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Case Report

Characteristic Hypomyelination with Basal Ganglia Calcifications in a Chinese Girl: A Case of Cockayne Syndrome

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Abstract Cockayne syndrome (CS) is a rare autosomal recessive disorder with severe growth failure and developmental delay. There are multisystem manifestations including premature aging, microcephaly, cataract, pigmentary retinopathy, sensorineural deafness, photosensitivity, peripheral neuropathy and dysmorphic facial features. Characteristic neuroimaging findings include hypomyelination, basal ganglion calcifications and brain atrophy. This is the first local case report of CS in Hong Kong.

Key words *Cockayne syndrome; Developmental delay; Growth failure*

Case Report

A girl was referred to our neurology clinic at the age of 4 with global delay, poor weight gain and evolving spastic gait, suspected of cerebral palsy.

She was born at 33 weeks of gestation with birth weight at 10th-25th centile, height at 3rd-10th centile and head circumference at 50th-75th centile. She was admitted to Neonatal Intensive Care Unit due to prematurity, respiratory distress, uncomplicated necrotising enterocolitis and grade 1 intraventricular haemorrhage which resolved subsequently. She was discharged from neonatal unit on Day 57. She was the second daughter of a non-consanguineous Chinese couple. Her elder sister was diagnosed with autistic spectrum disorder.

On subsequent follow up, she was noted to have feeding problem at infancies. There was no choking despite being a small and slow eater. Despite attempts to increase caloric support, her growth parameters all fell below 3rd centile since first year with delayed development. Formal developmental assessment at 27 months old showed global developmental delay, showing developmental age of 12 months old.

Serial investigations were performed including complete blood count, bone profile, thyroid, liver and renal function, creatinine kinase, lactate, pyruvate, ammonia, acylcarnitine profile, venous gas, glucose and dried blood metabolic screening were normal. Urine cytomegalovirus culture and urine metabolic screening were unremarkable. Magnetic resonance imaging (MRI) brain at age of 34 months old and genetic screening at Clinical Genetics Service was unremarkable.

She attended special child care centre for training. She could only manage to walk independently and scribble at 38 months of age without any meaningful words. Subsequent swallowing assessment showed mild oropharyngeal dysphagia. Despite all these, parents preferred not for inpatient management. Nonetheless,

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subsequent follow up showed evolving dysmorphism and spastic gait, she was referred to neurology clinic at the age of 4.

Physical examination showed a cheerful girl with subtle dysmorphism with elongated face, sunken eyes, pointed chin and dental hypoplasia (Figure 1a). No signs of photosensitivity or cold peripheries were noted. Her muscle bulk was small but there was increased tone and brisk jerks over bilateral lower limbs, plantar reflex was equivocal. Upper limbs examination was unremarkable. She showed gross motor regression and only walk with support with scissoring gait. Baclofen was tried with fair response (Figure 1b).

Despite the spastic gait and microcephaly, a prior normal MRI brain result makes cerebral palsy sounds less likely, though hereditary spastic paraplegia could be another possible diagnosis. Neurometabolic or syndromal diseases were to be considered.

Further investigation with bone age at 5 was normal. Repeated MRI brain and spine showed new finding of hypomyelination predominantly in bilateral cerebral hemispheric periventricular white matter. There were also bilateral putamen calcifications and generalised atrophy of cerebrum, cerebellum and brainstem (Figure 2).

Based on Schiffmann and van der Knaap's MRI algorithm on the diagnosis of white matter disease in 2009,[1] integrating the unusual MRI finding of hypomyelination and calcification of basal ganglion with symptoms, Cockayne syndrome (CS) was highly suspected. With support from chemical pathologist, next generation sequencing confirmed ERCC8 homozygous exon 4 deletion. (excision repair cross-complementing, group 8, MIM*609412, GenBank accession number: NM_000082.3). The diagnosis of CS (Type 1) was then substantiated. Both parents and sister were later confirmed as heterozygous carriers of CS. Formal genetic counselling were offered.

