Clinical Characteristics and Effects of Steroid Therapy in Children with Acute Cerebellar Ataxia

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Purpose: Acute cerebellar ataxia (ACA) is characterized by unsteady gait and instability of the trunk, and is caused by secondary autoimmune responses to infection or vaccination in healthy children. Although its prognosis is usually very good, full symptom recovery generally takes 2 to 3 months. This study aimed to investigate clinical symptoms, neuroimaging findings, and laboratory findings in children with ACA, and to evaluate the effects of steroid therapy on ACA according to the method of administration (intravenous methylprednisolone vs. oral prednisolone).

Methods: We retrospectively analyzed nine patients diagnosed with ACA or acute cerebellitis (AC) who received steroid therapy.

Results: Nine children were included in this study (mean age, 3.71 ± 2.89 years). The mean duration between prodromal febrile illness and cerebellar symptoms was 9.63 ± 4.66 days. Ataxia (limb and/or truncal) was the most common cerebellar sign. Steroids were administered in two ways: methylprednisolone (20 to 30 mg/kg/day) was changed to an oral steroid (prednisolone, 1 mg/kg/day) after 2 to 3 days of administration; an oral steroid was used from the beginning of treatment. The cerebellar symptoms began to improve within 2 to 4 days of steroid therapy. All patients fully recovered without sequelae. The mean interval until full recovery of the cerebellar symptoms was 28.0 ± 19.3 days, and was not significantly different between patients who received an oral steroid after methylprednisolone pulse therapy and patients who only received an oral steroid ($P > 0.05$).

Conclusion: Regardless of the method of drug administration, steroid therapy helps to improve cerebellar symptoms in children with ACA/AC.

Keywords: Cerebellar ataxia; Cerebellar diseases; Steroids

Introduction

Acute cerebellar ataxia (ACA), which is a disease characterized by unsteady gait with a sudden onset, is caused by a secondary autoimmune response to infection or vaccination in healthy children; the term ACA is commonly used together with acute cerebellitis

(AC), which refers to more severe cases [1-4].

Most ACA patients are young children who cannot describe their symptoms accurately, so it is often difficult to diagnose ACA. Furthermore, the exact frequency of the disease has never been investigated, as it occurs infrequently. However, ACA is known to be the most common cause of childhood ataxia, accounting for 30%

to 50% of childhood ataxia cases [5-7]. Garone et al. [8] reported that the number of patients with acute ataxia as the chief complaint was 0.021% of all patients who visited the emergency room, and 33.6% of patients with acute ataxia were diagnosed with postinfectious ACA, which was the most common cause of acute ataxia.

Postinfectious ACA associated with a viral infection usually does not require special treatment, and most patients fully recover without treatment after several weeks. Although steroid or intravenous immunoglobulin use has been reported in some severe cases, its effectiveness has not been clearly demonstrated [6,9,10].

The symptoms of ACA are alarming, because when a healthy child suddenly fails to balance and cannot walk well, his or her trunk is unstable during sitting, his or her pronunciation becomes inarticulate and the speed of articulation slows down, it causes the patient discomfort in everyday life, the child's quality of life decreases, and the child's parents become very embarrassed.

The aims of this study were to identify clinical symptoms, neuroimaging findings, and laboratory findings in children with ACA, and to evaluate the effects of steroid therapy on ACA according to the method of drug administration (intravenous methylprednisolone [MPD] vs. oral prednisolone).

Materials and Methods

We enrolled patients who received steroid therapy from January 2009 to December 2019 under the diagnosis of ACA or AC at the department of pediatric neurology of Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, and conducted a retrospective study.

The inclusion criteria for ACA/AC were: (1) healthy children without an underlying disease; (2) acute onset of cerebellar symptoms/signs (e.g., gait/truncal ataxia, nystagmus, or dysmetria); (3) children who had symptoms of infection within the last 3 weeks (febrile or non-febrile). Among the patients who matched the above criteria, those who had abnormal findings on brain magnetic resonance imaging (MRI) and/or changes in mental status were classified as having AC, while those who had normal mental status and normal brain MRI findings were classified as having ACA. Children with metabolic, endocrinological, or genetic problems or a history of trauma were excluded from this study.

