

SHORT REPORT

Efficacy of high dose steroid therapy in children with severe acute transverse myelitis

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Abstract

No effective treatment has been demonstrated for patients with acute transverse myelopathy. In a multicentre controlled study, 12 children with severe acute transverse myelopathy were treated with intravenous methylprednisolone (IVMP) and compared with a historical group of 17 patients. The treatment had a significant effect on the proportion of patients walking independently at 1 month and on the proportion with full recovery at 1 year, with no differences in the frequency of complications between the two groups.

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Acute transverse myelopathy is a rare and severe disorder which usually involves the sensory and motor tracts of the spinal cord. The incidence has been estimated at 1.34/million in the Israeli population¹ but there has been no specific evaluation of the paediatric incidence. It is characterised by rapid onset of paraplegia or tetraplegia, loss of sensibility, and sphincter disturbances. The disease leads to permanent disability in about 40% to 60% of patients, based on findings from the main series.¹⁻⁶ There is no evidence that any effective treatment exists. The presumed immune mediated pathophysiological mechanism for the disease,⁷ the high risk of residual neurological deficits, and reports of potential benefit of corticosteroids in acute disseminated encephalomyelitis,⁸ prompted us to evaluate the effects of high dose intravenous methylprednisolone (IVMP). In 1996, we performed an open pilot study applying this treatment to five patients. The outcome of these patients was compared with that of a historical group of 10 patients who did not receive IVMP treatment.⁹ The results suggested that IVMP could shorten the duration of the disease and improve the outcome at 1 year. In the light of these promising results, we decided to expand the series using the same methods. We chose to treat patients displaying complete flaccid paralysis of the legs, which is associated with a high risk of poor outcome.^{5, 10}

Patients and methods

Twenty nine children, including the 15 patients from the original series,⁹ were admitted between 1975 and 1999 to several European centres with the diagnosis of severe acute transverse myelitis and presenting with at least a complete flaccid paralysis of the lower limbs. All the children (mean age 8.6 years; range 1 to 14 years) fulfilled the classic criteria for the diagnosis of acute transverse myelopathy^{1, 4, 6, 11}: briefly, no antecedent neurological illness, acute onset of bilateral spinal cord dysfunction, and exclusion of patients with spinal trauma or irradiation. Compressive spinal cord lesion was also excluded by MRI (22 patients), myelography (two patients), and Queckenstedt test (two patients). These investigations were not performed in the remaining three patients presenting with myelopathy associated with optic neuritis. Patients in whom neurological symptoms had recurred were not enrolled (except one patient who had a single relapse followed by full recovery and no recurrence during a 3 year follow up period). Twelve were treated with IVMP at a dosage of 1 g/1.73 m²/day for three (five patients) or five consecutive days (seven patients), followed in 10 of the 12 patients by oral prednisone (1 mg/kg/day) for a total period of 2 (eight patients) or 3 weeks (two patients). One patient received an initial dose of 0.5 g/1.73 m². Only children whose parents gave informed consent took part in the study. Their outcome was compared with that of a historical group (17 patients), receiving either no specific treatment or low dose corticosteroids which, according to previous studies, do not affect the outcome.^{4, 6} For the group as a whole, the mean follow up duration was 3.9 years (range 1 to 15 years). The main outcome criteria were: (1) the proportion of patients with full recovery, with motor recovery, and with sphincter recovery within 12 months; (2) the proportion of patients able to walk independently after 1 month; (3) the proportion of patients with complications—namely, corticosteroid adverse effects (persistent hyperglycaemia, high blood pressure), bedsores, and urinary tract infections. We also studied the median time to independent walking and the quality of recovery. The quality of recovery after 1 year was evaluated using Paine's scale³: (1) "normal": full recovery; (2) "good": gait essentially normal,

Table 1 Characteristics of the two groups of patients

	IVMP group (n=12)	Control group (n=17)	p Value
Year of observation (range)	1994–9	1975–1998	
Mean age (y (range))	9.5 (2–14)	8.0 (1–14)	0.4
Sex ratio (M/F)	8/4	5/12	0.05
Clinical features:			
Back pain	4/12	7/17	0.7
Hyperacute onset (<12 h)	3/12	4/17	>0.999
Supramedullary symptoms	4/12	5/17	>0.999
Complete flaccid paraplegia	12/12	17/17	1.0
Sphincter disturbances	11/12	17/17	0.4
Sensory level	10/12	15/17	>0.999
Increased CSF cell count	8/12	8/17	0.45
Mean follow up (months)	14.6	66	0.001

IVMP=Intravenous methylprednisolone.

but mild urinary symptoms and/or minimal sensory and upper motor neuron signs; (3) “fair”: mild spasticity but independent ambulation, urgency of micturition and/or constipation with some sensory signs; (4) “poor”: unable to walk or severe gait disturbances, absence of sphincter control and sensory deficit. Percentages were compared using a χ^2 or exact Fisher’s test. The median time to independent walking was compared using the Kruskal-Wallis test. Student’s *t* test was used to compare the mean age and duration of follow up between the two groups.

Results

The clinical features of the patients are summarised in table 1. The characteristics of both groups, especially those known to be of prognostic value, were identical—namely, back pain,⁴ hyperacute onset,^{4,6} and severity of initial course.^{3,9} The mean time between disease onset and IVMP administration was 8.1 days (range 1 to 21 days). The proportion of patients who walked independently after 1 month was 66% (eight of 12) in the IVMP group versus 17.6% (three of 17) in the control group ($p=0.02$). Full recovery within 1 year was seen in 54.6% of patients (six of 11) in the treated group versus 11.7% (two of 17) in the control group ($p=0.03$). At 1 year, seven of 11 treated patients had achieved a complete motor recovery versus four of 17 in the control group ($p=0.05$), and nine of 12 patients of the IVMP group had normal sphincter function versus three of 17 in the control group ($p=0.006$). Among patients who recovered walking, the median time to independent walking was shorter in treated patients than in the control group (25 days *v* 120 days; $p=0.05$). After 1 year, 75% of treated patients had a “normal” or “good” outcome versus 23.5% in the control group ($p=0.006$). The proportion of patients with complications was identical in both groups (two of 12 *v* five of 17; $p>0.66$).

