Official Journal of the European Paediatric Neurology Society

Case study

Successful treatment of two paediatric cases of anti-NMDA receptor encephalitis with Cyclophosphamide: The need for early aggressive immunotherapy in tumour negative paediatric patients

Pawan Kashyape [a,*], *Ellen Taylor* [a], *Joanne Ng* [b], *Deepa Krishnakumar* [a], *Fenella Kirkham* [a], *Andrea Whitney* [a]

[a] *Department of Paediatric Neurology, Southampton University Hospital, Southampton, United Kingdom*
[b] *Department of Paediatric Neurology, Great Ormond Street Hospital, London, United Kingdom*

ARTICLE INFO

Article history:
Received 25 May 2011
Received in revised form
9 July 2011
Accepted 17 July 2011

Keywords:
Anti-NMDA receptor encephalitis
Paediatric
Cyclophosphamide
Immunotherapy

ABSTRACT

We describe the clinical course and treatment of three unrelated female patients ranging in age from 27 months to 14 years with anti-NMDA receptor encephalitis. The third case is reported as an addendum to the paper. None of the cases were paraneoplastic. All received initial immunotherapy consisting of steroids and IVIg, and two of them received 3 and 8 plasma exchanges respectively, without consistent or sustained clinical improvement. All three girls were then treated with monthly cycles of Cyclophosphamide. All had resolution of their movement disorder and a dramatic and sustained clinical improvement of their other symptoms in the domains of cognition, language and behaviour. The clinical improvement began after the first cycle in two and the second cycle in the third and continued with the subsequent cycles. None developed side-effects of treatment. In light of the recent review of the condition and our own clinical experience in the paediatric age group, we propose that second line immunotherapy should be considered early after failure of first line immunotherapy.

1. Introduction

Though anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was originally reported in young adult women as a paraneoplastic disorder in association with ovarian teratoma, it is being increasingly recognised in the paediatric population, with 40% of patients in a case series of 81 being under 18 years of age.[1] The disease is caused by antibodies that target the NR1 subunit of the NMDAR. The mainstay of treatment includes tumour removal, immune suppressing medications and supportive care. It is recognised that tumour negative patients may not respond to first line immunotherapy and a recent review of anti-NMDAR encephalitis suggests Cyclophosphamide and rituximab, either alone or in combination as the

* *Corresponding author*. Department of Paediatric Neurology, G Level East Wing, Room EG217F, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, United Kingdom. Tel.: +44 7952597641; fax: +44 2380 794750.
E-mail address: pawankashyape@yahoo.co.uk (P. Kashyape).
1090-3798/$ – see front matter © 2011 European Paediatric Neurology Society. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejpn.2011.07.005

second line immunotherapy in these patients.[2] We describe two paediatric cases of anti-NMDAR encephalitis, both aged 27 months at presentation, who had limited or ill-sustained clinical benefit from a combination of high dose steroids, IVIg and plasma exchange, but responded dramatically to monthly cycles of Cyclophosphamide. This case report adds to the increasing pool of clinical experience of anti-NMDAR encephalitis and suggests the benefit of early consideration of second line immunotherapy even for the youngest paediatric patients.

2. Case reports

Both cases were 27 months old unrelated Caucasian females who presented in 2009 and 2010 respectively.

Both presented with a stereotypical course, consisting of an initial neuropsychiatric phase lasting for nearly two weeks manifesting as speech regression, change in personality and sleep pattern, with progressive deterioration leading to an encephalopathic stage with a florid movement disorder involving the oral-buccal region and limbs.

During the encephalopathic stage, case 2 demonstrated autonomic instability in the form of episodic tachycardia and hypertension as well as seizure activity. Both cases demonstrated episodes resembling psychosis with screaming, aggression towards carers and self biting. Both cases required admission to the paediatric intensive care unit for sedation as well as carrying out plasma exchange in the second case. The detailed clinical features are summarised in Table 1.

The diagnosis was confirmed in both cases based on strongly positive serology for anti-NMDAR antibodies in the serum, after consultation with the regional neuroimmunology lab. Cerebrospinal fluid (CSF) was not tested by the lab based on the current evidence that serum antibody levels are higher than CSF levels in the vast majority of cases.[3] Also, absolute titres were not reported by the lab at the time.

