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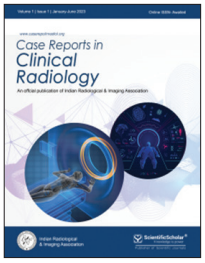


Case Series

Siblings with 4H leukodystrophy – A rare cause of hypomyelination

Zillani Alam[1], Shilpa Sankhe[1], Sana Ashraf Khan[1]

[1]Department of Radiology, Seth G. S. Medical College and KEM Hospital, Mumbai, Maharashtra, India.

***Corresponding author:**
Sana Ashraf Khan,
Department of Radiology,
Seth G. S. Medical College
and KEM Hospital, Mumbai,
Maharashtra, India.

sana18597@gmail.com

Received: 15 January 2023
Accepted: 05 April 2023
EPub Ahead of Print: 09 May 2023
Published: 26 July 2023

DOI
10.25259/CRCR_3_2023

Quick Response Code:

ABSTRACT

A 35-year-old man presented with slowly progressive ataxia since childhood, failure of development of secondary sexual characteristics, primary infertility, delayed dentition, and moderate sensorineural hearing loss on both sides. On physical examination, there were unerupted first molar teeth on both sides, lack of axillary and facial hair and a small-sized penis. He underwent a magnetic resonance imaging (MRI) examination of the brain which showed diffuse hypomyelination with relative sparing of bilateral posterior limbs of the internal capsule, the ventrolateral nucleus of the thalamus, and optic radiations, along with a hypoplastic anterior pituitary gland. Hence, 4H leukodystrophy was suggested radiologically which made us curious to ask for family history which revealed similar symptoms (absence of secondary sexual characters) in his younger male sibling. MRI brain screening was also performed for the sibling, which showed diffuse cerebral hypomyelination.

Keywords: Hypomyelination, Hypodontia, Hypogonadotropic hypogonadism

INTRODUCTION

4H leukodystrophy is a rare genetic disorder of POLR3A or POLR3B gene mutation with autosomal recessive inheritance.[1] 4H stands for hypomyelination, hypodontia, and hypogonadotropic hypogonadism. By knowing the specific imaging pattern and quantifying the hypomyelination and atrophy using imaging, we can help the patient improve their quality of life by administering hormonal supplements.

CASE 1

A 35-year-old man presented with slowly progressive ataxia since childhood, failure of development of secondary sexual characteristics, primary infertility, delayed dentition, and moderate sensorineural hearing loss on both sides.

Physical examination – Unerupted first molar teeth on both sides, lack of axillary and facial hair and small-sized penis.

Laboratory tests – Decreased testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels.

CASE 2

The 22-year-old male sibling of Case 1 had a similar clinical history of absence of secondary sexual characters but did not have sensorineural hearing loss or ataxia. Magnetic resonance imaging (MRI) brain screening was done for him.

Imaging diagnosis

The patient has primary infertility with low levels of anterior pituitary hormones and hypoplastic anterior pituitary gland on MRI. On MR imaging, there is diffuse cerebral hypomyelination with relative sparing of bilateral posterior limbs of the internal capsule, the ventrolateral nucleus of the thalamus and optic radiations. Multiple hypointense T2 dots (normally myelinated areas) in the background of T2 hyperintensity (hypomyelinated region) s/o myelin islets are found in subcortical and periventricular white matter predominantly in the frontal and parietal region [Figure 1]. This MRI pattern is classical for 4H leukodystrophy. Based on the signal intensities in different white mater areas on T1 and T2 weighted MR images, Hypomyelination score calculated for this patient as shown in Table 1 was 26 out of 44. Assessment of atrophy of supra- and infra-tentorial brain parenchyma is done to calculate the atrophy score which was 5 out of 10 in this patient [Table 1].

MRI brain screening of the sibling also revealed diffuse cerebral hypomyelination with myelin islets, thus confirming the genetic inheritance [Figure 2].

Follow-up

The genetic testing of the younger sibling (Case 2) was done in his childhood which was positive for the POLR3B gene. Genetic testing of the elder sibling (Case 1) is not done as presented later. There was uneruption of 1st molar (Hypodontia) in Case 1 as shown in Figure 3., thus helping with the diagnosis of 4H leukodystrophy.

