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Case Reports

Encephalitis Lethargica in a Twelve-year-old Girl: The Response to Levodopa Therapy

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Abstract Encephalitis lethargica is an acute encephalopathic illness characterised by sleep disturbance, neuropsychiatric and extrapyramidal symptoms. It is rarely reported in children and the diagnosis is made by exclusion of infective, biochemical, degenerative, autoimmune, toxic or metabolic causes of acute encephalopathy. It is recently postulated to be part of a spectrum of poststreptococcal autoimmune disease. We report a 12-year-old Chinese girl who presented with acute encephalopathic illness with predominant features of rigidity and dystonia. The diagnosis of encephalitis lethargica was contemplated in view of her major presenting neurological features and exclusion of other common causes of acute encephalopathy. She had a prompt and remarkable improvement in both motor and cognitive functions after treatment with levodopa. Encephalitis lethargica, though rare, does occur in children and early dopaminergic therapy not only alleviates symptoms but also heralds the recovery.

Key words Dystonia; Encephalitis lethargica; Extrapyramidal; Levodopa

Introduction

Encephalitis lethargica (EL) is an acute encephalopathic illness characterised by sleep disturbance, neuropsychiatric and extrapyramidal symptoms. It was first described by von Economo who recognised the outbreaks of "sleeping sickness" between 1916 and 1927 after a pandemic of influenza infection, and subsequent sporadic cases were reported in recent years.[1] The diagnosis of encephalitis lethargica relies on the relevant clinical features and exclusion of other disorders.[2] Recently, it has been postulated to be part of a spectrum of poststreptococcal autoimmune disease.[3] We report a twelve-year-old Chinese adolescent girl who presented with clinical features compatible with encephalitis lethargica, and a prompt and substantial response to the treatment of levodopa was observed.

Case Report

A 12-year-old Chinese girl presented with a one week history of altered consciousness and behavioural changes. She was previously well except history of squint with operation performed and was left with minimal residual left partial ptosis. She presented with sudden onset of behavioural changes including mutism, agitation, anxiety and reduction in conscious level. Her sleep pattern was disturbed and she had excessive daytime somnolence but insomnia at night. There were episodic attacks of dystonia and rigidity of left limbs which were occasionally associated with uprolling eyes. Attacks usually lasted for an hour. There was no history of preceding upper respiratory tract infection or drug intake.

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Physical examination showed low grade fever of 38 degree Celsius. She was found to have increased left partial ptosis. She had masked face with episodes of oromotor dyskinesia. She had left upper and lower limb rigidity, brisk tendon reflexes and intermittent uprolling eyes. Urgent Computed tomography of brain was normal. Cerebrospinal fluid (CSF) examination showed 4 white blood cells per cubic mm, protein 0.17 g/L and normal glucose level. Bacterial and viral cultures showed no growth. CSF polymerase chain reaction (PCR) for enterovirus, herpes simplex virus (HSV) and mycoplasma were negative, and paired titres of HSV and varicella were not elevated. Oligoclonal bandings were present in CSF but not in the serum. Blood tests include complete blood count, erythrocyte sedimentation rate, C-reactive protein, liver and renal function tests, fasting lactate and pyruvate, antinuclear antibodies, thyroid function test, copper and ceruloplasmin level and serum anti-mycoplasma IgM were normal. Monospot test was negative, and anti-streptolysin-O titre was less than 200 IU/ml. There was no change in the paired sera viral antibody titres for Japanese encephalitis virus, mumps, measles, HSV, varicella zoster virus, mycoplasma pneumoniae, enterovirus and influenza A and B. Viral cultures from nasopharyngeal aspirate, throat swab and stool showed no growth. Urine for toxicology screening was negative. Also serum prolactin and phenylalanine level were normal, and urine for metabolic screening was negative.

