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Severe steroid-resistant post-infectious encephalomyelitis

General features and effects of IVIg

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Abstract Based on their presumed immuno-mediated etiology, post-infectious CNS disorders are commonly treated with high-dose steroids. Factors influencing treatment effectiveness, possible alternative options for steroid-resistant cases, and their outcome profiles, remain unclear. We here describe the clinical features, the prognosis and the efficacy of i. v. immunoglobulins (IVIg) in a series of severe ADEM refractory to steroids. We performed an inception cohort study on inpatients of the Neurologic and Infectious Disease Clinics, consecutively admitted over eight years, with a minimum two-year follow-up. Nineteen patients affected by classic and site-restricted ADEM were treated with IVIg after steroid failure. Five other patients received IVIg as first-line treatment due to steroids contraindications: although not included in the analysis, they were monitored for anecdotal comparison. Steroids were administered as IV 6-methylprednisolone (6-MP) 500/1000 mg daily until a maximum dose of 6–8 g; IVIg were administered at 0.4 g/kg/day for 5 days. The outcome was assessed by the Scripps Neurological Rating Scale (SNRS) score with determined periodicity. We observed that steroid-resistant patients showed high prevalence of PNS damage (89 %) and myelitis (95 %). Other features were old age, severe disability at onset, and moderate to severe blood-brain-barrier (BBB) damage on CSF. In 10/19 patients (53 %) IVIg were effective, the clinical improvement beginning within the end of the five-day cycle, without relapses. Prominent effects of IVIg were detectable on motor dysfunction. Milder onset disability ($p = 0.013$) and lower CSF albumin ($p = 0.006$) were the predictors of IVIg response. Among steroid-free patients, 3/5 were responsive to IVIg. We conclude that IVIg can be useful in a portion of patients with severe steroid-resistant ADEM and prominent motor dysfunction. Unsolved issues regard the usefulness of IVIg in less selected groups, and the spectrum of their clinical effects.

Key words encephalomyelitis · ADEM · myelo-radiculo-nevritis · intravenous immunoglobulins

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Introduction

Post-infectious CNS disorders are characterized by acute onset of neurological symptoms in close temporal relationship with spontaneous infections or vaccinations [1, 2]. Based on the site and extent of the anatomical involvement, these disorders include: (a) acute disseminated encephalomyelitis (ADEM), (b) site-restricted variants (post-infectious myelitis), and (c) forms with additional PNS damage [3–5]. Although spontaneous recovery has occasionally been reported [2], most cases require pharmacological treatment in view of the rapid progression of symptoms. Since the disease is thought to be immuno-mediated, treatment is usually based on high-dose steroids. However, no randomized controlled study is available to prove the efficacy of this treatment, and in several cases severe residual disability or even death have been reported [6–8], associated with unresponsiveness to steroids. Recently, plasmapheresis [9] or intravenous immunoglobulins (IVIg) have been successfully used in both pediatric [10–12] and adult patients [8, 13] with steroid-resistant ADEM. However, since these reports include isolated cases or very small groups of patients, it is difficult to establish which disease features can predict the effectiveness of either treatment. Post-infectious encephalomyelo-radiculoneuritis and myelitis seem to be associated with even lesser responsiveness to steroids and poorer outcome than classical ADEM, but no data are available on the use of alternative treatments in these conditions [14–18]. We have previously reported failure of steroid treatment in one-third of a large cohort of ADEM patients [19]. Here we report on the clinical features, laboratory and instrumental findings, and long-term outcome in a cohort of 19 patients with severe steroid-resistant ADEM treated with IVIg.

