

Case Report

18q-Deletion Syndrome: Characteristic MRI Features

WWC Tsui, EYL Kan, WS Mak, STH Fung

Abstract We illustrate the MRI findings of a child confirmed with 18q-deletion syndrome. Neurologic manifestations of this condition frequently involve the white matter, which is likely a result of haploinsufficiency of myelin basic protein as it is a major contributor to the formation of central nervous system myelin. In our case report, MRI demonstrated bilateral symmetric white matter T2 hyperintense signal with diminished gray-white matter differentiation suggestive of a delayed myelination pattern. Follow-up imaging 5 years later showed minimal progression of myelination.

Key words 18q-deletion; Hypomyelination; Myelin basic protein

Introduction

The reported incidence of 18q-deletion syndrome is estimated to be 1 in 40,000 births.¹ It is characterised by partial deletion of the long arm of chromosome 18. Majority of individuals with 18q-deletion syndrome are non-familial and is a result of a de novo random event occurrence during fertilisation.² There is a wide spectrum of clinical presentations ranging from neurological deficits, musculoskeletal, genitourinary, endocrine, and immunological abnormalities.³

The most often described neurological manifestation is hypomyelination of the central nervous system (CNS). The deleted segment of the long arm of chromosome 18 contains the gene for myelin basic protein (MBP), which plays an important role in myelin formation.⁴ We report a confirmed case of 18q-deletion syndrome with MRI showing abnormal myelination and minimal progression of myelination over time.

Case Report

A 7-year-old girl first presented at birth with multiple anomalies. She was born at 36 weeks gestation with low birth weight of 2150 grams and Apgar scores of 8 at one minute and 9 at five minutes. Multiple anomalies included dysmorphic facial features, hearing loss, hypoplastic first ribs, congenital vertical talus, sacral dimple, and ectopic anal opening. Non-paralytic hypotonia, microcephaly, delayed growth velocity with failure to thrive and short stature were evident soon after birth. Screening for congenital hypothyroidism was initially negative. A sigmoid colostomy and subsequent closure with posterior sagittal anorectoplasty were performed before 6 months old. Repair of tarsals and metatarsals with bilateral Achilles tenotomy were performed at age 1. Global developmental delay (GDD) with discrepant social and speech development with mild grade learning disability was noted

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since 18 months old requiring special needs education. Further endocrinological workup showed autoimmune hypothyroidism, requiring thyroxine supplement. Blood for IgA was normal. Diagnosis of 18q-deletion syndrome was made by karyotype analysis demonstrating partial deletion of the long arm of chromosome 18, del(18)(q21.3). To the best of our knowledge, this is the first case to be reported in Hong Kong with MRI correlation.

MRI brain was performed at 1 and 6 years of age. The initial scan revealed diminished myelination at the internal capsules and bilateral peripheral white matter (Figure 1). Abnormal and symmetrical T2-hyperintense signals were noted in the deep white matter bilaterally (Figure 1). Follow-up imaging performed 5 years later demonstrated lack of progression of myelination pattern with poor deep and subcortical white matter myelination on T2-weighted

