Does early treatment improve outcomes in *N*-methyl-D-aspartate receptor encephalitis?

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ABBREVIATION
NMDA *N*-methyl-D-aspartate

N-methyl-D-aspartate (NMDA) receptor encephalitis is a treatable cause of autoimmune encephalitis in both children and adults. It is still unclear if the natural history of the condition in children is altered by early treatment with immunosuppressive therapy. We looked at the outcomes of five children (two males, three females; mean age 6y 9mo, range 4–8y) who were treated empirically for autoimmune encephalitis within a brief period of presentation. Features that led clinicians to suspect autoimmune encephalitis included prominent neuropsychiatric features, movement disorder, seizures, and dysautonomic features. Immunosuppressive therapy was carried out in all cases. In this series of children, in whom the median time from symptom onset to treatment was 5 days and median length of time for follow-up was 24 months, four out of the five (80%) recovered to their baseline. Early initiation of immunosuppressive therapy may result in improved clinical outcomes.

N-methyl-D-aspartate (NMDA) receptor encephalitis is a cause of autoimmune encephalitis in both children and adults. It is still unclear if the natural history of the condition in children is altered by early treatment with immunosuppressive therapy. There is speculation, however, that earlier treatment results in improved outcomes with fewer residual deficits. Finke et al.[1] demonstrated an improved cognitive outcome in a small cohort of adult patients with anti-NMDA encephalitis who were treated with immunomodulatory therapy within 3 months of disease onset compared with those who were treated at a later stage or not at all. The authors proposed that a delay in treatment led to permanent hippocampal damage.[1] In their study of autoimmune encephalitis in children, Hacohen et al.[2] report that 29% of children with anti-NMDA and anti-voltage-gated potassium channel autoimmune encephalitis made a full recovery; however, their report does not state the time interval between presentation and treatment. A study by Titulaer et al.[3] examining a large cohort with anti-NMDA receptor encephalitis reported that the average time from symptom onset to treatment in children was 21 days, and that 60% of children had a modified Rankin Scale score[4] of 0, at a median follow-up time of 24 months. No study to date has shown definitively that earlier immunological treatment in children alters outcome.

We studied the outcomes of five children who were treated empirically for autoimmune encephalitis within 1 week of symptom onset. The children presented at two teaching hospitals in Dublin between 2007 and 2012. Review of anonymized data was permitted by the hospital audit board.

Before the onset of symptoms, all five children had attained typical developmental milestones and attended mainstream school. Details of individual cases are presented in Table I.

The median time from neurological or psychiatric symptom onset to empirical treatment with immunosuppression was 5 days (range 3–6d).

The median length of follow-up was 24 months (range 2–36mo). At follow-up, four children had a modified Rankin Scale score of 0 and were attending mainstream school (cases 1, 2, 4, and 5). Only one child (case 3) did not recover to the pre-illness baseline. This child continues to experience seizures, exhibits marked behavioural and cognitive difficulties, and attends a special school (modified Rankin Scale score 2).

Immunosuppressive therapy was instituted in all children before the results of the NMDA antibody test became available because they had features consistent with autoimmune encephalitis. Intravenous methylprednisolone was prescribed at a dose of 30mg/kg/day for 3 days, followed by oral prednisone for 2 to 4 weeks (2mg/kg/d) and, where prescribed, 0.4g/kg/day intravenous immunoglobulin for 5 days.

Features that led clinicians to suspect autoimmune encephalitis in cases 1 to 4 included prominent neuropsychiatric features (sudden and marked behavioural change and the onset of vivid visual hallucinations), prominent movement abnormalities (orofacial dyskinesia, choreoathetosis), and dysautonomic features (unstable pulse, blood pressure, and flushing). In case 5, although there was only one white cell in the cerebrospinal fluid, the diagnosis was considered as the child presented with coma, bitemporal magnetic resonance image changes, and hyponatraemia, a

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feature more often described with anti-voltage-gated potassium channel receptor encephalitis than with anti-NMDA receptor encephalitis.

All children continued on antimicrobial therapy and antiviral therapy until polymerase chain reaction or cultures were negative.

In this series of five children, in whom the median time from symptom onset to treatment was less than 1 week, four recovered completely, in comparison with 29% and 60% of children in previous studies.[2,3]

This may suggest that earlier initiation of immunosuppressive therapy results in improved outcomes; however, this case series is limited by small numbers. In addition, follow-up neuropsychological assessment was not carried out in cases 2 and 5 because of rapid return to baseline and good outcome reported by parents and school.

A systematic review and meta-analysis of NMDA cases in the literature might determine whether early treatment of anti-NMDA receptor encephalitis results in an improved outcome.

What this paper adds

- Early treatment of *N*-methyl-D-aspartate (NMDA) receptor encephalitis in children may improve outcome.

