the Intensive Care Unit (ICU), eventual discharge destination from the hospital and eventual need of mechanical ventilation. Boxes depict interquartile ranges (IQR) with median values marked with a line inside the box. The whiskers represent the nearest data points within 1.5 times the IQR. The hollow dots represent individual outlier data points.