All patients were admitted and underwent the following tests: complete blood count, blood chemistry, cerebrospinal fluid (CSF) study, and MRI of the brain. In some patients, the following additional tests were conducted: electroencephalography (EEG), respiratory polymerase chain reaction (PCR) through a nasopharyngeal swab, *Mycoplasma* immunoglobulin M (IgM) in blood/PCR through a throat swab, cytomegalovirus (CMV) IgM/G in blood,

varicella zoster virus (VZV) IgM and PCR in blood, and glutamic acid decarboxylase (GAD) antibody test in blood.

After checking the results of these tests, steroid therapy was started on the date of diagnosis or the following day. Steroids were administered in two ways: (1) MPD (20 to 30 mg/kg/day) was changed to an oral steroid (prednisolone, 1 mg/kg/day) after 2 to 3 days of administration, or (2) an oral steroid (prednisolone, 1 mg/kg/day) was used from the start of treatment. Symptom improvement after steroid therapy was based on the patient's clinical symptoms such as walking appearance and sitting posture, the performance of the finger to nose test and tandem gait, and the disappearance of truncal ataxia, dysarthria, nystagmus, and tremor.

In addition to demographic factors, we also identified early-onset symptoms (cerebellar or non-cerebellar symptoms), the interval between symptom onset and the patient's visit to the hospital, a history of recent infection or vaccination, and the period until complete recovery based on follow-up observations.

1. Statistical analysis

The statistical analysis was done using Stata/IC version 15.1 (StataCorp LLC, College Station, TX, USA). The median test was applied to the data to confirm non-parametric equality and a *P* value of < 0.05 was regarded as indicating statistical significance.

2. Ethics statement

This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (KC20WISI1033). The study was exempted from the requirement for informed consent due to its retrospective nature.

Results

We enrolled nine patients (three males and six females). Of them, six and three patients were diagnosed with ACA and AC, respectively. The mean age of the nine children was 3.71 ± 2.89 years (ACA, 2.9 ± 1.55 years; AC, 5.33 ± 4.65 years), and most patients visited the hospital within 3 days after symptom onset (2.22 ± 1.56 days). Before the cerebellar symptoms, eight out of nine patients showed gastrointestinal symptoms or upper respiratory symptoms with fever, and the mean duration between the gastrointestinal or upper respiratory symptoms and the cerebellar symptoms was 9.63 ± 4.66 days.

Ataxia (limb and/or truncal) was the most common cerebellar sign, which was seen in all subjects, and other cerebellar symptoms included dysarthria ($n=2$), dysmetria ($n=2$), and nystagmus ($n=1$).

To rule out other diseases (e.g., infectious or metabolic diseases),

a lumbar puncture was performed in all subjects. The CSF examinations in eight patients were normal. One patient (patient no. 9) showed an increase in CSF protein levels (136.4 mg/dL) and CSF pleocytosis (white blood cell, 570 cells/ μ L) with lymphocytic predominance, but both CSF culture (bacterial, fungal culture) and viral/mycobacterial studies (enterovirus real-time PCR [RT-PCR], herpes zoster virus type 1 and 2 PCR, *Mycobacterium tuberculosis* PCR) in the CSF were negative (Table 1).

A detailed history was taken and additional tests were performed (respiratory RT-PCR, *Mycoplasma* IgM or PCR, VZV PCR, CMV IgM/IgG, GAD antibody test) to determine the cause of ACA/AC. Only two patients (patients no. 2 and 7) showed abnormal results in the above tests (equivocal for *Mycoplasma* IgM and positive for CMV IgM, respectively). None of the patients had VZV infections or had been vaccinated within 3 months prior to symptoms, and none were PCR-positive for VZV (Table 1).