Methods

Study design and patients

All consecutive patients hospitalized for ADEM who were resistant to steroids were prospectively included in this study. ADEM was defined as a neurological syndrome characterized by acute CNS or CNS + PNS symptoms occurring within 30 days from a systemic infection or a vaccination; both classical disseminated encephalomyelitis and site-restricted post-infectious syndromes (pure encephalitis and myelitis) were considered. Disease course and outcome was followed-up for a minimum period of two years, and alternative diagnoses, including MS, primary CNS vasculitis, sarcoidosis, systemic lupus erythematosus, and Devic's disease, were excluded. The results of biochemical analysis of blood and CSF, including virological screening, the neuroradiological and neurophysiological diagnostic work-up, as well as the clinical syndromes are detailed in a previous study [19]. In particular, the patients were assigned to 5 groups, according to the involved anatomical areas: 1) encephalitis (E); 2) myelitis (M); 3) encephalomyelitis (EM); 4) myeloradiculoneuritis (MRN); 5) encephalomyeloradiculoneuritis (EMRN).

Over an 8-year recruitment period, 70 patients fulfilled the diagnostic criteria for ADEM. Sixty-five patients were treated with steroids as a first line treatment, while five received IVIg due to steroids contraindications. In 21/65 (33 %) patients steroids were ineffective: 2 patients died during or shortly after the IV steroid course, the other 19 patients received IVIg as second line treatment. The five patients receiving IVIg as first line treatment were used as a comparison group.

Outcome measures and treatment

The global functional impairment was assessed using the Scripps Neurological Rating Scale (SNRS) [20], while specific functional systems (motor, cerebellar, brainstem, urinary, visual, and cognitive) were assessed by the Kurtzke score. Clinical and functional records were taken by members of the same neurological team at baseline, before and during treatments, at the end of treatments and 48 hours later, and then every two weeks until the achievement of stable neurological conditions for at least one month. Thereafter, the functional assessment was performed every three months over the follow-up period.

Patients who fulfilled the inclusion criteria, and had no systemic contraindications, received IV 6-methylprednisolone (6-MP), at a dosage of 500 or 1000 mg daily, depending on whether they were older or younger than 65 yrs, until a maximum dosage of 6–8 g. Steroids effectiveness was defined as an improvement of at least 30 points in the SNRS score or the achievement of a final SNRS score ≥ 90 points at the end of the i. v. cycle and 48 hours later. To patients showing significant improvement but incomplete recovery, we administered oral prednisone 1 mg/kg/day, tapered over 1–2 months depending on the clinical response.

Patients with contraindications to, or failing to improve after, IV treatment with steroids, received IVIg 0.4 g/kg/day for 5 days. Sudden recurrence or worsening of the initial neurological syndrome in close temporal relationship with steroid tapering was also classified as steroid ineffectiveness and prompted IVIg treatment. The same rating schedule described above for the steroids treatment was used for evaluating the effectiveness of IVIg treatment.

The final clinical evaluation, which was performed at 18–24 months, led to the following categorization of the outcome: (a) good (e. g. normal walking or need of unilateral help, normal or mildly compromised bladder function, normal or mildly compromised cognitive function); (b) bad (walking with double assistance or wheelchair, severe bladder dysfunction, severe cognitive dysfunction).

Results

A total of 24 patients (15 women and 9 men aged 25–75 years, mean 55 yrs ± 16.7SD, 47 % of patients ≥ 60y rs), received IVIg (Table 1). The follow-up period ranged from 2 to 7 years. Only three patients had isolated CNS involvement in the form of encephalitis (1 patient) and encephalomyelitis (2 patients); the other 22 patients had combined encephalomyelitis and radiculoneuritis (n = 9), or myelo-radiculoneuritis (n = 12). Axonal neuropathy was the prevalent pattern of PNS involvement (13/21, 61 %). All patients had severe disability at onset (mean SNRS 44.7 ± 18.8 SD) and reached the maximum neurological deficit within 24–48 hours. Only two patients had normal CSF, while increased albumin and IgG were found in 22 patients (92 %), together with lymphomonocytic pleocytosis in 18 (75 %). Albumin-cytological dissociation occurred in 2 patients with EMRN

