Severe childhood encephalopathy with dyskinesia and prolonged cognitive disturbances: evidence for anti-*N*-methyl-D-aspartate receptor encephalitis

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LIST OF ABBREVIATIONS

NMDA	*N*-methyl-D-aspartate
SCD	Sickle cell disease

AIM We report four cases of acquired severe encephalopathy with massive hyperkinesia, marked neurological and cognitive regression, sleep disturbance, prolonged mutism, and a remarkably delayed recovery (time to full recovery between 5 and 18mo) with an overall good outcome, and its association with anti-*N*-methyl-D-aspartate (anti-NMDA) receptor antibodies.
METHOD We reviewed the four cases retrospectively and we also reviewed the literature.
RESULTS Anti-NMDA receptor antibodies (without ovarian teratoma detected so far) were found in the two children tested in this study.
INTERPRETATION The clinical features are similar to those first reported in 1992 by Sebire et al.,[1] and rarely recognized since. Sleep disturbance was not emphasized as part of the disorder, but appears to be an important feature, whereas coma is less certain and difficult to evaluate in this setting. The combination of symptoms, evolution (mainly seizures at onset), severity, paucity of abnormal laboratory findings, very slow recovery, and difficult management justify its recognition as a specific entity. The neuropathological substrate may be anatomically close to that involved in encephalitis lethargica, in which the same target functions (sleep and movement) are affected but in reverse, with hypersomnolence and bradykinesia. This syndrome closely resembles anti-NMDA receptor encephalitis, which has been reported in adults and is often paraneoplastic.

In 1992, Sebire et al.[1] reported a series of six children presenting with a novel combination of intense dyskinesia and severe regression with prolonged cognitive impairment but who made an unexpected excellent recovery.[1] Since then, similar cases have been described. The disorder is sometimes called Sebire syndrome and is considered inflammatory or infectious in aetiology.[2–5] Hartley et al.,[6] in a paper entitled 'Immune-mediated chorea encephalopathy syndrome in childhood', specifically commented on the marked similarity between their cases and those of Sebire et al. Sleep disturbances (hypersomnolence) and dyskinesia (parkinsonism) are hallmarks of encephalitis lethargica, a condition increasingly recognized in children and presumed to be of autoimmune aetiology. In some cases, phases of insomnia and hyperkinesia, as in Sebire syndrome, may occur, suggesting that the localization of the acquired brain dysfunction may be in closely related areas and that common pathogenetic mechanisms are involved. This clinical picture is similar to the recently recognized entity, anti-*N*-methyl-D-aspartate (anti-NMDA) receptor encephalitis,[7] which may be the underlying cause of the disorder reported by Sebire et al.

We describe four new cases of Sebire syndrome, in which sleeplessness was a highly significant clinical feature 'masked' by severe dyskinesia and agitation, persisting long after dyskinesia had resolved. Anti-NMDA receptor antibodies were found in the two individuals who were tested. Their serum was analysed at the Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, UK (Prof. A Vincent), for antibodies against anti-NMDA receptor (reacting with the NR1, NR2A, and NR2B subunits). Enzyme-linked immunosorbent assays were used to measure antibody titres. Cerebrospinal fluid (CSF) analyses were not performed. All of the carers gave their consent to the publication of these results. The institution's ethics committee did not consider that their approval was required.

Case 1

This 3-year-old female had fever and sore throat 9 days before onset of the first neurological symptoms. She presented with a right-sided partial motor seizure, without fever. Within 9 days of the seizure she lost motor skills and eye contact, and became irritable. She had a second partial seizure and, 3 days later developed several additional seizures with eye deviation

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to the right and axial hypertonia. She stopped speaking and experienced periods of violent restlessness (including at night) and episodes of sudden respiratory distress. Over the same period, the dyskinesia evolved to a hyperkinetic state characterized by intense bursts of extrapyramidal movements (choreiform and dystonic episodes and orofacial dyskinesias). Treatment included antiepileptic drugs (carbamazepine, phenytoin, phenobarbital), aciclovir, corticosteroids, sedatives, and neuroleptics (chlorpromazine, tiaprid, diazepam, chloral hydrate). One month after the first seizure, recovery began with a decrease in restlessness and improvement in motor abilities and visual contact. Within 2 weeks, she was able to walk again. One month later, in tandem with the disappearance of extrapyramidal movements, fine motor skills returned. Object use and recognition returned at 3 months, and emotional and communication skills (verbal and gestures) at 4 months. Full recovery occurred within 7 months. At 13 years, she was normal and doing well at school.