Differential diagnosis

The differentials of diffuse hypomyelination should be ruled out which include: Cockayne syndrome, Pelizaeus-Merzbacher disease and Hypomyelination and congenital cataract. Presence of parenchymal calcifications is characteristic of Cockayne syndrome.[2] In PMD, there is involvement of optic radiation, internal capsule, dentate nucleus and medial lemniscus as well, which are spared in 4H leukodystrophy.[3]

Differential diagnosis	Differentiating points on imaging
1. CS	Like 4H leukodystrophy; hypomyelination of supratentorial parenchyma, corpus callosum and cerebellar atrophy are also found in CS. However, calcification of the putamen is a typical feature of classical or late-onset CS. These brain parenchymal calcifications are characteristic of CS which helps us easily differentiate it from 4H leukodystrophy on imaging[2]
2. PMD	It is also a diffuse hypomyelination disease like 4H leukodystrophy with progressive white matter atrophy and one of the closest differentials for 4H leukodystrophy. However, in 4H leukodystrophy disorder, other than diffuse hypomyelination, myelination of optic radiation, internal capsule, dentate nucleus, and medial lemniscus is relatively preserved in contrast to PMD. In 4H leukodystrophy apart from hypomyelination, there is also hypodontia and low anterior pituitary hormones which are not seen in PMD[3]
3. HCC	This disease is characterized by supratentorial hypomyelination, predominantly involving the periventricular white matter causing progressive neurological impairment, bilateral congenital cataracts, and peripheral neuropathy

CS: Cockayne syndrome, PMD: Pelizaeus–Merzbacher disease, HCC: Hypomyelination and congenital cataract

DISCUSSION

4H leukodystrophy is a genetic disorder of POLR3A or POLR3B gene mutation which has an autosomal recessive inheritance. The onset of the symptoms of this disease is usually in childhood and has slow progression with variable presentation. The major clinical findings are as follows:

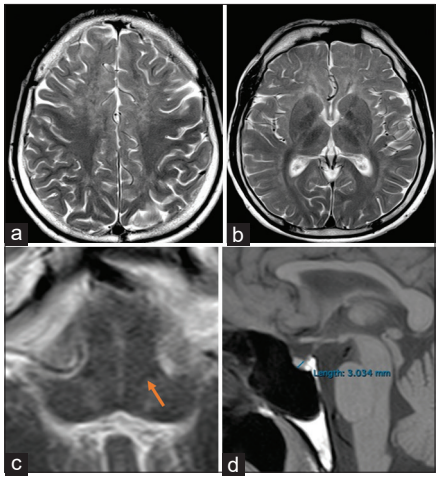
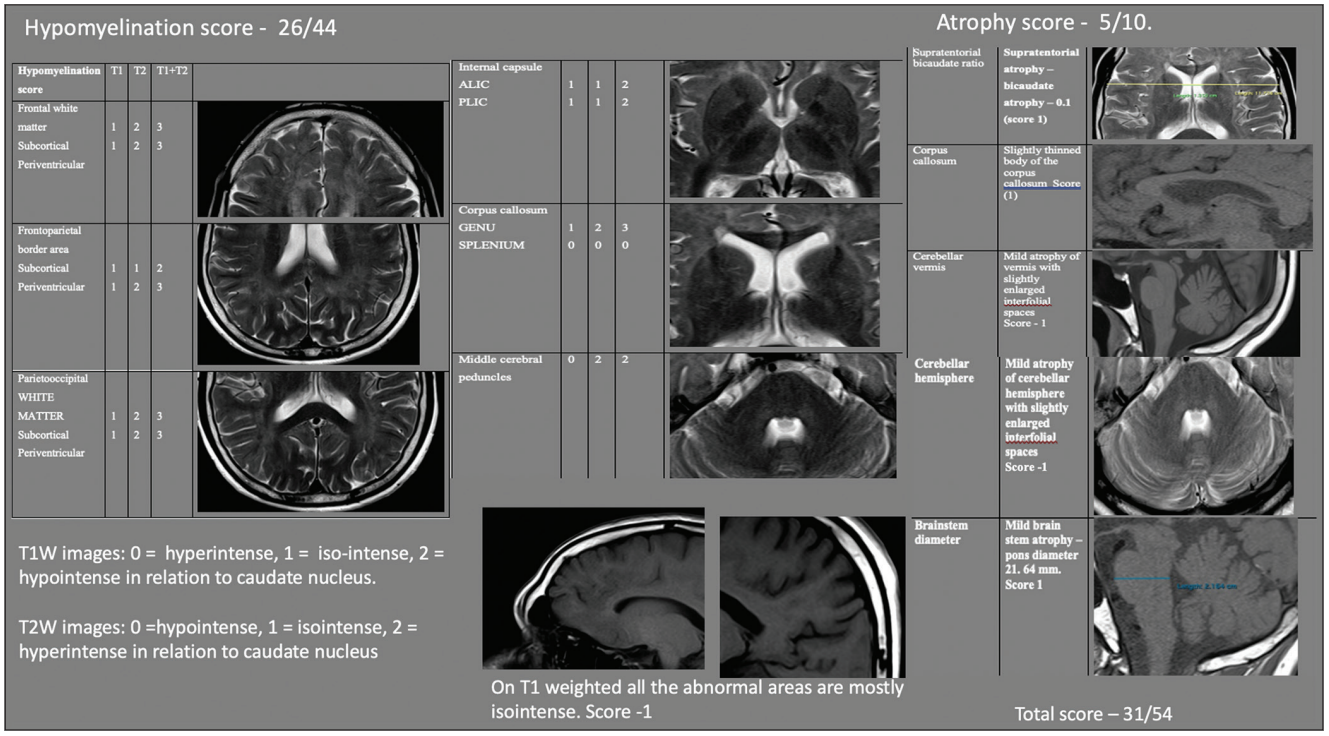