Table 1 Demographic and disease features of ADEM patients receiving IVIg

	Steroid-resistant (n = 19)	Steroids-free (n = 5)
Age mean (SD)	52.6 (16.7)	64.2 (14.5)
Sex (F:M)	12:7	3:2
Syndrome		
E	1	0
EM	2	0
EMRN	9	0
MRN	7	5
CSF		
cells, mm^3	65.5 (109.44)	10 (6.7)
albumin, mg/dl	125.2 (83.9)	81.4 (37.3)
CSF/S albumin ratio, %	3.13 (2.5)	1.9 (0.7)
IgG, mg/dl	20.68 (17.3)	14.2 (5.1)
Onset SNRS	43 (18.8)	51.2 (19.67)
Timing steroids (days)	2.88 (1.9)	–
Total 6-MP dosage (grams)	6.3 (1.39)	–
SNRS after steroids	52 (18)	–
Time IVIg (days)	20.1 (17.57)	7.4 (10.4)
SNRS after IVIg	70.9 (21.7)	75.2 (19.05)

E encephalitis; *EM* encephalomyelitis; *EMRN* encephalomyeloradiculonevritis; *MRN* myeloradiculonevritis; *SNRS* Scripps Neurological Scale Score
Values of numerical variables are expressed as means (SD)

and in one patient with EM. IVIg treatment was effective in 13/24 patients (54 %); the improvement began between the second and the fifth day of the cycle and progressed during the two-month follow-up. The response, if any, was stable with no disease relapse.

The five steroid-free patients all had MRN and were treated as early as 36 to 72 hours from the disease onset. In three patients the treatment was effective, though one had a poor final outcome due to severe bladder dysfunction.

IVIg administration after steroids failure

In this group, 52 % of patients had received steroids within the first 48 hours from the disease onset (mean 2.88 ± 1.9 SD days, range: < 24 hours – 7 days). IVIg were administered 7 to 58 days from the disease onset (20.1 ± 17.57 SD). In three patients the administration of IVIg was delayed due to initial steroid effectiveness followed by acute worsening during oral steroid administration and unresponsiveness to a further cycle of high-dose 6-MP. IVIg treatment was effective in 10/19 patients (53 %). Before starting IVIg, we documented the persistence of inflammatory indices in the CSF of 7/13 patients, including BBB damage (3/13), increased cells (1/13), or both (3/13). Likewise, 6/12 patients still showed the presence of MRI lesions with enhancement. The distribution of persistent CSF or MRI signs of active inflammation was similar among responders and non-responders.

Patients with milder disability at onset or lower CSF albumin responded better to IVIg ($F = 7.73$, $p = 0.013$, and $F = 9.67$, $p = 0.006$). The degree of SNRS variation after steroids and the timing of IVIg administration did not influence the response to IVIg (Table 2). For instance, in the case shown in Fig. 1, the IVIg treatment was effective, albeit it was performed late in the course of disease. The pattern of PNS involvement (axonal vs. demyelinating) and the extent of PNS involvement did not influence the response to IVIg (Table 2).

We could observe that the efficacy of IVIg was prominent on motor dysfunction and sensory ataxia. The most common residual deficits after steroids were sensory and motor disturbances related to spinal cord involvement and urinary retention, while steroids were usually effective on symptoms of brain involvement, including impairment of consciousness, rigor, cognitive disturbances, and focal deficits (Fig. 2). Only two patients with encephalitis had residual cognitive disturbances after steroids. In these patients, the administration of IVIg improved the associated motor dysfunction but were ineffective on cognitive dysfunction. The most common residual disability after IVIg was urinary dysfunction of various degrees (20/24 at the end of the cycle and 13/24 two months later). The final outcome was good in all the responders, though mild residual urinary dysfunction occurred in 7/10, and in 1/9 non-responders, who recovered the cognitive dysfunction at the 24-month follow-up. Eight patients with EMRN had a poor outcome, including one patient who died 14 days after the disease onset due to ventilatory failure secondary to brainstem involvement. One patient underwent plasmapheresis and a second patient underwent plasmapheresis + cyclophosphamide, without benefits.