She was treated as acute encephalitis with intravenous acyclovir and the fever subsided three days later. There were increasing episodes of limb rigidity, dystonia and uprolling eyes which were accompanied with oromotor dyskinesia, dysphagia and walking difficulties. Carbamazepine and oral lorazepam were given for suspected seizure attacks but there was only partial response. Intermittent intravenous bolus of midazolam was required to abort prolonged dystonic attacks. Electroencephalogram showed slow and asymmetric background activity which was more obvious over right hemisphere. There were no epileptiform discharges in relation to episodes of limb spasm. Magnetic resonance imaging (MRI) of brain performed on day 3 was normal. Due to the worsening of the dystonia, persistent impaired consciousness, more apparent oculogyric crisis and increasing mutism, levodopa/carbidopa (1.5 mg/kg/day levodopa three times daily) was started empirically on day 18. Involuntary movements and agitation were significantly reduced one day after initiation of levodopa. She became more alert and emotionally stable. The dosage of levodopa was titrated gradually to 3.7 mg/kg/day in four divided doses within one week. Complete resolution of the dystonic symptoms was achieved on the second week of treatment. She was able to walk independently and her oromotor function and verbal communication gradually returned to normal. Her cognitive and neurological status remained normal on subsequent follow ups and levodopa was successfully tailed off after two months of treatment with no neurological sequelae. There was no recurrence of symptoms upon cessation of levodopa therapy. She returned school three months afterwards with no functional impairment. The presumptive diagnosis of encephalitis lethargica was made in view of her major neurological features and exclusion of common causes of acute encephalopathy.

Discussion

Encephalitis lethargica (EL) is an acute encephalitic illness associated with sleep disturbances (somnolence, insomnia or sleep inversion), extrapyramidal movements (parkinsonism and dyskinesias), and neuropsychiatric symptoms (obsessive-compulsive disorder, catatonia, mutism, apathy and conduct disorder).[3] The disease was first described by von Economo and was generally known as "sleeping sickness". Although the epidemic EL coincided with the pandemic influenza, von Economo thought that, based on clinical grounds, the 1918 influenza virus was not the cause of the illness.[1] This was further supported by the recent examination of the archived EL postmortem brain tissue which failed to demonstrate influenza RNA.[4]

EL can occur at any age, but there is a higher incidence rate between 10 and 30 years of age. It is a clinical diagnosis made by exclusion with unknown aetiology. Howard and Lees[5] have proposed diagnostic criteria and suggest that any patient with an acute or subacute encephalitic illness and at least three of the following seven features should be considered to have EL (Table 1). Additional features of EL

Table 1 Diagnostic criteria of encephalitis lethargica[5]

1.	Signs of basal ganglia involvement
2.	Oculogyric crisis
3.	Opthalmoplegia
4.	Obsessive-compulsive behaviour
5.	Akinetic-mutism
6.	Central respiratory irregularities
7.	Somnolence and/or sleep inversion

include epileptic seizures, opthalmoplegia, ptosis, pupillary disturbances and autonomic symptoms. EL is a retrospective diagnosis, and the initial presentation is that of acute encephalitis or encephalopathy. Therefore, all children should be extensively investigated in order to exclude other disorders. Diagnostic investigations should include cerebrospinal fluid examination which may show lymphocytic pleocytosis and oligoclonal bands. Infections associated with postencephalopathic extrapyramidal features such as Epstein-Barr virus, herpes simplex virus or mycoplasma should be excluded by negative PCR and serology. Serum copper and ceruloplasmin level and toxicology screening should also be performed to rule out other possibilities.[3] Electroencephalogram findings could be nonspecific with or without epileptiform discharges. MRI brain showed normal findings in most of the reported cases but inflammation of the midbrain and basal ganglia had been described.[3] Our patient presented with clinical features fulfilling the diagnostic criteria, together with the negative investigation findings, the presumptive diagnosis of encephalitis lethargica was made.

Other possible differential diagnoses have been considered in our patient. Immune-mediated chorea encephalopathy syndrome in childhood described by Hartley et al[6] is one of the possible conditions. They reported four patients in the series, although not fulfilling all the contemporary criteria for EL, showing some similarities to our patient including encephalopathy, extrapyramidal features, mutism and the presence of CSF-specific oligoclonal bands. However the characteristic extrapyramidal feature described in the series was generalised chorea instead of dystonia, and all patients made full recovery after three to four months. Paediatric neurotransmitter disease such as tyrosine hydroxylase deficiency is another possible diagnosis for patients presenting with ophthalmoplegia and extrapyramidal symptoms. Biochemical markers including serum prolactin and biogenic amines profile in the cerebrospinal fluid can be checked for suspected cases. However, this disease is usually presented in early childhood with chronic neurodevelopmental problems requiring long term dopaminergic therapy. Our patient has complete remission of neurological symptoms after cessation of levodopa treatment which makes this diagnosis unlikely. Other possibilities of secondary dystonia including neurometabolic disease such as Wilson's disease or other demyelinating diseases like multiple sclerosis have also been considered and ruled out in our patient. Furthermore, the majority of patients with secondary dystonia will have other associated neurological features and typical biochemical and radiological findings.