Discussion

These results demonstrate a favourable effect of IVMP on the outcome of severe acute transverse myelopathy in children. This treatment increased the proportion of patients with full recovery, accelerated the recovery of walking, and reduced the severity of sequelae.

These findings are in agreement with the high rate of recovery seen in an uncontrolled study using the same IVMP regimen in

children with acute transverse myelopathy.¹² Recent studies suggested that high dose steroid treatment might delay the onset of neurological progression for up to 6 months in some isolated demyelinating syndromes but that its protective effect is ultimately lost over several years of follow up.¹³ However, the long term effect of this treatment in acute transverse myelopathy, as well as in related conditions has yet to be ascertained. By contrast, two other studies showed that low dose corticosteroid treatment comparable with that used in our control group did not affect the outcome.^{4,6}

The frequency of a good outcome after 1 year, in patients not treated with IVMP as reported in the literature, is about 40% to 60%, irrespective of severity of disease.^{1–6} Our control group had a poorer outcome. This is due to the fact that only severely affected patients—namely, those presenting complete paraplegia (predictor of poor prognosis)—were included in this study because of the potential risks of IVMP.^{5,10} It is noteworthy that the recovery rate we found in our control group was similar to that reported in other series when using the same selection criteria.⁵

There had been some differences in the means of investigations between the two study groups. However, the earlier patients were as comprehensively investigated as the current patients. The two groups share the same classic diagnostic criteria for acute transverse myelopathy. On the other hand, those earlier patients had a fairly long follow up (mean 66 months). This makes the risk of relapsing or chronic progressive disease unlikely.

Acute transverse myelitis represents a heterogeneous group of conditions in which the postinfectious aetiology largely predominates, especially in children.² It is most often considered as a localised form of acute demyelinating encephalomyelitis.¹⁰ The occurrence of occasional and relatively mild supramedullary symptoms in a few of our patients might therefore reflect some rostral extension of this continuum. On the other hand, the proportion of patients with supramedullary symptoms was similar in the two groups. This rules out the risk of unbalanced distribution. The control group showed a female predominance. In adults, women with acute transverse myelopathy have a tendency to show a high correlation with a future neurological progression to multiple sclerosis and might be regarded as carrying a worse prognosis. By contrast, the sex in childhood acute transverse myelopathy was not shown to influence the evolution of the disease. Moreover, the diagnosis of multiple sclerosis seems very unlikely in our young patients as: (1) multiple sclerosis is rare in childhood (2.7% to 4.4% of cases of multiple sclerosis begin before the age of 16 years and only 3% of these children present initially with transverse myelitis)^{14,15}; (2) no recurrence was noted in our patients despite a long follow up period (except for one patient with a single relapse). In the only relevant study assessing the risk of evolution towards multiple sclerosis in childhood acute transverse myelopathy, no patient

developed definite evidence of multiple sclerosis⁶; (3) CSF protein electrophoresis performed in our patients did not show any oligoclonal antibody synthesis. Oligoclonal bands in CSF were only studied in a few cases of childhood acute transverse myelopathy.² In these cases, synthesis of oligoclonal immunoglobulins was detected very rarely. The sum of these findings provides substantial arguments for distinct repartition of aetiopathogenic mechanisms in children compared with adults with acute transverse myelopathy. The disease results from different pathophysiological mechanisms in which the postinfectious aetiology largely predominates in children, whereas in adults, other conditions, such as relapsing autoimmune diseases and spinal infarcts, prevail.² Spinal cord infarction is unlikely in our patients as it is very rare in childhood. Moreover, our patients did not present any of the major predisposing factors such as cardiovascular diseases or coagulopathies.¹⁶

The aetiology of ATM in childhood remains obscure, but a postinfectious autoimmune process is suggested by the seasonal clustering, association with a previous infection, the frequent inflammatory reactions detected in the CSF, and by anatomical studies showing infiltration of the spinal white matter by immune cells.⁷ The myelin sheath seems to be the target of the pathological process, as suspected clinically by the association with supramedullary demyelinating symptoms, such as optic neuritis, and confirmed by anatomical studies showing areas of spinal cord demyelination. Moreover, peripheral blood lymphocytes from patients with acute transverse myelopathy show a significant proliferative response when cultured in vitro in the presence of myelin proteins such as myelin basic protein.⁷ Thus, acute transverse myelopathy might be the consequence of a cell mediated autoimmune response directed against a component of the myelin sheath. The efficacy of IVMP in related diseases such as optic neuritis¹⁷ and multiple sclerosis¹⁸ led us to study its use in the treatment of severe paediatric forms of acute transverse myelopathy. The mechanism of action of IVMP has not been fully elucidated. In peripheral blood, IVMP induces a transient lymphopenia with a significant reduction in CD4 positive cells.^{19, 20} An anti-inflammatory effect has also been demonstrated in vitro in

CNS cells. For example, glucocorticoids down regulate the production of cytokines such as interleukin-6 and TNF- α by microglial cells and peripheral macrophages.²¹

In our opinion and taking into account the results of our study, the likelihood of a beneficial effect of IVMP in childhood acute transverse myelopathy is so strong that a double blind placebo controlled study would raise some concerns.

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