Figure 1: Magnetic resonance images of Case 1 (a) axial T2-weighted images through the brain show multiple T2/fluid-attenuated inversion recovery (FLAIR) hypointense dots (normal myelinated area) in the background of T2/FLAIR hyperintensity seen in both frontal lobes suggestive of myelin islets. (b) Axial T2-weighted image through the brain at the level of basal ganglia shows relative hypointensity of bilateral posterior limbs of the internal capsule, the ventrolateral nucleus of the thalamus, and optic radiations as compared to background white matter s/o preserved myelination of these regions. (c) T2-weighted zoomed-in axial image at the level of medulla shows "closed eye sign" – better myelination of medial lemniscus (arrowhead) in contrast to Pelizaeus–Merzbacher disease where hypomyelination of medial meniscus gives rise to open eye sign. (d) Sagittal T1-weighted image of the brain shows a hypoplastic anterior pituitary gland with a pituitary height of 3.0 mm (the normal range for this age is 3.9–6.4 mm).

Table 1: Hypomyelination score and atrophy score for "Case 1."



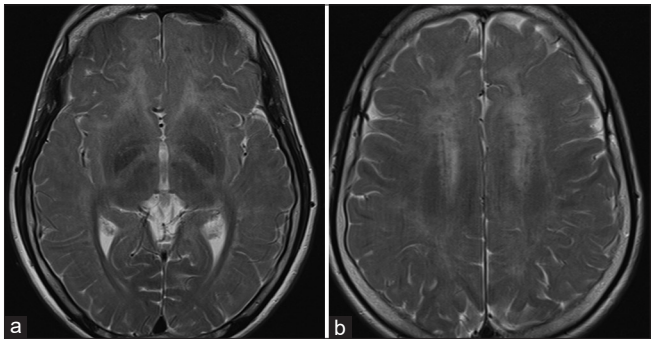


Figure 2: Magnetic resonance images of Case 2 (a) axial T2-weighted image through the brain at the level of basal ganglia shows more hypomyelination of the internal capsule (i.e., more hyperintense on T2), as compared to his elder sibling (Case 1). (b) Axial T2-weighted images through the brain show multiple T2/fluid-attenuated inversion recovery (FLAIR) hypointense dots (normal myelinated area) in the background of T2/FLAIR hyperintensity seen in both frontal lobes suggestive of myelin islets.

1. Neurological dysfunction (hypomyelination) – Mild-to-severe intellectual disabilities, progressive cerebellar dysfunction leading to ataxia
2. Dental (hypodontia) – Delayed or uneruption of the teeth
3. Endocrine abnormalities (Hypogonadotropic hypogonadism) – Delayed puberty, primary infertility, low FSH, and LH not responding to gonadotropin-releasing hormone.

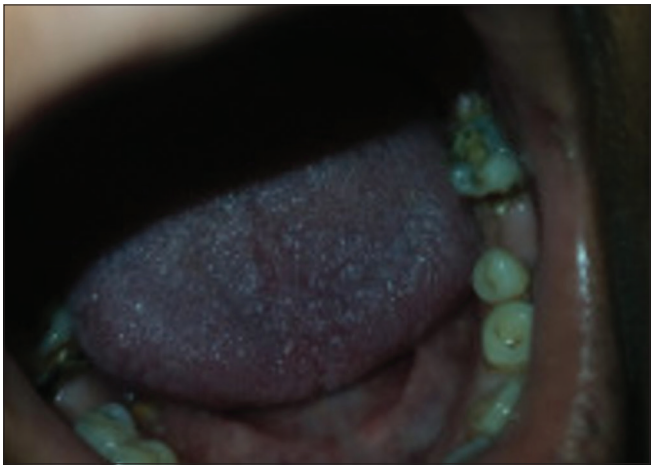


Figure 3: Hypodontia – Non-eruption of 1st molars in Case 1.