Brain imaging was normal and electroencephalography (EEG) showed a diffuse and generalized slowing. Polymerase chain reactions (PCRs) and serologies for common neurotropic viruses were negative in blood and in CSF. In CSF, we found an elevation of white cells (18/mm^3), with the presence of oligoclonal bands. The blood and CSF findings are listed in Table I.

Case 2

This healthy 8-year-old female, with a background of reading and arithmetic difficulties, was admitted after a partial complex seizure, 1 month after an episode of fever and sore throat. Neurological examination was normal, but her mother commented that her speech had changed. Over the following days, progressive dysarthria and choreiform movements of the left upper limb appeared. There was a dramatic worsening of signs over the following days, with left hemichorea, progressive disinhibition, mutism, incontinence, and severe eating difficulties. Ten days later, dystonic movements, oculogyric crises, and orofacial dyskinesias emerged with persistent tachycardia without change in breathing patterns. There was no response to therapy, including to corticosteroids and immunoglobulin. One month later, new symptoms of intense agitation with autonomic symptoms (tachycardia, sweating, facial hyperaemia) appeared, and persisted for 3 months. Severe sleep disruption occurred, the child sleeping only 5 to 10 minutes at a time and not responding to various sedatives. This pattern continued for 2 months and then gradually disappeared. Three months after onset, eye contact improved and there was aimless walking. One month later she ate unaided, and 6 months after onset she started speaking again, initially single words with limited understanding. Over the following month, expression and comprehension recovered fully.

Table I: Laboratory findings of the reported cases

	Case 1	Case 2	Case 3	Case 4
Blood				
Leucocyte count	Normal	Normal	Normal	Normal
Sedimentation rate	Normal	Normal	Normal	Not done
Immunological work-up				
Anti-streptolysin (n<240)	Not done	Negative	Negative	Negative
Anti-thyroid antibodies	Not done	Negative	Negative	Not done
Lupus markers	Not done	Negative	Negative	Not done
Antineoplastic antibodies (anti-YO/HU/RI)	Not done	Negative	Not done	Not done
Anti-voltage-gated calcium/potassium channel antibodies	Not done	Negative	Not done	Not done
Anti-NMDA antibodies	Not done	Positive	Positive	Not done
Viral studies (PCR/titres)				
Common neurotropic agents[a]	Negative	Negative	Negative	Negative
Cerebrospinal fluid				
Day performed	D12/D15/D31	D7/D11/D43	D5/D10/D16/D46	D30/D44/D89
White cells (maximal)	18/mm^3	15/mm^3	47/mm^3[b]	18/mm^3
Proteins (Norm: 0.1–0.3g/L)	Normal	0.3g/l	0.395g/l	0.39g/l
Oligoclonal bands	Present	Present	Present	Absent
Common neurotropic viruses[c]	Negative	Negative	Negative	Negative
Electroencephalography				
Number	3	5	5	5
Most characteristic findings[d]	Diffuse slowing	Diffuse slowing	Diffuse slowing	Diffuse slowing
Brain MRI/CT	2 CT/2 MRI	5 MRI	1 CT/3 MRI	Gaseous encephalography
Day performed	D7, 16/D10, D33	D7, D11, D18, D48, D108	D3/D5, D12, D49	D7
Description	Normal	Normal[e]	Normal	Normal
Pelvic MRI	Not done	Normal	Normal	Not done

[a]Herpes group virus (herpes simplex virus, human herpesvirus 6, human herpesvirus 7, cytomegalovirus, Epstein–Barr virus, varicella), Coxsackie, Influenza, Mycoplasma, Borrelia *burgdorferi*. [b]Elevated α-interferon. [c]Herpes group virus (herpes simplex virus, human herpesvirus 6, human herpesvirus 7, cytomegalovirus, Epstein–Barr virus, varicella), enterovirus, and adenovirus. [d]No epileptic abnormality. [e]Last magnetic resonance image (MRI) shows a general brain atrophy, attributed to steroid treatment. CT, computed tomography; NMDA, *N*-methyl-D-aspartate; PCR, polymerase chain reactions.