Table I: Features of children with *N*-methyl-D-aspartate (NMDA) encephalitis

Case no.	Age at onset (y)	Sex	Length of in-patient stay (wks)	Prodrome (duration)	Reason for presentation to medical services	Other features of NMDA encephalitis	Investigations	Intensive care unit	NMDA antibody	Time from admission to treatment	Outcome
1	6	F	6	No infection	**Change in behaviour** for 3d then seizure with residual left hemiparesis	**Dysphasia, hallucinations, orofacial dyskinesia,** chorea, self-mutilation, **sleep cycle disturbance,** fever, **dysautonomia**	CSF white cells 26/μL, abnormal MRI, abnormal EEG, no tumour	No	+ve serum, CSF not tested	Day 2 i.v. methylprednisolone and oral taper	Complete recovery, mainstream school
2	6	M	4	Throat infection (10d)	Admitted through psychiatry service with 2d history of confusion, **bizarre behaviour** and **hallucinations**	Seizure, **dysphasia, orofacial dyskinesia,** tremor, **sleep cycle disturbance,** fever	CSF white cells 1/μL, abnormal MRI imaging, abnormal EEG, no tumour	No	+ve serum, +ve CSF	Day 2 i.v. methylprednisolone and oral taper, day 2 i.v. immunoglobulin for 5d	Complete recovery, mainstream school
3	7	F	7	Fever and arthralgia (2d)	Generalized seizure	**Behavioural change, dysphasia,** agitation, **hallucinations, orofacial dyskinesia,** chorea, myoclonus, fever, **dysautonomia**	CSF white cells 4/μL, abnormal MRI, abnormal EEG, no tumour	Yes, 16d	−ve serum, +ve CSF	Day 4 i.v. methylprednisolone and oral taper, day 11 i.v. immunoglobulin for 5d	Ongoing seizures and behavioural issues, special school
4	11	F	12	Abdominal pain (14d)	Admitted with 3d history of confusion, **behavioural change,** aggression, inappropriate speech and cursing	Seizure, **dysphasia,** agitation, **hallucinations, orofacial dyskinesia,** chorea, echolalia, **sleep cycle disturbance,** fever, **dysautonomia**	CSF white cells 107/μL, normal MRI, abnormal EEG, no tumour	Yes, 23d	+ve serum, +ve CSF	Day 3 i.v. methylprednisolone and oral taper, day 11 i.v. immunoglobulin for 5d, day 16 PLEX (eight cycles)	Complete recovery but with weight gain, mainstream school
5	4	M	3	Gum infection (2d)	Admitted with lethargy, confusion and **coma** for 2d (GCS score 11/15)	**Dysphasia,** agitation, **low sodium,** fever, **dysautonomia**	CSF white cells 1/μL, abnormal MRI, abnormal EEG, no tumour	Yes, 7d	+ve serum, CSF not tested	Day 3 i.v. methylprednisolone and oral taper	Complete recovery, mainstream school

Features that led clinicians to suspect NMDA receptor encephalitis are highlighted in bold. F, female; M, male; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; EEG, electroencephalography; GCS, Glasgow Coma Scale; PLEX, plasma exchange.

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Book Review: Childhood Headache, 2nd edition

Edited by Ishaq Abu-Arafeh
London: Mac Keith Press, 2013
£95.00 (Hardback) pp 329
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This book is a valuable resource for all who are interested in neurological problems and specifically in headaches occurring in children and young people. It can be read chapter by chapter to gain a better understanding of this complex topic or, because it has a comprehensive index, it can be also used as a ready reference guide.

Headaches in children are extremely common; the prevalence is 60%. Twenty per cent of school children complain of headaches more than once a week and around 10% more than 2 days a week. Headaches in children represent a significant workload for general practitioners, emergency department staff, paediatricians, and paediatric neurologists. It is a common cause for children missing school. As such, there is a need for a comprehensive source of advice and knowledge on the diagnosis and management of childhood headache disorders; *Childhood Headache* provides this and more.

The book is written by 31 well-known and respected experts in the field of headache. The chapters take you on a journey from the history of headaches to our current understanding of the various types of headaches in childhood. Chapter 2 ('History of headache in childhood: from headache tablets to headache tablets') provides a fascinating insight into the understanding and treatment of childhood headaches through the centuries and clearly describes the rapid advancement of our understanding in this area that has occurred over the last few decades. Chapters on the pathophysiology, genetics, classification (using the current International Classification of Headache Disorders, 2nd edition – ICHD-II), and quality of life issues are followed by chapters on migraine, tension-type headaches, chronic headaches, and symptomatic headaches (including those due to brain tumours, idiopathic intracranial hypertension, craniofacial causes, and trauma).

There are chapters dealing with the management of children with headaches in general practice and specialist clinics. The final chapter ('Drawing as an expression of migraine symptoms in children: can a picture really paint a thousand words?') explores children's expression of headaches and associated symptoms through drawings. This chapter vividly highlights the debilitating nature of headaches and the significant impact they have on the lives of children and their families. It clearly reinforces the need for us to take seriously headaches in children and young people and to ensure that we manage and treat them appropriately and effectively.

Throughout the book the authors draw attention to the importance of taking a careful history (including family history) and performing a detailed examination. They provide relevant approaches to diagnosis and treatment and support these with the inclusion of clinical cases. The multidisciplinary approach to the management of headaches is given due recognition and importance. There are also chapters covering psychological aspects and treatment (including dietary management) of headache.

Although each of the authors brings their own unique style of writing to the book, their styles complement each other very well. All the chapters are well-referenced, concise, and easily digestible. The authors appreciate that it can be difficult to differentiate one type of headache from another in children and young people, and thus offer a pragmatic approach to diagnosing, classifying, and treating headaches which can be easily utilized in a busy clinical setting.

This second edition builds on the strong foundation of the first (published in 2002); but significant changes have been made. The editor, Dr Ishaq Abu-Arafeh, must be congratulated on bringing together experts in the complex and expanding field of childhood headaches, and for compiling a comprehensive, relevant, and easily readable text which is of value not just to medical and nursing students, nurses, doctors, and allied health professionals but anyone who works with children and young people. This book is a useful addition to my library and I am sure that I will be referring to it on a regular basis.

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