Discussion

CS is a rare autosomal recessive neurodegenerative syndrome that was first described by Dr. Cockayne in 1936 characterised by dwarfism, retinal atrophy, and deafness.[2] Its incidence is 1 in 250,000 live births.[3] It is a genetic DNA repair disorder with premature aging. Fibroblasts of these patients often exhibit impaired transcription-coupled nucleotide excision repair.[3] Recently, there are more and more reported case in Chinese population, however the carrier rate is unknown.

CS presents with a spectrum of distinctive clinical presentation. CS consists of cutaneous photosensitivity,

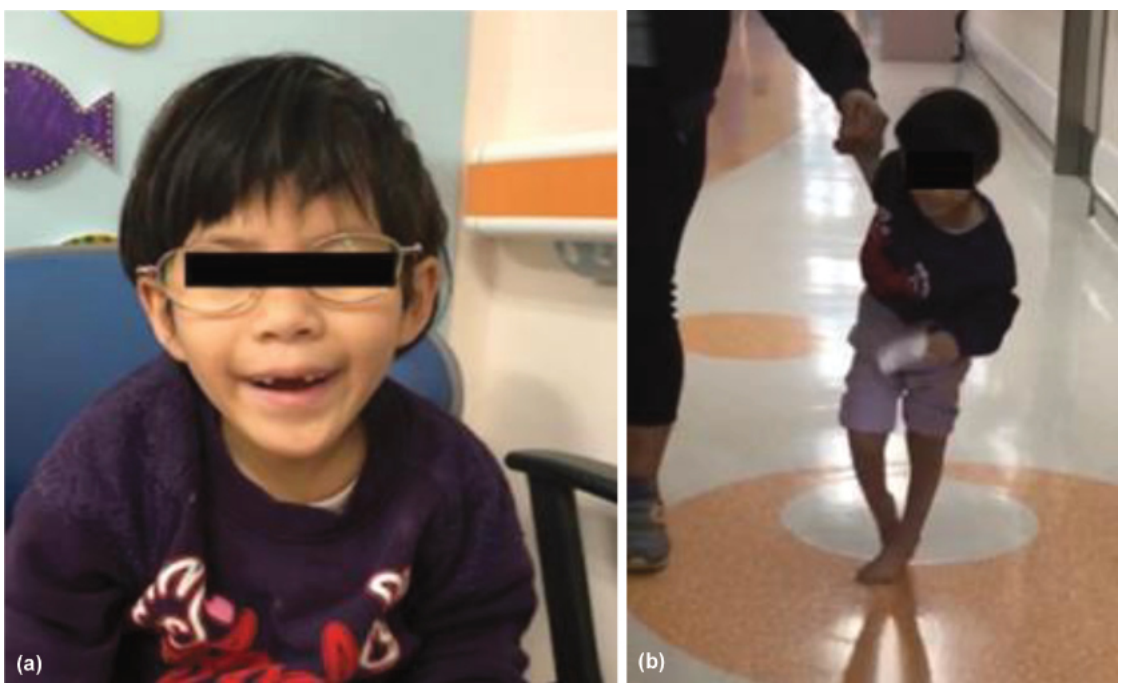

Figure 1 Photos of patient taken at 6 years old. (a) showing facial dysmorphism; (b) showing patient required assisted walking and walked with scissoring gait.

visual impairment due to pigmentary retinopathy or cataracts, hearing impairment, premature aging, failure to thrive, microcephaly, ataxia, developmental delay, and dysmorphism caused by loss of subcutaneous fat including sunken eyes, thin pointed nose, large ear, small chin.[3-5] CS is caused by mutations in either CSA (ERCC8) and CSB (ERCC6) gene which encode proteins involved in the transcription-coupled sub pathway of the nucleotide excision repair. Defects in repair of oxidative lesions and transcription defects explained the clinical pictures.[3,5,6]

CS consists of a phenotypic spectrum with different subtypes based on age of onset, severity and disease progression. CS type I (or CSA) is the commonest subtype, known as classic type or moderate form, which is caused by mutation in the gene ERCC8. Similar to our patient, it is characterised by normal prenatal growth followed with progressive growth failure and developmental delay with visual, hearing and peripheral nerve impairment onset after infancies.[3,4] This leads to early morbidity and mortality in first to second decades of life.[4,6]

