

A Prognostic Value of Neuron-Specific Enolase in Cerebrospinal Fluid of Acute Cerebellar Ataxia

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We examined 16 patients with acute cerebellar ataxia (ACA) to determine whether clinical manifestations or laboratory findings could predict the prognosis of ACA. We divided the patients into two groups: a benign group of patients whose cerebellar symptoms completely disappeared within 21 days (9 patients), and a prolonged group of patients whose cerebellar symptoms persisted for more than 22 days (7 patients). The two groups were compared on the basis of demographic and clinical characteristics, and laboratory variables.

The cerebellar symptoms did not differ significantly between the two groups, except in duration. The level of neuron-specific enolase (NSE) in the cerebrospinal fluid (CSF) of the prolonged group was significantly higher than that of the benign group ($p < 0.01$); other parameters, including protein and cell count in the CSF, were not significantly different. The results suggest that the NSE level in CSF is of prognostic value in ACA.

Key words: acute cerebellar ataxia, acute cerebellitis, neuron-specific enolase

INTRODUCTION

Acute cerebellar ataxia (ACA), which manifests itself as a sudden disturbance of gait and balance, is considered to be a self-limiting disease following viral infections. Connolly *et al.* reported that although the majority of patients with ACA recovered normal gait and fine motor control after 1 to 2 months, 9% of patients with ACA presented cerebellar symptoms more than 4 months later, and whereas the persistence of gait ataxia for 6 months was not predicted [1].

Prognosis of ACA has varied considerably in previous reports [2-6]. However, there have been few reports of the prognosis and sequelae of ACA [7-8]. In this study, we investigated the demographic and clinical characteristics of ACA to determine the prognostic factors of ACA.

PATIENTS AND METHODS

From April 1, 1984, to January 3, 2002, we examined 16 children (11 boys, 5 girls) with ACA who were admitted to Saitama Children's Medical Center. ACA was diagnosed in the case of acute onset of gait ataxia and the absence, after a thorough examination, of neuroblastoma or other tumors, polyneuritis, opsoclonus polymyoclonia syndrome, meningitis, intoxication, metabolic disease, and familial/degenerative disorders as the cause of the ataxia [1, 9]. ADEM and other neurological diseases were distinguished by the MRI test, WBC count and protein concentration in the cerebrospinal fluid, nerve conduction evaluation, and anti-ganglioside antibody measurement.

We divided the patients into two groups; a benign

group whose cerebellar symptoms improved within 21 days, and a prolonged group whose cerebellar symptoms exceeded 21 days. We compared the clinical symptoms and laboratory variables between the two groups to determine prognostic indicators.

None of the patients had a history of seizure or epilepsy. None of the patients in the benign group were administered drugs. In the prolonged group, three patients were not administered drugs, two were administered oral prednisolone, and two were given steroid pulse therapy.

The demographic and clinical characteristics of all patients with ACA were studied. These included gender, onset age, interval period (from prodromal illness to the onset of cerebellar symptoms), duration of cerebellar symptoms, nystagmus, truncal ataxia, tremor speech disturbance, imaging study, and laboratory variables. Truncal ataxia was estimated as grade 1 (waddling gait), grade 2 (wide-base stance), grade 3 (sitting alone), grade 4 (lying) at the peak of the symptoms. Laboratory variables included protein concentration, cell count and neuron-specific enolase (NSE) in the cerebrospinal fluid (CSF). The interval between the onset of ACA and CSF sampling in the benign group was 2.33 ± 1.5 days (mean \pm S. D.); for the prolonged group, 8.43 ± 9.9 days. The average interval in the prolonged group was longer, but there was no significant difference between them ($p = 0.053$ by the Mann-Whitney test).

Our protocol was approved by our pediatric department's review board. Informed consent was obtained from all patients and their guardians for review of the patient data.

Table 1 Demographic characters

		Benign group	Prolonged group
No. of patients		9	7
Male/Female		7/2	4/3
Onset age (month)	Average	48.3	50
	Range	11-145	17-132
Interval period* (day)	Average	6.8	9
	Range	3-14	4-15
Duration of cerebellar symptoms (day)	Average	10.5	139
	Range	7-21	28-365

* interval period: from prodromal illness to onset of cerebellar symptoms

Table 2 Comparison of cerebellar symptoms

		Benign group n (%)	Prolonged group n (%)
Nystagmus		2 (22.2)	4 (57.1)
Tremor		5 (55.5)	6 (85.7)
Speech disturbance		0 (0.0)	3 (42.8)
Truncal ataxia*			
	grade1	2 (22.2)	2 (28.5)
	grade2	1 (11.1)	2 (28.5)
	grade3	3 (33.3)	1 (14.2)
	grade4	3 (33.3)	2 (28.5)

* grade 1: waddling gait, grade 2: wide-base standing, grade 3: sitting alone, grade 4: lying

Statistical analysis of cerebellar symptoms was established using a χ square test. A non-parametric analysis of variance (Mann-Whitney's U test) was performed to assess any differences in the data between the two groups.

RESULT

The demographic characteristics of the two groups are shown in Table 1. The benign group consists of 9 patients (7 boys and 2 girls); the prolonged group, 7 patients (4 boys and 3 girls). All children had had prodromal illnesses. In the benign group, four patients had had chickenpox; one, rubella; and four, presumed viral illness. In the prolonged group, one had had chickenpox; and six, presumed viral illness. There were no significant differences in onset age or interval period between the two groups; in cerebellar symptoms between the two groups with concerning nystagmus, speech disturbance or truncal ataxia (Table 2); or between the two groups without frequency of tremors.