A detailed neuropsychological assessment (Wechsler Intelligence Scale for Children, 4th edition) was performed 15 months after onset. The subscores were 86 for verbal intelligence, 92 for perceptive reasoning, 88 for speed processing, and 62 for working memory; the total IQ was 78, lowered by the working memory score and attention problems. Learning difficulties (dyslexia, dysorthography, and dyscalculation) were noted before the encephalitis. She is currently attending a specialized classes and will return to mainstream school 2 years after the onset of illness.

Brain MRIs were normal (except for a generalized brain atrophy on the last MRI, attributed to steroid treatment) and EEG showed a diffuse and generalized slowing. An extensive blood and CSF work-up was performed (see Table I): PCR and serology for common neurotropic viruses were negative in blood and CSF. In CSF we found elevation of white cells ($15/mm^3$), with the presence of oligoclonal bands.

Anti-NMDA receptor antibodies were found in serum. No ovarian teratoma was detected on pelvic MRI.

Case 3

A previously healthy female aged 6 years and 6 months presented following a generalized tonic–clonic seizure lasting 40 minutes. There was a prodrome of 48 hours during which she was 'clingy', was 'off form', and had an episode of incontinence. A few hours before the seizure, an abnormal posture of the left foot was noted during sport, followed by restlessness and sleeplessness overnight. On examination, she was alert and interactive, with signs of a left hemiparesis with dystonic posturing. Over the following week, her condition fluctuated and deteriorated. She became stuporose and then agitated, with marked choreiform movements and orofacial dyskinesia (Videos, supporting information published online). There was aggression with variable responsiveness, bizarre language, hallucinations, total sleep disruption, and self-mutilation. She was intermittently mute. There was autonomic instability, occasional oculogyric crises, and three further seizures. The acute illness lasted 6 weeks. At follow-up 22 months later she was attending mainstream school but receiving special needs assistance because of memory, language, and socialization difficulties. She continues to show ongoing recovery.

Brain imaging was normal and EEG showed a diffuse and generalized slowing. In addition to the laboratory findings listed in Table I (notably elevation of white cells in CSF [$47/mm^3$] and the presence of oligoclonal bands), during the acute phase serum and CSF α-interferon and CSF neopterin, tetrahydrobiopterin, and immunoglobulin G index were elevated, suggesting a virus-associated encephalopathy. The most relevant finding was anti-NMDA receptor antibodies found in serum; no ovarian teratoma was detected on pelvic MRI.

Case 4

In April 1975, a 7-year-old female had a generalized tonic–clonic seizure following mild gastroenteritis. The next day, she was admitted after a partial left-sided seizure. On neurological examination, a left arm paresis was found. Three days later, a 'strange theatrical behaviour' was noted.

Two weeks later, she was admitted following three partial seizures. She developed athetoid movements of both hands and marked eating difficulties, requiring tube feeding. One month later, speech output decreased with eventual mutism but apparent preservation of comprehension of language. At the same time, an extrapyramidal syndrome occurred with dystonia and orofacial dyskinesia; she became incontinent. During the next 4 months there was extreme restlessness, with sleep disturbance and hallucinations. A very gradual improvement in her behaviour was noted 6 months after onset, enabling transfer to a rehabilitation centre. At this time, there was a left-sided paresis, without pyramidal signs.

She remained an in-patient in rehabilitation for 5 months. Recovery began with self-feeding (initially hyperphagic), and return of sphincter control. From the date of onset of first symptoms, there was independent walking at 8 months, return of speech in the form of singing at 10 months, and complete recovery at 1 year.