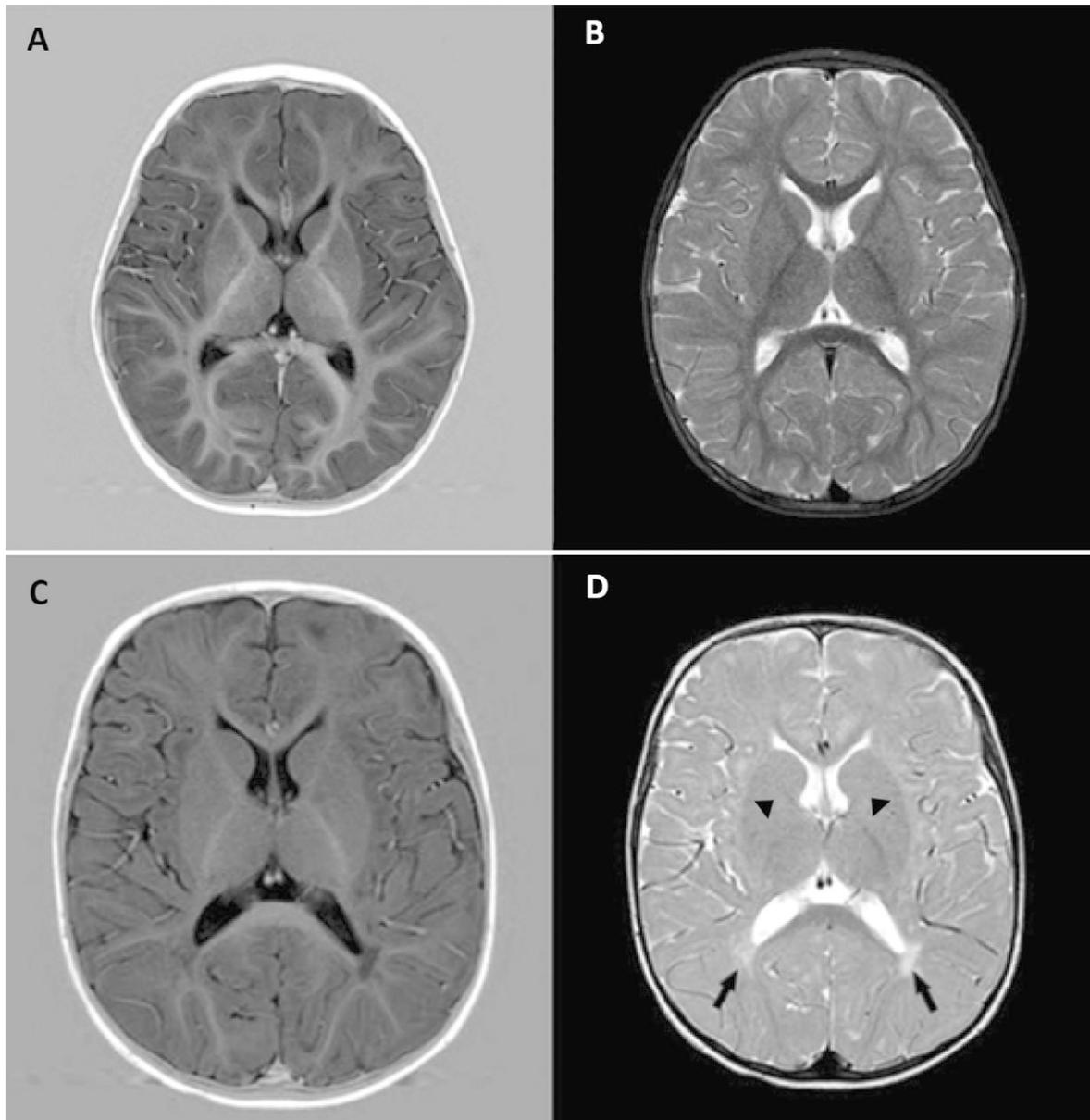


Figure 1 MRI at 1-year of age. (A and B) T1-weighted inversion recovery (IR) and T2-weighted images of 1-year-old showing normal myelination, respectively. (C) T1-weighted IR sequence shows delayed myelination, notably at the anterior limb of internal capsule, frontal, and temporal central and occipital peripheral white matter. (D) T2-weighted axial image shows symmetric abnormal T2-hyperintensity involving peri-trigonal deep white matter (black arrows) as well as delayed myelination at the anterior limb of internal capsules (arrowheads).

images (Figure 2). There was also diffuse white matter reduction and thinning of the corpus callosum (Figure 2). Both MRI studies showed the cerebellum was not affected.

Discussion

18q-deletion syndrome results from a partial deletion of the long arm of chromosome 18. The deletion encompasses a number of genes, of which MBP is most notable and has been described as a major component of the CNS.⁵ Up to 40% of the CNS is composed of MBP.⁶ MBP is expressed in oligodendrocytes for the maintenance and formation of myelin.⁷ Expression of MBP in oligodendrocytes and not Schwann cells could explain the involvement of the CNS and possible sparing of the peripheral nervous system.

The phenotype varies greatly between individuals but generally includes mental retardation, hypotonia, short stature, flat midface, ear anomalies, abnormal genitalia, and foot deformities. It was proposed that the variability derives from the heterogeneity of the deletion size and content.¹

Thyroid dysfunction is not uncommon in 18q-deletion patients, where 12% of cases are affected according to Schaub et al.¹ They observed that thyroid status is not static in these patients and progress from euthyroid to hypothyroidism over time.¹ Yet, the mechanism is not known. Initial neonatal hypothyroidism screening was

negative in our case. However, further endocrinological investigation was prompted by the picture of GDD revealing autoimmune hypothyroidism.

18q-deletion syndrome is classified among the hypomyelination disorders.⁸ Loevner et al showed the most common MRI findings were diffuse symmetrical T2-hyperintense signals in bilateral deep white matter, with the posterior periventricular regions most severely affected.⁷ Our case showed a pattern of delayed myelination as evidenced by minimal grey-white matter differentiation on T2-weighted imaging. Minimal changes in the abnormal white matter remained largely the same over the follow-up period, which is consistent with previous observations of persistent abnormal white matter pattern despite long periods of time.⁴ Consistent with previously reported MRI findings, the cerebellum and brainstem were largely unaffected in our case.⁷

It has been considered that the abnormal white matter on MRI signifies hypomyelination. However, Tada et al has studied magnetic resonance spectroscopic findings in a patient with 18q-deletion and found elevated choline levels suggestive of increased turnover of myelin as a dysfunction of oligodendrocytes or myelin fibres.⁹ This could correlate with our observed findings of minimal myelination despite a period of years, such that there may be an altered balance of myelination and demyelination rather than simply a process of hypomyelination.