CS type II (or CSB) is the severe form caused by mutation in the gene ERCC6. They usually present with dysmorphic features at infancies. Growth failure started since birth with cataracts, microcephaly and poor neurodevelopment with joint contractures. They usually present with premature death within first decade of life.[4,6]

CS type III is the mild form with late onset of symptoms. They could usually survive into adulthood.[4,6]

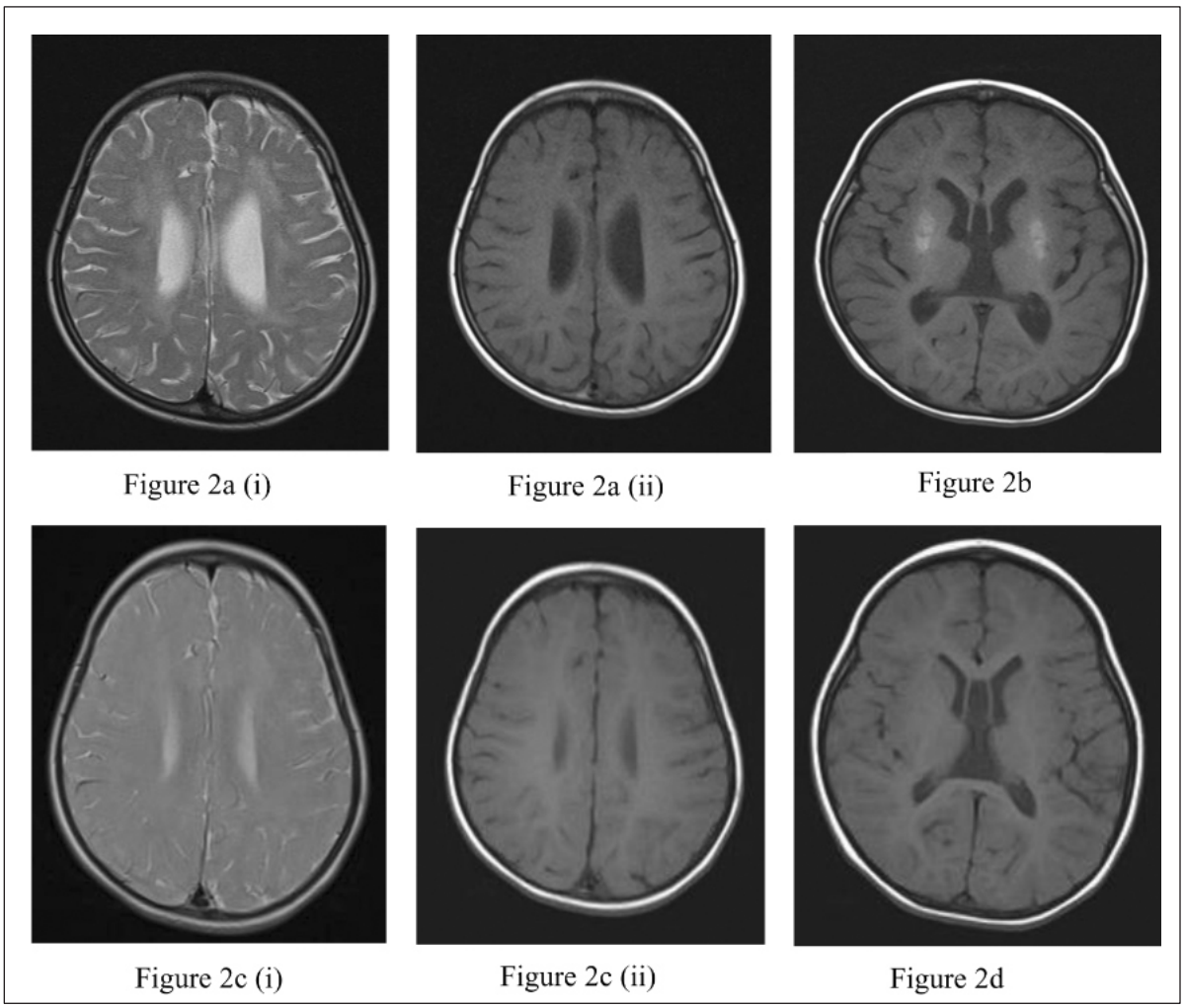

Figure 2 (a-b) Show MRI brain images at 5 years old. Figure 2a(i), axial T2-weighted image shows mild hyperintensity in bilateral periventricular white matter. Figure 2a(ii) shows normal T1-weighted signal. These suggest hypomyelination. Figure 2b, axial T1-weighted image shows bilateral putamen calcifications; (c-d) Show unremarkable MRI brain images at 34 months old at similar image cut as Figure 2a-b for comparison.