Discussion

As part of a prospective study concerning classical ADEM and "site restricted" variants [19], we have investigated the outcome and the response to IVIg treatment in a selected group of patients with severe, steroid-resistant post-infectious CNS syndromes. We observed the following features: 1) 50 % of patients were over the sixth decade; 2) in all patients the clinical onset was severe, with rapid progression of neurological failure over the next 24–48 hours; 3) all but two patients had altered CSF parameters including BBB breakdown. 4) one patient had isolated encephalitis and two had encephalomyelitis. In all the other patients, the CNS damage was associated with mild to moderate PNS involvement. This observation suggests that classical ADEM and site restricted forms limited to the CNS respond to steroids better than those characterized by additional

Table 2 Comparison among patients responding to IVIg vs. nonresponders in the steroid-resistant group

	Responders n = 10	Nonresponders n = 9	F/X*	p
Syndrome				
E	0	1	–	–
EM	1	1	–	–
EMRN	3	6	–	–
MRN	6	1	–	–
Sex (M:F)	4:5	3:7	0.42*	0.43
Age	53.60 ± 17.62	51.67 ± 16.59	0.60	0.89
PNS involvement	9/10	7/9	2.48*	0.21*
Axonal	4/9	5/7	1.68*	0.43*
Demyelinating	5/9	2/7		
Mean cMAPs (#)	3.3 ± 1.7	2.9 + 1.5	0.010	0.61
Mean CVs (#)	42.5 ± 5.3	37.8 + 8.6	0.8	0.16
CSF				
cells, mm^3	41.7 ± 84.16	92 ± 132.21	1.001	0.33
albumin, mg/dl	78.5 ± 68.9	177 ± 68.9	9.76	0.006
IgG, mg/dl	32.9 ± 18.1	10.8 ± 8.3	11.91	0.003
CSF serum/albumin ratio, %	1.88 ± 0.72	4.2 ± 3.022	3.35	0.094
Onset SNRS	52.7 ± 15.6	32.22 ± 16.498	7.73	0.013
Total steroid dose (g)	5.6 ± 1.08	7.05 ± 1.3	6.17	0.024
Delta-SNRS after steroids**	8.1 ± 4.88	10 ± 8.67	0.35	0.55
Timing steroids (d)	3.28 ± 1.97	2.44 ± 1.87	0.88	0.36
Timing IVIg (d)	20 ± 19.32	20.22 ± 16.56	0.001	0.97
SNRS after IVIg	86 ± 7.8	52.13 ± 18.4	27.93	0.0001

Values of numerical variables are expressed as means ± SD
** SNRS difference between the acute phase and after steroids
F one-way analysis of variance; *X** chi square
(#): Mean ± SD value of the mean of four motor nerves for each patient: tibial – peroneal and ulnar – median, depending on the segment affected by myelitis (PNS involvement was not considered significant when occurring at the same levels of myelitis)

