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Classic late infantile neuronal ceroid lipofuscinosis in a Chinese patient

一華人患者典型晚期幼兒神經元蠟樣脂質瘤

Neuronal ceroid lipofuscinoses are a group of rare neurodegenerative disorders that are characterised by an accumulation of autofluorescent lipopigments in neurons and extraneuronal tissues. We report on a 4-year-old boy who presented with an acute onset of seizures followed by rapid psychomotor deterioration, ataxia, and visual failure. Photic stimulation at 1 to 3 Hz elicited discrete spike and wave discharges in the electroencephalogram, which were diminished at a higher frequency of stimulation. The electroretinogram was extinct. Magnetic resonance imaging of the brain showed generalised cerebral and cerebellar atrophy. Electron microscopic examination of lymphocytes and samples of muscle and skin revealed characteristic curvilinear inclusion bodies. To our knowledge, this is the first case of late infantile neuronal ceroid lipofuscinosis to be reported in a Hong Kong Chinese patient.

神經元蠟樣脂質瘤是一組罕見的神經變性病便，它以積聚在神經元及其外部組織的自體熒光脂色素為特徵。我們研究了一名出現急性癲癇急性發作，隨後快速精神運動性衰退，運動失調及失明的4歲男童。1至3 Hz的感光模擬誘出腦電圖中分散的刺突和波釋放，它在更高頻模擬時變小。視網膜電圖是熄滅的。腦的磁力共振圖顯示出普遍性的大小腦萎縮。淋巴細胞和肌肉皮膚樣品的電子顯微鏡檢查顯露出特有的曲線型包涵體。據我們所知，這是所報告的香港華人患者首個晚期神經元蠟樣脂質瘤的病例。

Key words:
Child, preschool;
Convulsions/etiology;
Electroencephalography;
Magnetic resonance imaging;
Neuronal ceroid-lipofuscinosis

關鍵詞：
兒童，學前；
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Introduction

The neuronal ceroid lipofuscinoses (NCLs) are a group of lysosomal storage disorders that are characterised by the intracellular accumulation of autofluorescent lipopigments in neurons and other tissues. The disorders are classified into the infantile (INCL), late infantile (LINCL), juvenile (JNCL), and adult-onset NCL, as well as a heterogeneous group of atypical subtypes. Eight genetic loci (*CLN1* to *8*) have so far been identified, and four *CLN* genes have been isolated (*CLN1*, *CLN2*, *CLN3*, and *CLN5*).[1] The disorders represent one of the most common neurodegenerative diseases in childhood, which affects 1 in 12 500 births in northern European populations.[2]

Classic LINCL presents at the ages of 2 to 4 years. It is characterised by progressive myoclonic epilepsy, ataxia, mental deterioration, and visual failure. The symptomatology usually evolves over a period of months. Electrophysiological studies reveal characteristic features, and biopsies of the skin, conjunctiva, or rectal mucosa typically reveal curvilinear intralysosomal inclusion bodies. Reports of LINCL among the Chinese population are rare.[3-5] In this report, we describe a 4-year-old Chinese boy who presented with intractable, generalised absence and myoclonic

seizures, developmental regression, and ataxia. To our knowledge, this is the first proven case of classic LINCL in the Hong Kong Chinese population.

Case report

A 4-year-old boy with normal antenatal and perinatal history presented to the Department of Paediatrics at the Caritas Medical Centre in June 1999, with a 2-year history of mild-grade mental retardation with autistic features. The boy had begun having repeated seizures when he was aged 2 years. The seizures included generalised tonic-clonic convulsions, myoclonia, atonic seizures, and atypical absence seizures. Frequent brief staring spells would sometimes occur more than 60 times a day and be accompanied by irregular, fragmentary, asynchronous, and asymmetrical myoclonic jerks. Epilepsia partialis continua involving the left upper limb had also been observed. When the patient was aged 3 years, he could walk up and down the stairs with assistance, run about, and kick a ball. He could scribble and was dry during the day, although there was no verbal communication. He had become increasingly ataxic and doubly incontinent during the next year, when he had lost the ability to walk or vocalise.