Both cases showed either minimal or short lasting response to first line immunotherapy including steroids, IVIg and in the second case, plasma exchange. However, both cases had a dramatic and sustained clinical response to intravenous pulse Cyclophosphamide treatment which was evident from the first pulse (Table 1). Further serology was not done. Monthly pulse doses were given till complete resolution of clinical signs and attainment of pre-morbid status. Case 1 needed 6 cycles whereas case 2 needed 4 cycles. Both cases recovered completely to their pre-morbid status. Neither received long-term immunosuppression. Both remain well at 1 and 2 years follow-up respectively.

3. Discussion

The immune mediated pathogenesis of anti-NMDAR encephalitis was initially described by Dalmau et al who demonstrated presence of antibodies in serum and cerebrospinal fluid (CSF) that react with cell surface of neurons.[4] These antibodies were demonstrated to be specific to the NR1 subunit of the NMDAR and further characterized to be of the complement-fixing IgG1 subclass.[5] The clinical phenotype of anti-NMDAR encephalitis has been well described in the form of distinct stages which include an initial neuropsychiatric syndrome followed by an acute encephalopathy with movement disorder and autonomic instability.[1,2,4,5] The initial neuropsychiatric features which develop over days to weeks include a change in personality, behaviour, amnesia, confusion, dysphasia with or without psychiatric features including hallucinations, agitation, psychosis, anxiety and depression. In children, the most common features are change in behaviour and seizures. This is followed by an acute encephalopathy accompanied by choreoathetoid movement disorder affecting orofacial region and limbs. This stage is also accompanied by dysautonomia consisting of changes in heart rate/blood pressure, hyperhidrosis, persistent pyrexia and central hypoventilation. Most patients need admission to intensive care during the acute stage of the illness.

Both our cases presented with the clinical course and features consistent with that described in the literature, including an initial neuropsychiatric phase, evolving into a severe generalised movement disorder with epileptic seizures. Based on our clinical experience with the first patient, the syndrome was suspected relatively early in the second patient on the 3rd day of admission when she developed the acute movement disorder in addition to the encephalopathy. Thus, once the clinician is aware of this condition, it is relatively straightforward to suspect and diagnose, and immunotherapy can be started early in the course of illness. However, in the absence of a consensus on immunotherapy at the time, it was difficult to start second line immunotherapy soon enough after the failure of first line immunotherapy was apparent in the second patient, considering the potential side-effects of Cyclophosphamide.

The study by Irani et al. demonstrated that there is a good correlation between reduction in serum NMDAR antibody levels with immunotherapy and clinical improvement.[5] It is now well recognised that in patients without a tumour or with delayed diagnosis, additional treatment with second line immunotherapy (Cyclophosphamide, rituximab or both) is usually needed.[2] In their review, Dalmau et al. have proposed an algorithm which considers using second line agents Cyclophosphamide and rituximab either alone or in combination after failure of first line immunotherapy.[2]

The benefit of second line immunotherapy has been evident in both our cases who responded completely only after Cyclophosphamide was introduced. It can thus be postulated that earlier introduction of this treatment after failure of steroids and IVIg would have reduced the duration of illness. However, parents/carers need to be carefully counselled about the potential short and long-term complications of these treatments.

The safety of pulsed intravenous Cyclophosphamide has been reviewed by Riley et al.[6] The short term side-effects are infection (only 9% needing inpatient treatment), alopecia and dermatitis. The three main reported long-term side-effects, namely malignancy, infertility and gonadal failure have mainly been reported in adults receiving cumulative doses higher than 50 gm. Long term follow-up of boys who received Cyclophosphamide for nephrotic syndrome showed normal sperm counts in adulthood in those receiving a cumulative dose of less than 10 gm. Both our patients received a cumulative dose of 5 and 3 gm/m^2 (2.75 gm and 1.65 gm) respectively, which is unlikely to cause long-term complications, though continued

Table 1 – Presenting features, investigations and treatment details.

