Annals of Case Reports & Reviews

Case Report

doi: 10.39127/2574-5747/ACRR:1000155.
Win Ms and Goonetilleke R. Annal Cas Rep Rev: ACRR-155.

Unusual Case of Growth Hormone Deficiency and Progressive Ataxia

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Citation: Win Ms and Goonetilleke R (2020) Unusual Case of Growth Hormone Deficiency and Progressive Ataxia. Annal Cas Rep Rev: ACRR-154.

Received Date: 21 September 2020; **Accepted Date:** 25 September 2020; **Published Date:** 02 October 2020

Summary

A 3-year-old boy that presented to the paediatric clinic with short stature had inadequate growth hormone response to the glucagon stimulation test and therefore growth hormone treatment was initiated. He later developed symptoms of progressive ataxia, long eyelashes and bilateral pigmentary retinopathy. His MRI scan results showed cerebellar atrophy and his mutational analysis confirmed that he had two variants of the PNPLA6 gene, which was suggestive of Oliver-McFarlane Syndrome. Hence, this boy not only had the characteristic features of Oliver-McFarlane Syndrome such as chorioretinopathy, pituitary dysfunction and trichomegaly but also had cerebellar atrophy [1]. Although there is peripheral neuropathy or cerebellar ataxia in half of the cases that are known to be a phenotypic continuum of PNPLA6 mutation-related symptoms, to the best of our knowledge, this seems to be the first case of paediatric Oliver-McFarlane Syndrome with cerebellar atrophy as the other three cases with cerebellar atrophy were diagnosed only in adulthood.

Background

Oliver-McFarlane Syndrome, also known as trichomegaly retina pigmentary degeneration-dwarfism syndrome, is an extremely rare genetic disorder. Its prevalence is <1/1000,000, and it is characterized by hair abnormalities, severe chorioretinal atrophy, hypopituitarism, short stature and intellectual disability [2,3]. The first case was recognized in 1948, and its genetic association with PNPLA6 was discovered in 2015 [4,5]. According to a literature review, sixteen cases have been reported to date.

Case Presentation

His initial presentation to the paediatric clinic was short stature; height was in the 0.4th centile at 3 years of age, weight was in the 9th centile, head circumference was in the 50th centile and birth weight was in the 50th centile. There was no relevant family history, and the rest of the family members were fit and well. The mid parental height was in the 50th centile.

At the age of 3-4, he started to have visual symptoms such as a reduction in the peripheral visual field, especially at night and in crowded situations.

From the age of 4, he had progressive ataxia and noticed that he had long eyelashes. His peripheral neurophysiological examination was normal. There was no evidence of motor or sensory neuropathy, and he had normal reflexes and normal cranial nerve examination. He also had normal tone, posture, and full range of active and passive movements. However, he had ataxic gait and was ataxic on finger nose pointing as well. He did not have any obvious neurocutaneous features, conjunctival telangiectasia, seizures or hearing difficulties. He was independent in daily activities.

He was born at 36 weeks and his mother had gestational diabetes. There was no known consanguinity. He smiled, sat, walked and talked at the appropriate ages. Due to his poor balance, he could not ride a cycle at 8 years of age. He does well academically.

Investigations

He had investigations for short stature and the results showed low IGF1 and inadequate growth hormone response to glucagon stimulation test.

Electrodiagnostic tests were done due to visual symptoms and showed severe bilateral generalized retinal dysfunction of both the rod and cone systems at the level of the photoreceptors, and there were bilateral pigmentary patches in the peripheral retinal area and posterior pole with a healthy disc and vessels.

His MRI scan at 4 years of age showed cerebellar atrophy and his mutational analysis confirmed that he had two variants of the PNPLA6 gene, which was suggestive of Oliver-McFarlane Syndrome.

Treatment

His height was monitored closely and growth hormone treatment was started. He had good response to growth hormone treatment.

Outcome and Follow-Up

He is being monitored by neurologists, an endocrinologist and an ophthalmologist and is supported at school by participating in the exercise programmes (Fizzy Programmes) that assist in balance and motor skills. The prognosis is not fully understood as there is only one article in the literature about the long-term prognosis of Oliver-McFarlane Syndrome [6].

Discussion

Oliver-McFarlane Syndrome is an extremely rare genetic condition with a total of 16 reported cases in the literature, and the prognosis is still uncertain. The syndrome is known to be caused by the variants of the PNPLA6 gene and is characterized by trichomegaly, congenital hypopituitarism and retinal degeneration. Oliver-McFarlane Syndrome can be sporadic or autosomal recessive [7]. As PNPLA6 gene dysfunction affects different systems and organs, including the nervous system, retina, pituitary gland, cerebellum and the epidermis, there are other syndromes associated with this mutation, such as Boucher-Neuhäuser Syndrome, Gordon Holmes Syndrome, Laurence-Moon Syndrome and spastic paraplegia type 39. Laurence-Moon Syndrome has similar clinical features as Oliver-McFarlane Syndrome but lacks trichomegaly [5,8].

We reviewed all reported cases of Oliver-McFarlane Syndrome presenting with trichomegaly and pigmentary degeneration of the retina, Table (1), and 11 out of 17 patients had hypogonadism and pubertal delay. Additionally, 10 out of 17 of the total number of patients presented with short stature and growth hormone deficiency [9]. Even though 64 % of patients, which is 11 out of 17 patients, have peripheral neuropathy or ataxia, only 4 patients have cerebellar atrophy, in which our patient is the first paediatric patient who has cerebellar atrophy and ataxia. It has been noticed that chorioretinopathy usually appears within the first 5 years of age and that progressive spinocerebellar symptoms present later in life, but according to our review and case report, they can occur earlier [10,11]. Thus, neuroimaging should be considered, as Oliver-McFarlane Syndrome can be associated with cerebellar atrophy [4].

	GH def	Hypo Thyroid	Hypo Gonad	Cerebellar atrophy	Peripheral Neuro	Tricho Megaly	Retinitis Pigment
Oliver 1965	-	+	-	+	+	+	+
Cant 1967	+	-	+	-	+	+	+
Corby 1971	-	-	-	-	-	+	+
Zaun 1984	-	-	-	-	-	+	+
Zaun 1984	-	+	-	-	-	+	+
Patton 1986	+	+	+	-	+	+	+
Mathieu 91	-	-	+	-	+	+	+
Mathieu 91	+	-	+	-	+	+	+
Harito 03	NM*	NM*	+	-	+	+	+
Haimi 05	+	-	+	-	-	+	+
Haimi 05	+	-	-	-	-	+	+
Sonmez 08	+	+	+	-	+	+	+
Shanker 94	+	-	+	-	+	+	+

Sheng 13	-	-	+	-	-	+	+
Pedroso 13	+	+	+	+	+	+	+
Patsi 18	+	+	+	+	+	+	+
Our case	+	-	-	+	+	+	+
*NM-not mention *GH-growth hormone *Hypothyroidism *Hypogonadism *Peripheral Neuropathy							

Table 1: Reported Oliver-Mcfarlane Syndrome cases and their associated signs and symptoms.

Learning Points

1. Cerebellar atrophy can present in paediatric patients with Oliver-McFarlane Syndrome.
2. As cerebellar ataxia is part of the presentation of variants of PNPLA6 , neuro imaging is recommemded to diagnose or rule out cerebellar atrophy .
3. Anterior pituitary hormones testing is recommended even though growth hormone and thyroid hormone deficiency are noticed to be part of the syndrome but hypopitutarism can be part of the variants.

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