All patients were given CT and/or MRI scan, which showed no abnormality, except for one patient. The MRI scan of one patient in the prolonged group showed an area of increasing T2-weighted resonance in the left cerebellar hemisphere, which persisted for 4 months, and had atrophied when examined in a scan 3 years later. ^{123}I -IMP SPECT studies performed on four patients in the prolonged group revealed hyper-

perfusion in the left cerebellar hemisphere during the acute phase in just one patient: the one with abnormal MRI findings.

CSF protein concentration in the prolonged group tended to be lower than that in the benign group, while the CSF cell count in the prolonged group tended to be higher than that in the benign group, but there were no significant difference in these parameters between the two groups (Fig. 1).

The CSF NSE level in the prolonged group ($15.5 \pm 4.7\text{ng/ml}$) was significantly higher than that in the benign group ($10.6 \pm 2.7\text{ ng/ml}$) ($p < 0.01$) (Fig. 1). In the patient whose MRI and ^{123}I -IMP SPECT results displayed abnormal findings in the left cerebellar hemisphere, the level of CSF NSE level was 25 ng/ml: this was the highest among the 16 patients with ACA.

DISCUSSION

NSE, the γ -subunit of enolase, is localized mainly in neurons and neuroectodermal tissue. Elevation of the CSF NSE level is considered to be partially related to the destruction of neurons. The NSE levels in serum and in the CSF were poorly correlated ($p > 0.05$) [12]. Therefore, the CSF NSE level has been measured for use as a sensitive and specific marker of neuronal injury in various neurologic disorders [10-12]. It has also been reported that the neurologic outcome is worse in patients with higher NSE level in the CSF [12]. There

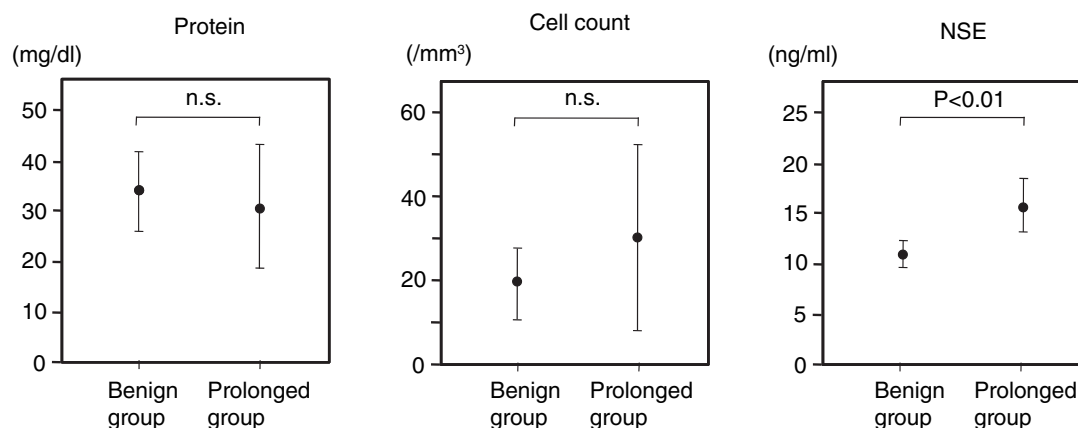


Fig. 1 Comparison of protein, cell count and NSE level in two groups
NSE level in the prolonged group was significantly higher than that in the benign group ($p < 0.01$).
There was no significant difference in protein or and cell count between the two groups.

are no reports of CSF NSE level in children with ACA.

In our study, the CSF NSE level of the prolonged group was significantly higher than that of the benign group ($p < 0.01$). Suzuki *Y et al.* have reported a mean \pm S.D. of CSF NSE level in West syndrome was 7.3 ± 3.6 ng/ml [12], which was similar to the published CSF NSE levels of Japanese infants without neurologic disease (6.3 ± 4.2 ng/mL, 5.8 ± 1.7 ng/mL, and 6.5 ± 2.2 ng/mL) [13–15]. Also, the CSF NSE level in patients with febrile seizures aged 4–84 months was 2.0 to 10.0 ng/ml [16]. Compared with these data, the CSF NSE level in the prolonged group (15.5 ± 4.7 ng/ml) was higher than in controls and other diseases in previous data.

According to our results, CSF NSE level might be a potent prognostic indicator of ASA. In 1959, Weiss *et al.* reported poor outcome in patients who presented many kinds of cerebellar symptoms such as gait disturbance, ataxia of trunk or extremities and abnormal eye movements [6]. However, few reports have mentioned the prognostic factors of ACA. Daaboul *et al.* emphasized the prognostic value of brain SPECT and MRI [17], but this was limited to a case report.

The maximum level of CSF NSE in our study (25.0 ng/ml) was observed in the patient with abnormal MRI and SPECT findings, and may reflect severe destruction in the cerebellum detectable by MRI and SPECT. Other patients with a CSF NSE level of more than 11.5 ng/ml did not show any damage in brain imaging scans. This indicates that CSF NSE level is more sensitive indicator for detection of cerebellum damage than MRI and SPECT scans. In the near future, optimum cut-off point for classifying the severity of ACA will be determine.

In a previous report, the serum NSE level gradually decreased on day 1, 2, 3, and 7 after status epilepticus [18]. In our study, there was no significant difference in the average interval between the benign group and the prolonged group. Furthermore, the average interval in the prolonged group was longer than that in the prolonged group (2.33 ± 1.5 days vs 8.43 ± 9.9 days). These data suggest that the CSF NSE level in the prolonged group was apparently higher than that in the benign group.

Our study suggests that CSF NSE level is an important predictor of prolonged ACA in children, and that a high CSF NSE level indicates a poor prognosis of ACA.

Abbreviations: ACA: acute cerebellar ataxia
CSF: cerebrospinal fluid
NSE: neuron-specific enolase

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