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Case Report

An Early Presentation of a Chinese Boy with (Childhood-Onset) Juvenile Huntington Disease

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Abstract Huntington disease (HD) is an autosomal dominant neurodegenerative disorder which is characterised by progressive motor, cognitive and psychiatric disturbances in adults. The prevalence of HD in childhood onset (<10 years old) is low and the presentation mimics other neurological disease which makes diagnosis difficult in children. We present a case of (Childhood-Onset) Juvenile Huntington disease of a 6-year-old boy in Hong Kong. This case report provides clinical evidence of HD presentation at childhood-onset patients in our locality. It also illustrates the atypical presentation of childhood onset HD. Early genetic confirmation, multidisciplinary care with symptomatic treatment are crucial for patient care.

Key words *Dystonia; Epilepsy; Huntington; Regression*

Introduction

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder which is characterised by progressive motor, cognitive and psychiatric disturbances in adults. It is related to the abnormal expansion of CAG-trinucleotide repeats on Huntingtin (*HTT*) Gene on chromosome 4.[1,2] Less than 10% of HD patients are <21 years old which belongs to the Juvenile-onset Huntington Disease (JHD). The prevalence of HD in childhood onset (<10 years old) is even lower and the presentation mimics other neurological disease which makes diagnosis difficult. Chorea may not be obvious during onset, while epilepsy could occur in children, unlike adult.

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Case Presentation

We present a case of a 6-year-old Chinese boy with early presentation of Juvenile Huntington disease. The boy was followed up at a child developmental-assessment centre for tics-like eye blinking, autistic features, and motor incoordination at 5 years old. He was the first child of a non-consanguineous couple with an unremarkable birth history.

The patient was admitted to an acute hospital for confusion with recurrent and afebrile prolonged convulsion in July 2022. The vital signs were stable with growth parameters at 25th percentile. Physical examination on admission showed no focal neurological signs except mild central hypotonia (after repeated doses of benzodiazepines). Systemic examination was normal.

The child was given Rocephin and Acyclovir for possible encephalitis while pending further investigation. Levetiracetam and clobazam was initiated.

Investigations showed normal white cell count (WCC), C-reactive protein, liver & renal function, glucose, thyroid function. Autoimmune markers were unremarkable. Cerebral spinal Fluid (CSF) showed raised WCC 40 per mm^3 (on repeat), compatible with encephalitis. Subsequent CSF bacterial and viral culture are negative with normal cytology, protein, lactate, and glucose.

Serials EEGs showed frequent high amplitude rhythmic theta discharges over the posterior area (see Figure 1). Magnetic Resonance Imaging (MRI) brain on Day 1 showed no focal lesions (see Figure 2) while MR Spectroscopy was normal. There were no serial MRI changes in week 2.

On gradual recovery for his general condition a week afterwards, there were evolving features of:

- Dystonia over limbs with episodic toes-clawing
- Reach-out tremor without past-pointing
- Intermittent eye-starring
- Frequent tics-like eye movement
- Slow in speech with unsteady gait
- Slow and untidy handwriting

There were no nystagmus nor cerebellar signs. Jerks were easily elicited, and plantar reflexes were equivocal. Parents were unaware of similar symptoms in the past but commented as clumsy since a year ago. On further enquiry, the family recalled paternal grandfather had cognitive regression and motor slowness since the age of 40^+s, thought as normal ageing. While clinical features could be compatible with autoimmune encephalitis, with the presentation of seizures, tremor, clumsiness and suspicious family history of cognitive regression, metabolic and neurodegenerative genetic disorder are high on our list of differential diagnosis.

Extensive metabolic workup including dried blood spot test, amino acids, ammonia, carnitine profiles, lactate, pyruvate, blood gas, prolactin, copper, ceruloplasmin, isoform transferrin, very long chain fatty acids and urine metabolic screening was consistently normal. Serum Anti-MOG and Anti-NMDA were negative. CSF neurotransmitter studies, CSF encephalitis panel and CSF Autoimmune panel including Anti-NMDA were all normal. Tumour markers and abdominal ultrasound screening were also unrevealing.

Immunoglobin (2 gm/kg) was empirically given for possible autoimmune encephalitis followed by a short course of oral steroids. Artane and Baclofen were started for dystonia and hypertonia, showing some improvement. Sinemet was empirically tried for possible Dopa-responsive dystonia while pending genetic result, though without significant improvement and was stopped. The patient was discharged in September 2022 with close follow up.