		Patient 1	Patient 2
Age at presentation		27 months, Female	27 months, Female
Early neuropsychiatric phase	Clinical history	- Untriggered temper tantrums - Rage attacks - Speech regression - Abnormal movements affecting arms, legs, mouth and tongue by day 7 - Decreased social interaction	- Untriggered temper tantrums - Speech regression - Poor balance - Frequent distressed nocturnal arousals - Progressive lethargy with drooling
	Duration	12 days	10 days
Progression of illness to Encephalopathic phase	Clinical features on admission	Day 1 of admission (day 13 of illness) - No speech, but responding to name, fluctuating consciousness - Episodes of hyper motor activity with screaming and reduced awareness - Dyskinetic movements affecting orofacial region, tongue and limbs - Intermittent dystonic posturing of left arm and leg	Day 1 of admission (day 11 of illness) - Conscious with reduced awareness and inability to follow instructions - Subtle distal limb dyskinetic movements - Ataxic gait with poor balance - Rage attacks with self biting - Mild pyrexia (up to 38.2)
	Evolving encephalopathic stage	Day 3 of admission Self biting, Increased severity of encephalopathy and movement disorder, insomnia	Day 4 of admission Episodes of tachycardia and hypertension Florid movement disorder: oral-buccal and limb dyskinesia Self biting Brief tonic clonic seizures
Investigations	CSF	Done on day 1 of admission White cells: 3. Chemistry, glucose, lactate: Normal CSF culture and viral markers negative Oligoclonal bands: Negative	Done on day 3 of admission White cells: 13 Neutrophils: 8 Chemistry, glucose, lactate: N CSF culture and viral markers negative Oligoclonal bands: Negative
	EEG	Done on day 2 of admission: Generalised slowing	Done on day 2 of admission: Generalised slowing, One elctroclinical seizure with rt frontotemporal discharge
	MRI (+ contrast and Diffusion Weighted Imaging)	Done on day 4 of admission Minimally increased T2 signal from Globus Pallidus. No diffusion restriction. Repeated week 5 of admission: subtle increased signal in periventricular white matter (doubtful clinical significance)	Done on day 1 of admission Normal No diffusion restriction
	Neurometabolic screen	Normal	Normal
	Autoimmune screen	Strongly positive serum Anti-NMDA antibodies	Strongly positive serum Anti-NMDA antibodies
	Pelvic ultrasound	No ovarian mass	No ovarian mass

Steroids		Methylprednisolone followed by prednisolone	Prednisolone
	Day started	Day 3 of admission	Day 4 of admission
	Duration	8 weeks	6 weeks
	Clinical Response	Some improvement of conscious level and vocalisation but worsened movement disorder	No change in clinical state
IvIG	Day started	Week 6 of admission	Day12 of admission
	Duration	5 days	5 days
	Clinical response (As judged over 1 week after completing the course)	Transient reduction of dyskinetic movements, increased vocalisation, but relapsed soon after course completed	No change in clinical state, continued deterioration of movements, sleep, secretions, airway, increased autonomic disturbance and seizures
Plasma exchange	Day started	Not done	Day 28 of admission
	Total cycles	0	8
	Clinical response (As judged over the course of cycles over 16 days)		No change in clinical state
Cyclophosphamide Dose Regime (Monthly IV Pulse) 1st dose: 500 mg/m^2 2nd dose: 750 mg/m^2 3rd dose: 750 mg/m^2 4th and subsequent doses: 1000 mg/m^2	Day started	Day 60 of admission	Day 53 of admission
	Clinical response	➢ Week 1: Increased awareness, fixing and following, reduction of chorea, increased non verbal communication ➢ Next 4 weeks: gradual improvement in speech, dystonia, balance and walking. Complete resolution of chorea. ➢ By end of sixth monthly pulse: Back to her pre-morbid state. Normal neuropsychology assessment	➢ Week 1: Increased awareness ➢ Next 2 weeks: complete resolution of movement disorder, more attentive, weight bearing ➢ By end of fourth monthly pulse: Age-appropriate neurodevelopmental status including language, achieving new milestones. Minor sleep problems and temper tantrums
Total pulses		6	4
Total dose		5 gm/m^2 (2.75 gm)	3 gm/m^2 (1.65 gm)

monitoring is necessary. Similar protocols have been used and proven to be safe in paediatric patients with dermatomyositis[6] and opsoclonus-myoclonus syndrome.[7] There are also single case reports of the successful use of rituximab in paediatric as well as adult anti-NMDAR encephalitis which did not respond to conventional immunotherapy, though we have no experience of using this drug. There are reports that it may have a better tolerability and side-effect profile compared to Cyclophosphamide in terms of leucopenia and infectious complications.