Other than these symptoms myopia can be seen in all patients and short stature is seen in 50% of the patients.

Etiopathogenesis

Mutation in POLR3A and POLR3B genes which encode for the two large subunits of RNA polymerase III enzyme complex (required for maintenance and development of myelin) is responsible for 4H leukodystrophy.[1]

The course of the disease is milder in patients with POLR3B mutation as compared to patients with POLR3A mutation.

Imaging features

MRI plays a crucial role in the identification and quantification of hypomyelination disorders. In 4H leukodystrophy disorder, there is diffuse cerebral hypomyelination manifested as diffuse T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity and T1 hypointensity with relative sparing of optic radiations, pyramidal tracts in the posterior limb of the internal capsule, dentate nucleus, and medial lemniscus (which are seen as T2/FLAIR hypointensity and T1 hyperintensity).[4] There are multiple hypointense T2 dots (normally myelinated areas) in the background of T2 hyperintensity (hypomyelinated region) s/o myelin islets found in subcortical and periventricular white matter predominantly in the frontal and parietal region. There is better myelination of the medial lemniscus (closed eye sign) and pyramidal tract in contrast to pelizaeus–merzbacher disease which shows an open eye sign.

MRI scoring of the hypomyelination and atrophy helps us quantify the disease severity and tells the patient's prognosis and the disease progression. Hypomyelination score depends on the signal intensity on T2- and T1-weighted images in frontal, frontoparietal, parieto-occipital white matter, internal capsule, corpus callosum, and middle cerebellar peduncle. Atrophy score includes supratentorial atrophy (bicaudate ratio), atrophy of corpus callosum, cerebellar vermis and cerebellar hemispheres, and brain stem (for brain stem atrophy, brain stem AP diameter).[5] Higher scores correlate with gross motor dysfunction, the higher chance of POLR3A mutation. Hypomyelination score in these patients remains the same with age, in contrast to atrophy score which shows progression with ageing. The hypoplastic anterior pituitary gland is commonly seen in these patients.

Prognosis and treatment

Due to broad clinical manifestations, coordinated care is required from the neurologist, dentist, and endocrinologist. Although everything is not reversible (hypomyelination), at least the desired growth can be achieved by administering pituitary supplements. Early diagnosis can help to improve the quality of patients' life.

CONCLUSION

MRI plays an important role, not only in the diagnosis of this entity but also can help us quantify the disease severity using the hypomyelination and atrophy score, thus helping predict the prognosis.

TEACHING POINTS

1. The "closed eye sign" seen in 4H leukodystrophy is suggestive of relative sparing of the medial lemniscus
2. The hypomyelination score remains the same with age, while the atrophy score shows progression with ageing.

SUMMARY OF CASES

The below table gives the summary of two cases of siblings of which the elder sibling presented to us at 35 years of age.

No.	Clinical features	Magnetic resonance imaging findings
Case 1: 35-year-old male	Ataxia since childhood, failure of development of secondary sexual characteristics, primary infertility, delayed dentition, and moderate sensorineural hearing loss	Diffuse cerebral hypomyelination with relative sparing of bilateral posterior limbs of the internal capsule, the ventrolateral nucleus of the thalamus, and optic radiations. Myelin islets are found in subcortical and periventricular white matter
Case 2: 22-year-old sibling of Case 1	Absence of secondary sexual characteristics	Diffuse cerebral hypomyelination with myelin islets

MCQs

1. Which of the following is not a hypomyelination disorder?
   a. Pelizaeus–Merzbacher disease
   b. Metachromatic leukodystrophy
   c. 4H leukodystrophy syndrome
   d. Cockayne syndrome

Answer Key: b

2. Which MRI findings favor 4H leukodystrophy syndrome over Pelizaeus–Merzbacher disease?
   a. Diffuse cerebral hypomyelination
   b. Relatively preserved myelination of medial lemniscus
   c. Hypoplastic anterior pituitary gland
   d. b and c

Answer Key: d

3. Which of the findings mentioned below are not consistent with 4H leukodystrophy?
   a. Presence of Myelin islet
   b. Progressive atrophy of supra and infratentorial brain parenchyma
   c. Delayed dentition
   d. The course of the disease is milder in patients with POLR3A mutation as compared to patients with POLR3B mutation.

Answer Key: d

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Alam Z, Sankhe S, Khan SA. Siblings with 4H leukodystrophy – A rare cause of hypomyelination. Case Rep Clin Radiol 2023;1:75-9.