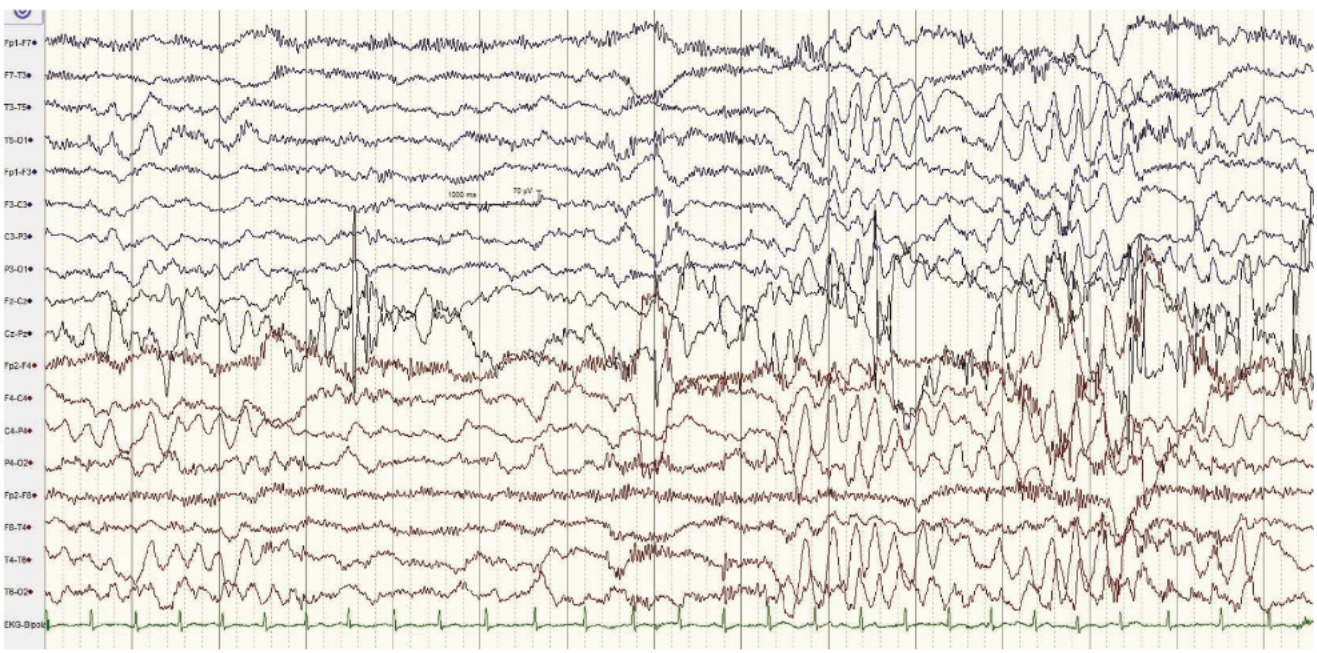

Figure 1. EEG showed frequent high amplitude rhythmic theta discharges over the posterior area.

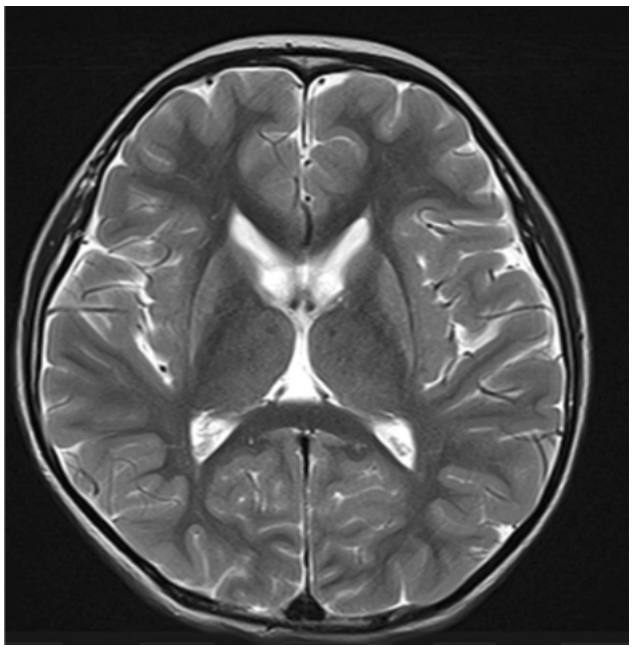

Figure 2. MRI Brain (with contrast) on Day 1. *MRI brain showed no focal lesion.