MRI was performed in all patients, and abnormal findings were found in three patients (patients no. 2, 3, and 9). All of them showed increased signal intensity in the cerebellar hemispheres (unilaterally or bilaterally), accompanied by diffuse cerebellar swelling on both T2-weighted and fluid attenuated inversion recovery sequences. EEG was obtained in four patients and the findings were normal in all of them (Table 1).

Steroid therapy was performed in two different ways. Six patients were treated with oral prednisolone after MPD pulse therapy. The other three patients received oral prednisolone from the start of treatment. Steroid therapy began on average 13.22 ± 5.31 days after the prodromal illness, but there was no statistically significant difference between the two groups (mean $\pm$ standard deviation [SD]: MPD pulse therapy+oral prednisolone, 10.33 ± 3.38 days; oral prednisolone only, 19.0 ± 3.0 days; $P > 0.05$). The mean duration of steroid therapy was 20.17 ± 8.13 days in patients who underwent MPD pulse therapy, whereas it was 16.67 ± 10.60 days in patients who received oral steroid therapy only; this difference was not statistically significant. The cerebellar symptoms began to improve within 2 to 4 days of steroid therapy (mean $\pm$ SD: 2.67 ± 0.87 days), and there was no statistically significant difference between patients who received pulse therapy and those treated with oral prednisolone only (mean $\pm$ SD: MPD pulse therapy+oral prednisolone, 2.83 ± 0.98 days; oral prednisolone only, 2.33 ± 0.58 days; $P > 0.05$) (Table 2).

The mean duration of follow-up was 7.1 ± 6.3 months, and the mean interval until complete recovery of the cerebellar symptoms was 28.0 ± 19.3 days. In patients who received MPD pulse therapy, complete recovery took 25.83 ± 20.61 days, while patients who received prednisolone only took 30.0 ± 21.0 days to fully recover. The interval until complete recovery was shorter in patients who

received MPD pulse therapy than in patients who received oral prednisolone only, but the difference was not statistically significant (Table 2).

Discussion

ACA/AC patients feel uncomfortable in everyday life because they cannot balance their bodies, and their parents often worry that the cerebellar symptoms may persist. In addition, physicians who see patients with this disease may also feel embarrassed because no treatment has yet been proven to be successful. ACA/AC is known to be a self-limiting disease with a benign course, but there are several reports of neurological sequelae, which may develop in up to 5% to 33% of cases [10,11].

In our study, the mean age of patients affected by ACA/AC was 3.71 ± 2.89 years, which aligns with the age range described in previous reports (2 to 6 years) [5,11,12]. In our study, the mean age of patients with ACA was lower than that of patients with AC. This is consistent with previous studies showing that the age at the onset of AC is higher than that of ACA [4]. However, unlike previous reports describing a male predilection for this disease [6,11], the proportion of females was twice as high in this study.

The mean interval between the onset of cerebellar symptoms/signs and visiting our hospital was 2.22 ± 1.56 days. As such, most patients visited a tertiary hospital within 3 days after the symptoms developed, showing that their parents took their symptoms very seriously.

The causes of ACA include varicella-zoster, mumps, Epstein-Barr virus, herpes simplex virus, influenza virus, coxsackie virus, mycoplasma, hepatitis A virus, human parvovirus B19, and as well as chickenpox, which is the most common cause in children [7,11,12]. In this study, eight patients (88.9%) had upper respiratory or gastrointestinal symptoms with fever before developing cerebellar symptoms, reflecting a slightly higher proportion than reported in previous studies (about 75%) [11,12]. However, only two patients showed abnormal test results suggestive of the cause of ACA (CMV, *Mycoplasma*), and none showed evidence of VZV infections. For most of the patients, it was not possible to determine the cause of ACA; therefore, we presumed that our patients developed ACA related to non-specific viral infections.