At presentation, the patient was found to have mental deterioration, marked ataxia, and poor truncal tone. He had difficulty in swallowing and there was significant drooling. Ophthalmological examination revealed bilateral optic atrophy. A complete blood count, liver and renal function tests, urine organic acid analysis, and serum amino acid chromatography gave normal results. Serum lactate and ammonia levels were also normal. Magnetic resonance imaging (MRI) of the brain showed cerebral and cerebellar atrophy. Photic stimulation at 1 to 3 Hz elicited discrete spike and wave discharges at the occipital region in the electroencephalogram (EEG). These features became diminished at a stimulation frequency of 6 to 10 Hz (Fig 1). The electroretinogram (ERG) was extinct. The flash visual-evoked potential (VEP) was normal in amplitude and latency, as was the brainstem auditory-evoked potential. No vacuolated lymphocytes were detected in the peripheral blood. The use of fluorescence microscopy did not detect autofluorescent lymphocytes. Trichrome staining of skeletal muscle did not show

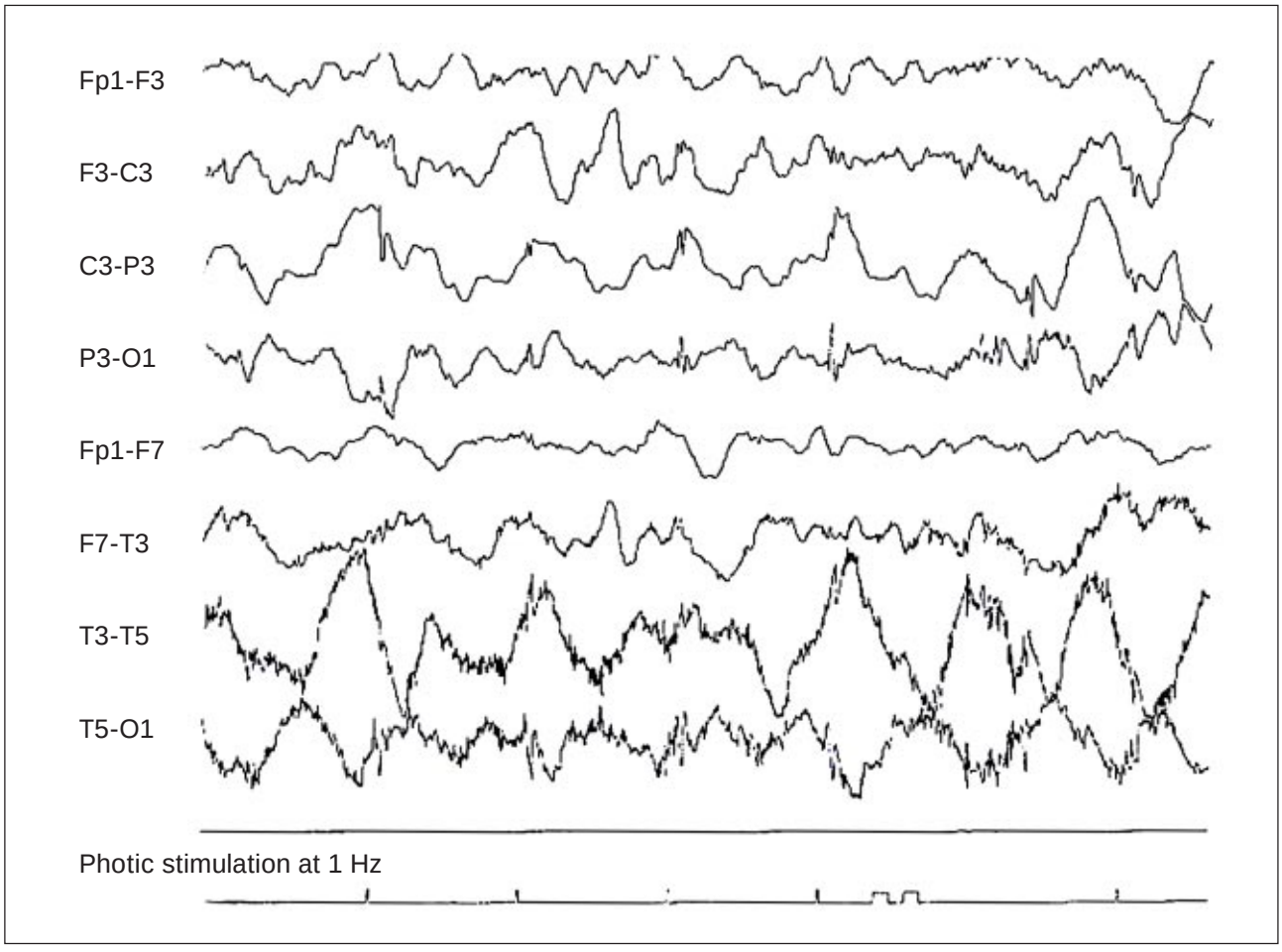

Fig 1. Photic stimulation at 1 Hz elicited discrete spike and wave discharges at the occipital region, which were synchronous with the stimuli

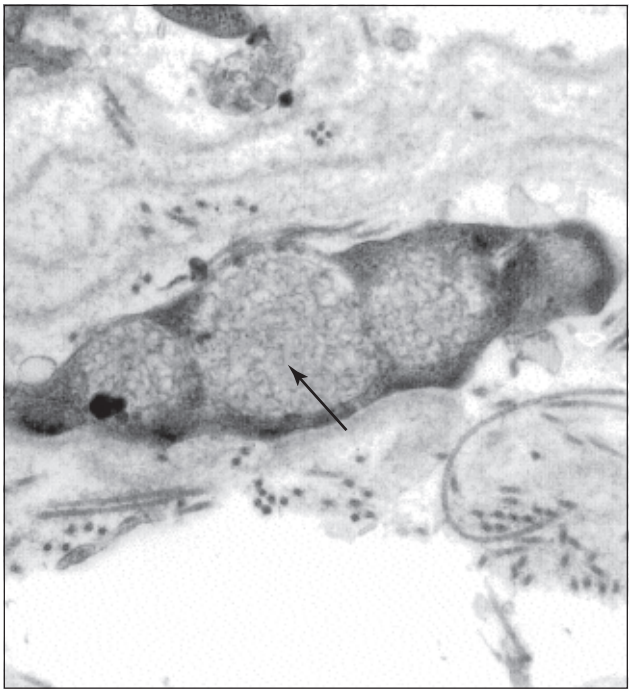

Fig 2. Electron microscopic examination of the skin showed curvilinear bodies in the cytoplasm (arrow) of a perineural cell (original magification x24 200)