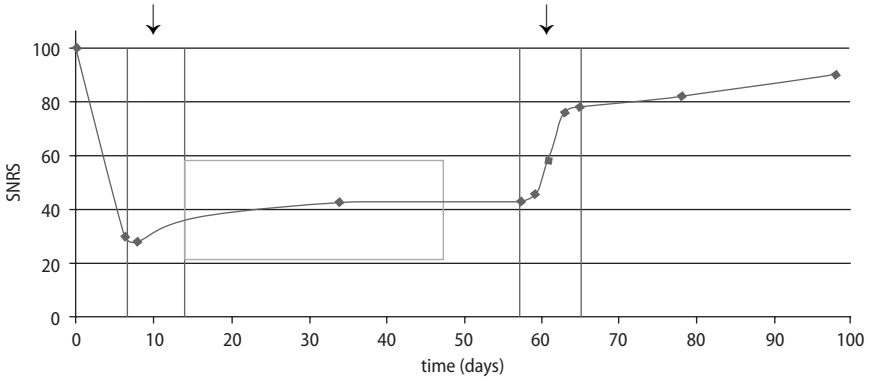

Fig. 1 Time course of neurological disability after steroids and after IVIg in one patient. One week after a flu-like illness, a 71-year-old man developed headache and generalized weakness. On hospitalization, he had flaccid tetraparesis more pronounced at the lower limbs, bilateral Babinski sign, stipsis, and urinary retention (SNRS 30). CSF examination revealed mildly increased albumin (78 mg %), raised CSF/serum albumin ratio (2.2 %) and lymphocytic pleocytosis (35/mm^3). Spinal cord MRI showed a T2-hyperintense lesion, C1 to C6, enhancing after gadolinium. He was diagnosed as MRN due to concomitant poly-radiculo-neuritic damage involving the upper and lower limbs. He received 6-MP 0.5 g/day for 6 days (arrows), followed by oral prednisone (PD), 100 mg/day for 20 days, tapered over one month, without benefit (the box indicates the time of oral steroids administration). Two months later, after the end of steroid treatment, the patient was still unable to walk (SNRS 42). Further CSF examination revealed persistence of BBB damage and lymphocytic pleocytosis. MRI of the spinal cord showed mild residual enhancement of the lesion. He was administered IVIg (arrows): within the third day of administration, upper limbs strength improved (SNRS 58). In the following few days lower limbs strength also began to improve. Two weeks later he could stand and walk with assistance (SNRS 82). One month after the end of the treatment, he could walk without assistance; bladder function did not improve (SNRS 90)

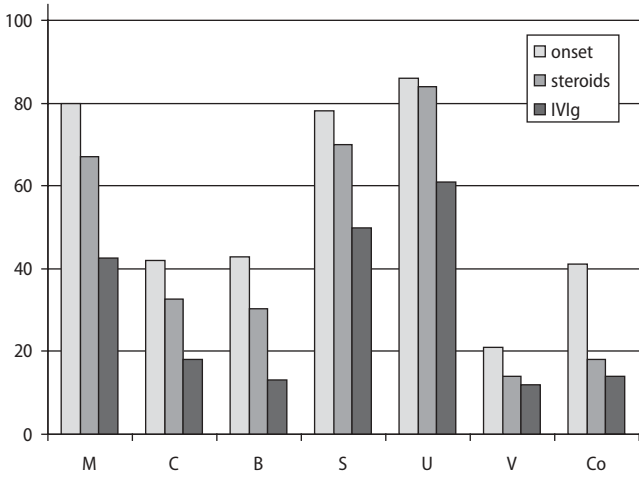

Fig. 2 Effectiveness of steroids and IVIg on specific functional systems. The bars represent the mean score on the Kurtzke scale at the onset, 48 hours after steroids, and 48 hours after the IVIg cycle. For each system, the score is expressed as percentage, with the highest score on the Kurtzke scale = 100 %. The effects of IVIg were more pronounced on motor, sensory, and urinary dysfunction ($Z = -3.331$, $p = 0.001$; $Z = -3.35$, $p = 0.001$; $Z = -3.109$, $p = 0.002$, Wilcoxon test for paired samples), while there was no clear effect above steroids on cerebellar, visual, and cognitive dysfunctions. A mild but significant effect of IVIg could also be observed on brainstem dysfunction ($Z = -2.264$, $p = 0.016$), for which steroids had also shown their efficacy ($Z = -2.26$, $p = 0.024$). Steroids, ineffective as a whole in this series, showed some effects on cognitive dysfunction ($Z = -2.4$, $p = 0.016$) and cerebellar involvement ($Z = -2.21$, $p = 0.021$). *M* motor; *C* cerebellar; *B* brainstem; *S* sensory; *U* urinary; *V* visual; *Co* cognitive

involvement of the PNS (encephalo-myelo-radiculoneuritis and myelo-radiculonevritis). Steroid failure may occur also in patients treated early in the course of disease: > 50 % of non-responders were treated within the first 48 hours. In three patients, the replacement of 6-MP with oral steroids was associated with neurological worsening, and a further high-dose cycle was ineffective. Steroid resistance may thus occur late in the course of the disease, and mimic disease relapses, but, unlike true relapses, the neurological worsening occurs before stabilization of symptoms, and is associated with variation of the steroid dosage.