4. Conclusion

Immunotherapy is the mainstay of treatment for anti-NMDAR encephalitis.

Based on the treatment algorithm outlined by the recent review of the condition by Dalmau et al.[2] and our own clinical experience, we propose that in cases with an incomplete response to first line agents, second line immunotherapy should be considered early even in the youngest paediatric patients.

5. Case 3

Case 3 was a previously healthy 14 year old girl referred to us subsequent to submission of the manuscript reporting the two cases described above. She had presented to her local hospital with a four day history of neuropsychiatric symptoms consisting of confusion, forgetfulness (forgetting her dance steps), expressive dysphasia, decreased co-ordination and a twenty four hour history of right hand paraesthesia and weakness. She was initially locally treated for presumed encephalitis but transferred to our regional centre in view of rapid deterioration in the next two days in the form of new onset generalised seizures, psychotic behaviour with prominent auditory and visual hallucinations and physical and verbal aggression towards staff and carers. She also developed subtle oral-buccal and limb dyskinesia which was not as prominent as the previous two cases.

CSF on admission showed pleocytosis (19 lymphocytes/ml) with normal protein and glucose concentrations and negative oligoclonal bands. EEG on day five of illness showed an excess of slow wave activity over left hemisphere. Both CSF and serology for anti-NMDA receptor antibodies were low positive on day seven of the illness. A wide range of investigations for other possible causes, including viral and bacterial causes of encephalitis, toxicology and metabolic screening was negative or normal. An abdominal ultrasound and MRI were normal with no evidence of tumour. Brain MRI on day eight of illness was normal.

She was initially treated with first line immunotherapy including methylprednisolone and IVIg. In spite of this, she developed worsening agitation, dystonic movements of limbs and severe psychotic episodes over the subsequent week and she required intensive care admission for sedation and ventilation. A trial of five cycles of plasma exchange was undertaken whilst in intensive care. This was followed by a decrease in the severity of her movement disorder, especially the oral-buccal dyskinesia. However she continued to have epileptic seizures and manifest severe psychotic aggression, requiring treatment with antipsychotics including risperidone and olanzapine. One to one nursing care was needed both to manage her behavioural manifestations and because she was unable to carry out activities of daily living.

Intravenous cyclophosphamide was commenced on day 28 of admission. This was followed by resolution of her residual movement disorder over the first two weeks of this treatment and a gradual improvement in her cognition and disappearance of all manifestations of psychosis over the next four to six weeks. She was weaned off her antipsychotic medications after the second pulse. Whereas it was impossible to assess her cognitive status before the second pulse, she scored 27 on a scale from 0 to 30 on the mini-mental state examination (MMSE) after the second pulse. She continues to have higher order executive dysfunction and is awaiting a formal neuropsychology assessment.

This case of anti-NMDA receptor encephalitis with unusually severe neuropsychiatric presentation showed a marked and sustained clinical improvement that coincided with the commencement of cyclophosphamide immunotherapy one month into the illness.

REFERENCES

1. Florance NR, Davis R, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and Adolescents. *Ann Neurol* 2009;**66**(1):11–8.
2. Dalmau J, Lancaster E, Martinez-Hernandez E, et al. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;**10**: 63–74.
3. Irani SR, Vincent A. Autoimmune encephalitis- new awareness, challenging questions. *Discov Med* 2011 May;**11**(60): 449–58.
4. Dalmau J, Tuzun E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* 2007;**61**: 25–36.
5. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. *Brain* 2010; **133**:1655–67.
6. Riley P, Maillard SM, Wedderburn LR, et al. Intravenous cyclophosphamide pulse therapy in juvenile dermatomyositis. A review of efficacy and safety. *Rheumatology* 2004;**43**: 491–6.
7. Wilken B, Baumann M, Bien CG, et al. Chronic relapsing opsoclonus-myoclonus syndrome: combination of cyclophosphamide and dexamethasone pulses. *Eur J Pediatr Neurol* 2008 Jan;**12**(1):51–5.