While the rare Cerebrooculofacioskeletal syndrome is characterised by the most severe fetal phenotype featuring prenatal developmental anomalies and growth failure with arthrogryposis, microcephaly, cataracts and microphthalmia. This is considered as allelic variant of CS.[4]

Cardinal features of neuroimaging features of CS include hypomyelination, cerebral calcifications and atrophy.[1,7] There are developmental problem of myelin sheath in CS causing hypomyelination, which usually affects cerebral cortex, internal capsule and corpus callosum.[1,7] Calcifications are typically located in the putamen and less common in the cortex and dentate nuclei. Brain atrophy is seen in supratentorial white matter, cerebellum, corpus callosum and the brainstem.[7] Patients often have heterogeneous clinical presentations due to varying degree of involvement to pyramidal, extra-pyramidal, cerebellar and peripheral nervous system. In our patient, she had more prominent pyramidal signs demonstrated, which is common in early phrase of disease. As disease progresses, it is anticipated that the tendon reflexes will become less brisk when the peripheral nerve dysfunction set in.[4]

The typical facial dysmorphism and neuroimaging features may not be apparent in early stage of disease.[4,6,7] Therefore, repeating MRI brain is necessary if patient developed evolving neurological symptoms. Also, CS shares similar clinical features with other neurological disorders which makes clinical diagnosis challenging. Some cases are being mislabelled as cerebral palsy or hereditary spastic diplegia before they are genetically diagnosed as CS.[8,9] Schiffmann and van der Knaap's MRI algorithm on the diagnosis of white matter disease in 2009 is crucial as illustrated in our case, to help narrowing down the possible differential diagnosis of hypomyelination to CS, hypomyelination with congenital cataract, Pelizaeus Merzbacher disease and Hypomyelination, hypogonadotropic hypogonadism and hypodontia (4H syndrome), etc.[1]

With the wider availability of genetic panel or whole exome sequencing, rare genetic diseases are diagnosed much earlier. For CS, early diagnosis facilitate counselling, interventions and complication screening. Wilson et al[5] suggested annual hearing and vision surveillance for sensorineural hearing loss, pigmentary retinopathy and cataract screening. CS patients often have poor feeding and growth failure due to genetic reason. Early introduction of non-oral feeding is essential for growth.[3-5] Regular monitoring of renal and liver functions with yearly USG screening are important as CS commonly presents with liver derangement or cholestasis, and sometimes renal impairment.[3-6] Patients should avoid Metronidazole as there are serious events reported with hepatotoxicity and liver failure.[10] Patients should be monitored for reflux, recurrent pneumonia, risk of glucose intolerance and premature onset of hypertension with atherosclerosis. Regular swallowing assessment is necessary. Regular dental screening is important for enamel hypoplasia with dental caries.[3-5] Excessive sun exposure should be avoided due to photosensitivity.[3,5] Multidisciplinary referral with allied health support is essential.[4,5]

For our patient, on surveillance, she was found to have severe hearing loss at 5 years old requiring hearing aid. She was subsequently screened to have pigmentary retinopathy and mild cataract at 6. She managed to walk with K-walker. Gastrostomy with fundoplication was performed. She plateaued the expected height potential for CS and had improved weight gain.

In summary we reported a case of Chinese girl diagnosed with CS presented with growth failure, developmental delay, dysmorphism and spastic gait. Neuroimaging findings of hypomyelination, calcifications and brain atrophy give us clue for the diagnosis. Early genetic studies can help establishing the diagnosis. With the multidisciplinary joint care, we hope to minimise the complications and bring hope for the family and patient.

Acknowledgement

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Decleration of Interest

None

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