ragged red fibres. Electron microscopic examination revealed many membrane-bound vacuoles that contained curvilinear inclusion bodies in the lymphocytes and samples of muscle and skin (Fig 2). The clinicopathological findings were consistent with a diagnosis of classic LINCL.

At a follow-up examination, the patient was found to have experienced rapid psychomotor deterioration: he was profoundly retarded, wheelchair-bound, and blind. The epilepsy was resistant to anticonvulsant therapy. Follow-up EEG studies revealed a generalised asynchronous slow background, which confirmed the encephalopathic condition.

Discussion

Classic LINCL was first differentiated by Bielschowsky in 1913,[6] as a distinct entity of NCL. Classic LINCL is characterised by an acute clinical course that results in a vegetative state over a period of months. The disorder is prevalent in Scandinavia and populations of European descent; reports in Asian populations are rare. A thorough *Medline* search found only three Chinese patients who were reported to have LINCL in the past decade,[3-5] whereas a nationwide survey in Japan revealed 36 cases of NCL, which included 15 cases of LINCL.[7] This disparity in prevalence probably represents an underdiagnosis of the disorder in our locality. The rare occurrence of LINCL often leads to a delayed diagnosis: Heim et al[8] found an average diagnostic delay of 12 months for patients with LINCL and 42 months for patients with JNCL in Germany. The delay may be attributed to a lack of awareness of the disorders by paediatricians and ophthalmologists.