The EEG showed a diffuse and generalized slowing. The laboratory findings are described in Table I. In CSF, we noted an elevation of proteins and white cells ($18cells/mm^3$), and absence of oligoclonal bands.

Thirty-two years later, she is a well-integrated married woman, mother of a 15-year-old boy, and working as a dental assistant. She does not remember anything about this dramatic period; the only sign of her childhood illness is a scar on her right thumb due to self-biting.

DISCUSSION

The four cases reported in this study share the unique combination of acquired massive oromotor and limb dyskinesia, a severe and prolonged cognitive regression, and remarkable recovery, as in the original report of Sebire et al.[1] In all cases, there was a preceding non-specific illness and, before onset of dyskinesia, an altered mental state, speech loss, restlessness, possible visual hallucinations, and isolated partial or generalized seizures (Table II). Sleep disturbance (insomnia) preceded the onset of dyskinesia, continued during the acute phase (despite sedatives), and persisted for some time after dyskinesia subsided. This suggests a primary sleep disruption rather than an effect of mental confusion, motor agitation, or dyskinesia. This feature has not been alluded to in previous reports. The movement disorder was a combination of moments of intense limb and orofacial (face, tongue, jaw) hyperkinesia, constant restlessness (motor agitation), and rare periods of normal sleep. The seizures were not severe, and EEG did not show spike discharges (Table I). There was no MRI abnormality, and the known infectious/parainfectious, toxic, immunological, and metabolic disorders associated with acute dyskinesia during a febrile illness were excluded.

Since the study by Sebire et al.[1] several similar cases have been reported,[2–6] suggesting that this represents a specific clinical entity, sometimes called Sebire syndrome.[8] In all reports, the same remarkable absence of MRI abnormalities has been noted, and evidence of an inflammatory process was often documented (prodromal infection, CSF pleocytosis, oligoclonal bands in the CSF). Further reports of movement

Table II: Clinical features

Features	Case 1	Case 2	Case 3	Case 4
Preceding infectious illness	Sore throat	Sore throat	Not described but 'off form'	Fever, gastrointestinal symptoms
Behaviour change	'Strange behaviour', poor speech	Infantilism, disinhibition	'Strange behaviour', clingy	'Strange behaviour', clingy
Visual hallucinations	Present[a]	Present[a]	Present	Present
Seizures, day[b]	Day 1 RP; day 6 RP; day 13 repeated P; day 20 RP with G	Day 1 PC; day 47 TCG	Day 3 GSE; day 1 TCG; day 14 TCG	Day 1 TC, G; day 6 LP; day 20 LP
Autonomic features	Respiratory distress	Flush and tachycardia	Tachycardia, temperature instability, apnoea	Not described
Sleep disturbances (duration)	Yes (1mo)	Yes (3mo)	3mo	Yes (approximately 3mo)
Characteristics of cognitive regression	Cognitive deterioration, mutism	Cognitive deterioration, mutism	Mutism, self-mutilation	Cognitive deterioration, mutism
Extrapyramidal signs and restlessness[c]	Dystonia, oculogyric crises, ballismus, choreoathetosis	Chorea, dystonia, oculogyric crises, orofacial dyskinesias	Choreic movements/ oromotor dyskinesias	Choreo-athetosis, orofacial dyskinesias
Sequence of recovery	Dyskinesia/motor/ comprehension/ expression	Dyskinesias/motor/ comprehension/ expression	Dyskinesia/motor/ feeding/speech	Dyskinesia/motor/comprehension/ expression
Time to full recovery	5mo	10mo	18mo	1y
Duration of follow-up	14y	18mo	22mo	32y

[a]As if fighting against something. [b]Day (of illness) was chosen as day of first clear neurological sign (i.e. first seizure). [c]In addition to paroxysmal movements, constant motor agitation was present in all individuals. R, right; L, left; P, partial; G, generalization; SE, status epilepticus; C, complex; TC, tonic–clonic.