Epilepsy gene panel and dystonia gene panel result (released 3 months later) were unremarkable. Further genetic test with whole genome sequencing yielded a heterozygous pathogenic expansion in trinucleotide CAG repeats on one allele of *HTT* gene with 60 CAG repeats. The other allele had 13 CAG repeats on the *HTT* gene. The clinical presentation together with the molecular finding is compatible with Childhood-Onset Juvenile Huntington disease. Diagnosis is genetically confirmed at the age of 6. Formal genetic counselling and psychological support was offered to the family, supportive care is continued.

Discussion

HD is a progressive but fatal autosomal dominant neurodegenerative disorder characterised by motor, cognitive, psychiatric, and behavioural changes typically manifest in adulthood with morbidity 6-14 per 100,000 population.[3] JHD comprises ~5% of patients, with symptom onset <21 years old. HD is related to the trinucleotide repeat expansion (CAG) in the *HTT* gene on chromosome 4p16.3. It is translated into an extended polyglutamine tract of protein. The expanded allele through a deleterious gain-of-function mechanism leads to neuronal dysfunction and neurodegeneration. It showed genetic anticipation, demonstrating worsening phenotype with subsequent generations[1,4] as below:

Number of CAG repeats	Clinical
<26 copies	Wild type
27-35 copies	Intermediate range, typically not pathological though
>36 copies	Disease-causing

About 80% of the JHD patients inherit repeat expansion via paternal transmission.[5] The length of the CAG repeat shows an inverse correlation with the age at onset and disease penetrance. Alleles that contain more than 40 CAG repeats are completely penetrant. Individuals with juvenile onset of symptoms usually have an *HTT* allele with CAG repeats greater than 60. The median disease duration after motor onset in (childhood-onset) JHD is around 9 years, compared to 18 years duration in adolescent and adult-onset group.

The diagnosis of JHD is tricky as the presentation is atypical to those of adult HD, and it mimics other neurological diseases.[3] Chorea is reported as the initial motor sign in 80% of Adult HD, but it is rarely seen in JHD.[6] On the contrary, dysarthria, loss of dexterity, tics and myoclonus are more frequently seen in JHD. The motor symptoms mimic those with ataxia showing incoordination and unsteady walking, leading to misdiagnosis. Cognitive deficits are reported as initial signs in 30-83% of JHD patients showing motor, language, and social delay.[6] For our patients, the symptoms of tics, mild autistic features and developmental incoordination are the early features of JHD rather than chorea.

Our patient has epilepsy, which is not typical for Adult HD. Studies showed a high prevalence of epileptic seizures (up to 30-35%) in the Juvenile HD population. Behavioral issues and psychiatric symptoms are commonly reported.[6]

The case demonstrates the limitation of next-generation-sequencing with some gene panel tests may only detected for single nucleotide variant, duplication or deletion, the molecular structure aberration with trinucleotide repeats expansion may not be detected by such gene panel tests.

The disease progression in childhood-onset JHD is rapid. Its survival is shorter than adult HD. Our patient has 60 copies of CAG repeats that are disease-causing showing high disease penetrance at early age. The early symptoms onset of our patient as compared with grandfather seems to reflect the evidence of genetic anticipation of HD.

It has been a year since the initial presentation for our patient. He is currently on levetiracetam, clobazam and perampanel for seizure control. However, there are symptoms progression with evolving ocular dyspraxia and episodic involuntary movement. There is increase dystonia, truncal tremor, and unsteadiness. He shows decline in cognitive function with difficulty calculation and verbal expression. He is now studying in a special school having intensive multidisciplinary training. He could only walk with support. Shredded diet is suggested for recent mild oropharyngeal dysphagia and dysarthria. Tetrabenazine was tried for involuntary movement. His latest Modified Unified Huntington Disease Rating Scale is 80 out of 124 in November 2023 indicating rapid progression involving the motor, behavioral and functional aspect since diagnosis.

Currently there is no definite curative treatment for JHD.[6] Early genetic diagnosis and symptomatic supportive treatment are crucial. With genetic counseling and multidisciplinary care, it is hoped that the quality of life of HD patients could be improved while with early supportive and rehabilitative care.

Conclusion

To our knowledge, this the first local case report of the genetically confirmed (Childhood-Onset) Juvenile Huntington disease in Hong Kong at 6 years old. This case report provides clinical evidence of Huntington Disease presentation at childhood-onset patients in our locality. The case also illustrates the atypical presentation of childhood onset HD may delay the diagnosis.

Declaration of Interest

The author(s) indicated no potential conflicts of interest.

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