The diagnosis of LINCL relies on the characteristic clinical presentation, electrophysiological and neuroradiological findings, and the identification of the ultrastructural abnormalities. The age at onset usually ranges from 2 to 4 years. Seizures and mental deterioration are shortly followed by myoclonus and ataxia. Visual failure appears later, with optic atrophy being detectable within 2.5 years. Photic stimulation below 3 Hz typically provokes high amplitude, polyspike, and wave discharges in the occipital region on EEG. The triad of (1) abnormal EEG discharges to slow photic stimulation, (2) a giant VEP, and (3) an early diminution or extinction of the ERG is highly characteristic of the disorder.[9] The photoparoxysmal response has provided important diagnostic clues to an atypical case of INCL in which results of extraneuronal biopsies were negative and MRI findings resembled leukodystrophy.[10] Occasionally, the initial VEP may appear normal, but becomes abnormally high at later stages.[11] While the sensory-evoked potential sometimes has a large amplitude, this feature is found less consistently than an enlarged VEP. Neuroimaging reveals progressive cerebral atrophy in all types of NCL. In LINCL, the atrophy is most obvious in the infratentorial region, as there is severe cerebellar involvement. Late infantile NCL is conventionally described as a grey-matter disease, but hyperintense signals on T2-weighted MRI scans that involve the periventricular white matter and which mimick leukodystrophy have also been reported.[12] This condition may represent Wallerian degeneration secondary to cortical neuronal loss.

The identification of cerebellar atrophy together with an involvement of the periventricular white-matter provides an important clue to the correct diagnosis. Ultrastructural examination reveals characteristic curvilinear, 'fingerprint' or osmiophilic inclusion bodies, which can be found in extraneuronal tissues such as skin, conjunctiva, lymphocytes, or rectal mucosa. In atypical cases in which the biopsy results are negative, the diagnosis may be obtained by a brain biopsy. Ultrastructural study is currently underutilised in Hong Kong. Its routine use is predicted to improve the diagnostic yield of neurodegenerative disorders.

The biochemical basis of NCL has remained obscured until recently. The major component of the lysosomal storage bodies of LINCL and JNCL (but not INCL) is the subunit c of the mitochondrial

adenosine triphosphate (ATP) synthase complex. Mutations in the *CLN2* gene that are associated with classic LINCL have been recently identified.[13] This gene maps to chromosome 11p15 and encodes a lysosomal pepstatin-insensitive peptidase, which is responsible for releasing N-terminal tripeptides from oligopeptides during protein degradation in lysosomes.[14] Immunodepletion of the human *CLN2* gene product from normal fibroblast extracts results in a loss in the degradative capacity of the subunit c of ATP synthase, thereby leading to its accumulation in lysosomes.[15] Twenty-six mutations have so far been identified in the *CLN2* gene, and they represent the largest number of mutations among the various *CLN* genes.[1]

Currently, there is no effective treatment for LINCL. In one reported case, the condition of a child who had received bone marrow transplantation continued to deteriorate during the following 2 years, although seizure control seemed to have improved.[16] The provision of new antiepileptic agents may help in the control of the intractable seizures.

This report describes the first proven case of classic LINCL in the Hong Kong Chinese population. The probable underdiagnosing of this disorder in Hong Kong may be related to the underutilisation of tissue examination during the diagnostic investigation of neurodegenerative disorders. Increased awareness of this rare disorder would prevent diagnostic delay. Any previously normal child who presents with intractable epilepsy, developmental regression, or visual failure without refractory anomaly should be referred immediately to a paediatric neurologist.[8] Ultrastructural study of relevant tissues is recommended for every patient who presents with a neurodegenerative condition.

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