The latency from prodromal illness until the development of cerebellar symptoms/signs has been reported to be 7 to 10 days on average [6,11,12], which is similar to that of our study (9.62 ± 4.66 days).

Ataxia was the most common cerebellar symptom in this study, and it developed in all patients. This finding is similar to those of previous studies that reported ataxia to be the most common

Table 1. Demographics, clinical characteristics, and findings of patients with ACA/AC

Case	Age at diagnosis (yr)	Sex	Past history	Duration from febrile illness to cerebellar symptoms (day)	First symptom	Disease duration before hospitalization (day)	Abnormal laboratory test	CSF study	Etiologic evaluation	EEG	Brain MRI
1	5.5	F	Febrile illness (URI)	8	Ataxia (limb) Dysarthria Dysmetria Tremor	2	N	N	Microbiological test: (-) RT-PCR for respiratory virus: (-)	-	N
2	4	F	Febrile illness (GI)	8	Ataxia (limb) Dysmetria Diarrhea	2	Elevated ESR (31 mm/hr)	N	RT-PCR for respiratory virus: (-) Mycoplasma IgM: equivocal VZV PCR: (-)	-	Abnormal
3	1.5	F	Non-febrile (URI)	-	Ataxia (truncal/limb)	6	N	N	RT-PCR for respiratory virus: (-)	N	Abnormal
4	2	M	Febrile illness (GI)	4	Ataxia (limb) Fever Vomiting Diarrhea	1	Elevated CRP (2.39 mg/dL)	N	RT-PCR for respiratory virus: (-) Mycoplasma IgM: (-)	-	N
5	2.5	M	Febrile illness (URI)	18	Ataxia (limb) Dizziness Vomiting	2	Leukocytosis (11,680/ μ L) Elevated ESR (37 mm/hr)	N	RT-PCR for respiratory virus: (-)	N	N
6	4	F	Febrile illness (URI)	10	Ataxia (limb) Headache	1	Elevated ESR (30 mm/hr)	N	RT-PCR for respiratory virus: (-) Mycoplasma PCR: (-)	-	N
7	2	F	Febrile illness (URI)	15	Ataxia (limb) Tremor	3	N	N	RT-PCR for respiratory virus: (-) Mycoplasma PCR: (-) CMV IgM: (+)	N	N
8	1.4	F	Febrile illness (URI)	6	Ataxia (truncal) nystagmus	1	N	N	RT-PCR for respiratory virus: (-) GAD Ab: (-)	N	N
9	10.5	M	Febrile illness (URI)	8	Ataxia (limb/truncal) Dysarthria Fever	2	Leukocytosis (WBC 14,460) Elevated ESR 20 mm/hr	WBC 570 (lymphocytes 60%) Protein 136.4, glucose 76	RT-PCR for respiratory virus: (-)	-	Abnormal

CSF reference range: WBC 0 to 5 cells/ μ L, protein 15 to 45 mg/dL, glucose $\geq 2/3$ of blood glucose level.

ACA, acute cerebellar ataxia; AC, acute cerebellitis; CSF, cerebrospinal fluid; EEG, electroencephalogram; MRI, magnetic resonance imaging; URI, upper respiratory infection; N, normal; -, negative findings; RT-PCR, real-time polymerase chain reaction; GI, gastrointestinal infection; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; VZV, varicella zoster virus; CRP, C-reactive protein; CMV, cytomegalovirus; +, positive findings; GAD, glutamic acid decarboxylase; Ab, antibody; WBC, white blood cell.