EL has been postulated to be part of a spectrum of poststreptococcal autoimmune disease.[7] Dale[3] has described twenty patients presenting with clinical features and course similar to epidemic EL, with half of the patients having previous upper respiratory tract infections. Raised titre of anti-streptolysin-O is found in 65% of cases, and 95% of patients have autoantibodies reactive against human basal ganglia antibodies compared to controls. However, anti-basal ganglia antibodies titres are not available in Hong Kong, therefore, the titres were not checked in our patient. Oligoclonal bands are present in the cerebrospinal fluid but absent in serum in 69% of cases. The presence of CSF oligoclonal bands is a nonspecific finding, and it is also found in cases of multiple sclerosis, central nervous system infections, or paraneoplastic disorders.

Levodopa is a dopamine precursor, and is considered to be the most effective treatment for Parkinson's disease. It is also used in various clinical conditions such as paediatric neurotransmitter diseases, movement disorders or postanoxic encephalopathy.[8] The response of levodopa in EL was also described in previous reports.[2,9,10] Our patient presents with acute encephalopathic picture, with predominant feature of dystonia and persistence of altered consciousness and sleep problems despite initial medical treatments. Although no formal neuropsychological test is performed as an objective measure, the improvement in the motor as well as cognitive aspects is clinically obvious and dramatic shortly after the initiation of levodopa treatment. It is likely that the rapid improvement is due to levodopa treatment rather than the natural course of the disease. Levodopa is started when patient is clinically in a downhill course. The remarkable improvement shortly after the start of medication supports the efficacy of levodopa therapy. In our patient, the treatment outcome seems to be comparable to other cases reported in the literature[2,10] (Table 2).

The outcome of EL is variable. According to the historical reports, von Economo suggests a rough rule of thirds: a third made a good recovery, a third had persistent movement or behavioural disorders, and a third died.[10] The prognosis seems to be more favourable in children, and in those who present with predominant neurological signs than those with prolonged psychological symptoms.[2]

Table 2 Comparison of patient demographics, clinical features and treatment outcome with other case series

	Age (Sex/Year)	Sleep disturbance	Extrapyramidal features	Psychiatric manifestations	Treatment	Outcome
Current case	F/12	Daytime somnolence Night time insomnia	Left limb rigidity and dystonia Oromotor dyskinesia Oculogyric crises	Emotional lability Mutism Anxiety Confusion	Levodopa Carbamazepine Lorazepam	Hospitalised for 5 weeks Full motor and cognitive recovery after 2 months
Van Toorn series[2]*	F/9	Somnolence Sleep inversion	Generalised dystonia Oculogyric crises	Visual and tactile hallucinations Obscessive-compulsive symptoms Emotional lability Anxiety	Levodopa Risperidone Clonazepam Sodium valproate Melatonin	Hospitalised for 2 months Required cognitive rehabilitation for 12 months, still receiving remedial support at school
	F/8	Somnolence	Generalised dystonia	Mutism Confusion Delirium	Levodopa Clonazepam	Hospitalised for 2 weeks Full motor and cognitive recovery after 3 months
Dale series[10]	M/8	Sleep inversion	Generalised dystonia Oromotor dyskinesia Bradykinesia	Agitation Confusion Obsessive-compulsive behaviours	Benztropine Levodopa Lorazepam Phenobarbitone Chloral hydrate Melatonin	Hospitalised for 3 months Full motor and cognitive recovery after 4 months
	M/13	Sleep inversion	Generalised dystonia	Agitation Visual hallucination Mutism	Levodopa Lorazepam Clonidine Melatonin Chloral hydrate	Improvement of motor disturbance after 3 months Full motor and cognitive recovery after 13 months

*Levodopa was used in 2 out of 5 patients in that case series

Conclusion

Encephalitis lethargica is a clinical diagnosis made by exclusion of other known causes of encephalopathy. Extensive diagnostic investigations need to be performed in suspected cases. Although EL is a rare condition, it should be considered in children presenting with an unexplained acute or subacute encephalopathy with predominating neuropsychiatric and extrapyramidal symptoms. Although the underlying aetiology and specific treatment for EL are not well established, dopaminergic agents could be given early to alleviate symptoms and herald the recovery.

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