We chose to administer IVIg to our steroid-resistant cases because IVIg are safer than other procedures, e. g. plasmapheresis, and are thought to promote remyelination, at least in peripheral nerves [22]. After IVIg, a subgroup (53 %) of patients had significant functional improvement, which began during the five-day IVIg cycle and reached a maximum within three weeks. Neither a partial response to steroids, nor the timing of IVIg administration seemed to condition the therapeutic effect. For instance, IVIg were effective in 5/9 patients in whom treatment was delayed, in one case as late as 58 days from the disease onset (Fig. 1). This result suggests that the inflammatory process is likely to remain active long after the disease onset, as also documented by the persistence of abnormalities in either CSF, MRI or both. In both steroid-free and steroid non-responder patients the effect of IVIg was persistent, with no early relapse. Distinctive features common to the responders were lower onset disability and lower CSF albumin, possibly reflecting less severe disease. The clinical effects of IVIg were mainly on motor dysfunctions, particularly those due to myelitis and PNS involvement. Compared to steroids, IVIg were more effective on motor, sensory, and urinary dysfunction (Fig. 2). Since these features could be related both to central and peripheral damage, which often co-occurred, it is difficult to establish which of the two was the main target of IVIg effects. We could not find a relationship between ENG parameters and treatment efficacy. We could not establish the effectiveness of IVIg on encephalopathy, since in most patients steroids had already been effective, and the steroid-free comparison group did not include patients with brain involvement. Since encephalopathy is rare in adult-onset ADEM [4, 23], there is little information on the effects of IVIg for this condition. The effectiveness of IVIg on signs of encephalopathy would have important practical applications: clinical manifestations, CSF and MRI findings in ADEM may be confused with encephalitis and meningoencephalitis due to direct infections, for which proper differential diagnosis may be time consuming, and in which high-dose steroids are contraindicated, while the administration of IVIg would be safe. Our own experience is limited to two cases with persistent cognitive impairment after steroids, in whom IVIg were ineffective as well.

In principle, the effects documented in the IVIg-responder patients could have occurred by chance, since this study was not controlled, the treatments were not randomly assigned, and the disease could be self-limiting. Moreover, a possible synergistic effect between steroids and IVIg cannot be excluded in the 19 patients who received both drugs. Both drugs may exert their anti-inflammatory activity through the inhibition of pro-inflammatory cytokines IL-1α and β, IL-2, IL-12, IFN-γ, and TNF-α, and upregulation of the anti-inflammatory cytokine IL-10. IVIg and steroids may thus act by similar mechanisms with a consequent additive therapeutic effect. However, the close temporal relationship between functional improvement and IVIg administration supports a real and independent effect of IVIg on the disease course; as already emphasized, clinical benefit was obtained also in patients with apparent stabilization of the clinical picture, as in the case reported in Fig. 1.

The results of our work suggest that IVIg are beneficial in a fraction of ADEM patients whose prognosis is frequently poor, like those affected by myelitis and combined involvement of CNS and PNS. The more prolonged disease course in patients with PNS involvement could account for failure of steroid treatment, and the improvement observed in cases that received IVIg – es-

pecially when administered late in the course of disease – could be partly due to spontaneous improvement. However, the disease course of our steroid-free patients, who were also affected by peripheral damage, does not support this hypothesis, because the three responders in this group showed prompt improvement after early treatment with IVIg. Polyradiculoneuritic involvement is now considered a well established, although rarely investigated, complication of ADEM [5, 23]. Interestingly, the first reports on the beneficial effects of IVIg in ADEM [18] concerned patients who had received an incorrect diagnosis of AIDP. However, our patients with combined ADEM and polyradiculoneuritis had features quite different from those commonly observed in AIDP: symptoms of CNS involvement were always prominent, the CSF consistently showed pleocytosis, and the peripheral pattern was usually axonal, rather than demyelinating. In these cases IVIg could improve the PNS symptoms as part of their effect on the immune response or by stimulating remyelination [22].

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