Table 2. Comparison of outcomes according to the method of steroid administration in children with ACA/AC

Methods of steroid administration	A	Pvalue	B	Pvalue	C	Pvalue
MPD pulse therapy with oral steroid therapy (n = 6)	10.33 ± 3.38	> 0.05	2.83 ± 0.98	> 0.05	25.83 ± 20.61	> 0.05
Oral steroid therapy only (n = 3)	19.0 ± 3.0		2.33 ± 0.58		30.0 ± 21.0	

Values are presented as mean ± standard deviation. MPD pulse therapy: methylprednisolone (20 to 30 mg/kg), oral steroid therapy: prednisolone (1 mg/kg). A: Duration between prodromal illness and the beginning of steroid therapy (day); B: Duration between steroid therapy and the beginning of symptom improvement (day); C: Duration between the beginning of steroid therapy and complete recovery (day).

ACA, acute cerebellar ataxia; AC, acute cerebellitis; MPD, methylprednisolone.

symptom of ACA (70% to 100%) [6,10,11].

Extracerebellar symptoms (e.g., fever, vomiting, diarrhea, headache, and dizziness) were also present, and these symptoms were similar to those described in previous studies [9,10]. Symptoms such as seizure and altered mental status, which have been reported to occur in some severe cases [4], were not observed in our patients.

The findings of CSF examinations are usually normal in ACA [3], but abnormal findings have been reported in some patients, most commonly lymphodominant pleocytosis and increased protein levels [5,10–12]. In our study, most patients showed normal CSF findings, but one of them showed abnormal findings that were the same as reported in other previous studies. Although epileptiform discharge or slowing on EEG was observed in some previous cases [10,12], EEG frequently shows normal findings in ACA patients, and all the patients in our study had normal EEG findings. Three of our patients showed abnormalities on MRI of the brain, which were the same as those previously reported in children with AC (i.e., hyperintensity in T2-weighted sequences) [4,10]. In previous studies, brain atrophy or diffuse cerebellar signal changes were observed in some patients on follow-up MRI of the brain [4,13], but all our patients showed improvement. These results suggest that abnormal findings on the initial MRI of the brain do not persist in all patients, and our patients generally showed improvements.

The prognosis of ACA is usually very good. Although a study reported full recovery of ACA within 24 days without treatment [12], it is generally recognized that full recovery of symptoms takes 2 to 3 months without treatment [3,11]. There is no consensus on the treatment for ACA, as some studies have reported that steroids were effective for ACA treatment [4], while others reported that they were not helpful [10]. We started using steroids on the day of ACA/AC diagnosis or the following day. All nine children began to show symptom improvement within 2 to 4 days of treatment, and all patients recovered fully within 30 days without neurological sequelae. Direct comparisons may be difficult, but this is considered to be somewhat faster than the generally known recovery time of ACA patients not treated with steroids (about 2 to 3 months).

These results suggest that using steroids may help to improve the symptoms of ACA/AC patients and promote recovery. ACA/AC is an autoimmune disease that develops after infection or immunization [3], and it is believed that the immunosuppressive and anti-inflammatory effects of steroids could contribute to a relatively rapid recovery [14]. Previous studies have not compared the speed of symptom improvement following steroid administration. In this study, we found no significant difference in the speed of symptom improvement in ACA/AC according to the method of steroid administration (intravenous vs. oral). Therefore, it is believed that proper steroid therapy in the early stages of the disease, regardless of whether an oral or intravenous steroid is administered, plays an important role in improving the quality of life by alleviating symptoms. As a result, if the patients' overall condition is good and regular follow-up is possible, and there is no gradual deterioration of symptoms, outpatient oral steroid treatment can also be considered.

The principal limitations of this study are the small number of patients and the retrospective design. The fact that no objective indicators or assessment tools were used to evaluate whether patients' symptoms improved, and clinicians relied on the improvement of clinical symptoms, is also a limitation of this study. Further prospective studies are needed on the effects of steroid therapy according to the severity of ACA/AC in a larger number of patients.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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JYL and IGL. Formal analysis: JYL and IGL. Methodology: JYL, JUM, DHY, JYH, and IGL. Project administration: JYL and IGL. Visualization: JYL. Writing-original draft: JYL and IGL. Writing-review & editing: JYL and IGL.

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