disorders following mild infections have been published without reference to the series of Sebire et al.[9–12] A recent report from the California Encephalitis Project described a severe hyperkinetic encephalitic syndrome of unknown aetiology with significant sequelae at hospital discharge.[13]

Hypersomnia and movement disorders (parkinsonism) were regarded as hallmarks of encephalitis lethargica in the 1920s. The condition has been increasingly recognized[14] and recently described in association with basal ganglia antibodies.[15] It appears likely that the disruption of the same functions (sleep and motor functions) but in the opposite direction (insomnia and hyperkinesia), as reported here, reflect pathology in closely related brain systems. Several recent cases showed insomnia or sleep disturbance (without hypersomnolence) and various forms of hyperkinesia, including orofacial involvement.[15,16]

A striking feature of the hyperkinesia is the orofacial component, occurring in bursts or paroxysms, a sign also prominent in a newly recognized syndrome, anti-NMDA receptor encephalitis. This condition has been described as a paraneoplastic (mostly ovarian tumour) immune-mediated neurological disorder and may occur without a detectable tumour.[7] MRI is often normal, and recovery is 'typically slow', with amnesia of the entire illness, as here reported. Seizures, neuropsychiatric symptoms, autonomic instability, and central hypoventilation are commonly seen. Autonomic changes were reported in the original series of Sebire et al.[1] and were noted in the present cases.

The neuropsychological profile in the prolonged recovery phase over many months (seen in all cases in this study) and beginning long after the dyskinesia has subsided is unusual in acute childhood encephalopathies. The prolonged loss of spontaneous speech (probably mutism rather than aphasia) and the massive cognitive deterioration with permanent amnesia of the whole illness are remarkable. In case 1, recovery, which occurred over 7 months, showed a transition phase of total absence of verbal and non-verbal communication and emotional expressions, whereas recognition and use of objects had returned. This suggests that the most affected brain systems (the last to recover) were those implicated in social communication and emotions. This syndrome may be a unique acquired localized brain dysfunction showing a transient, partial, and reversible 'autistic' phase.

Two of our four participants were tested and found positive for anti-NMDA receptor antibodies. The pathogenesis of anti-NMDA receptor encephalitis remains to be clarified. Such antibodies have been described in association with ovarian teratomas. Recent data suggest involvement of NMDA receptors in sleep disturbances, movement disorders, and autonomic dysfunction – three of the cardinal symptoms in these individuals. In animal studies, sleep induction can be obtained by injecting NMDA receptor agonists into the cerebral ventricular system,[17] whereas NMDA receptor antagonists, such as MK-801, produce hyperactivity and insomnia during the intoxication phase, and, subsequently, prolonged alterations in non-rapid eye movement sleep patterns.[18] NR1 disruption in animals also causes hypoventilation.[19] NMDA antagonist drugs, such as phencyclidine and ketamine, may induce sleep and movement disorders.[20] The anatomical distribution of the three known subunits of the NMDA receptor, NR1, NR2, and NR3, seems insufficiently specific to be closely correlated with distinct clinical symptoms.[21–23]

In management of the acute phase, immunotherapy should be supplemented by dealing with the exhausting features of agitation, insomnia, and dyskinesia, even if sedation interferes with the assessment of the level of consciousness. Knowledge of the protracted course of recovery is important for global psychological management and rehabilitative measures. Individuals with teratoma are managed by the removal of the tumour and with immunotherapy; immunotherapy (immunoglobulin, corticosteroids, plasmapheresis,[24] and possibly rituximab[25]) is the mainstay of treatment in those without tumour.

Relapse may occur with or without a detectable tumour, presumably owing to the persistence of antibody within the central nervous system.[26]

In conclusion, the very special combination of neurological signs in the prodrome, acute phase, and prolonged recovery period justify recognition of this specific entity, which has important management and prognostic implications. Anti-NMDA receptor antibodies should be sought in all cases, including stored serum from individuals with a history of this constellation of signs.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Videos Videos show the patient discussed in Case 3 exhibiting agitation with marked choreiform movements and orofacial dyskinesias.

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