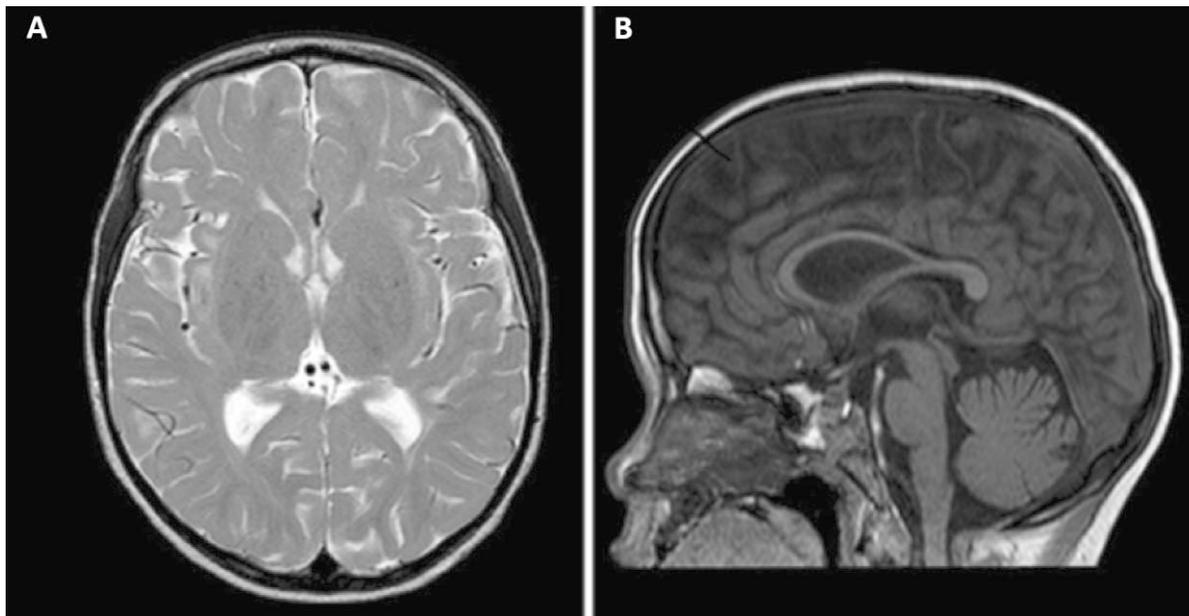


Figure 2 The previous radio-opaque appearance is no longer visible at control posterior-anterior chest X-ray (A) and there is no area compatible with atelectasis at control lung ultrasonography evaluation (B).

Radiological differential diagnoses of 18q-deletion syndrome include Pelizaeus-Merzbacher disease (PMD), Pelizaeus-Merzbacher-like disease, leukodystrophies with trichothiodystrophy, sialuria, fucosidosis and hypomyelination with atrophy of the basal ganglia and cerebellum (HABC). In PMD, Pelizaeus-Merzbacher-like disease, sialuria, and HABC, the cerebellum may become markedly atrophic, while in fucosidosis basal ganglia involvement is common. Derivation of the diagnosis involves combining clinical phenotype with radiological features of hypomyelination. PMD is an X-linked disease and occurs mainly in males. Nystagmus is usually more prominent and with earlier onset in PMD and Pelizaeus Merzbacher-like disease and evolving spasticity is also a feature of them. Marked skin hypersensitivity to sunlight occurs in trichothiodystrophy while in sialuria and fucosidosis, coarse facial features with organomegaly are common characteristics of storage diseases to help differentiate them from 18q-deletion syndrome. Extrapyramidal signs are often seen earlier in HABC than other hypomyelinating disorders.¹⁰ The myelination in 18q-deletion syndrome is much more advanced than in other hypomyelinating disorders.⁸ 18q-deletion syndrome differs from other hypomyelinating disorders such that its myelin deficit in MRI appears milder and patchier than in other hypomyelinating disorders.⁸ The clinical phenotype in this case together with MRI findings of hypomyelination provided clues for paediatricians to consider hypomyelinating diseases. This subsequently guided definitive diagnosis of 18q-deletion via karyotype analysis.

Conclusion

Partial deletions of the long arm of chromosome 18 are associated with a variable phenotypic clinical presentation. With regards to the CNS, the most commonly seen

neurological manifestation on MRI is a delayed myelination pattern, which may reflect an insufficiency of MBP. Together with clinical findings, MRI features can aid clinical diagnosis of 18q-deletion syndrome.

Declaration of Interest

We declare that we have no conflict of interests.

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