Uncombable Hair in a Case of Zellweger Syndrome – A New Association

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Abstract

Zellweger syndrome (ZS) is a rare autosomal recessive, peroxisomal biogenesis disorder (PBD) that occurs due to a mutation in any of the thirteen peroxin *(PEX)* genes. It is reported to manifest with varying degrees of severity, ranging from non-specific gastrointestinal abnormalities, nail and enamel defects to multisystem involvement (cerebro-hepato-renal syndrome, eye, ear, and neurological abnormalities). Uncombable hair syndrome (UHS) is a rare hair shaft disorder characterized by dry, frizzy, unmanageable hair. Diagnosis of UHS can be confirmed by scanning electron microscopy (SEM), which reveals a triangular cross-section of the hair. We report a case of UHS with a hitherto unreported association of ZS (due to a homozygous mutation of *PEX* 12).

Keywords: *PEX gene, uncombable hair syndrome, Zellweger syndrome*

Introduction

Peroxisomes are cell structures that are necessary for normal brain development and the formation of structures such as myelin, retina, cells of the liver, kidney, and bone.[1,2] The mutation in one or more of the peroxin (*PEX*) genes, that encode proteins responsible for peroxisomal function, causes Zellweger syndrome (ZS).[1-3] The genotype of the patient and age of onset can impact disease severity. The early findings (during the first months of life) are hepatomegaly, splenomegaly, prolonged jaundice, and sometimes, liver failure, but may also manifest with anorexia, vomiting, and diarrhoea, leading to failure to thrive. Uncombable hair syndrome (UHS) is a rare hair shaft structural anomaly, due to dysfunction of the inner root sheath/ dermal papilla,[4] characterized by dry, fragile, unmanageable hair. We present a case of a 6-year-old girl with mild ZS (contracted right lobe of the liver, neonatal cholestasis, jaundice) and UHS, an association probably reported for the first time. Atypical presentation of ZS with improved quality of life in those with *PEX* 12 mutations and an association with UHS may add to the existing literature.

Case Report

A 6-year-old girl presented to our outpatient department with complaints of frizziness and decreased hair growth since birth. The patient's parents provided a documented medical record of the contracted right lobe of the liver, cholestasis, jaundice, and splenomegaly in infancy, for which she is receiving ursodeoxycholic acid. There was no history of developmental delay, seizures, visual or aural abnormalities. A history of second-degree consanguinity was noted in the parents. Both were asymptomatic. The mother had a bad obstetric history ($G_6 P_2 L_1 A_4$).

The imaging done at one year of age showed normal magnetic resonance imaging (MRI) of the brain and a contracted right lobe of the liver (on abdominal ultrasound). Ocular and ear examinations were normal. Genetic testing of the patient done 3 years ago revealed a homozygous mutation of the *PEX* 12 gene and was diagnosed as ZS. Genetic testing of both apparently normal parents revealed heterozygous mutations of the *PEX* 12 gene.

The general examination showed the presence of icterus and a normal gait. On local examination, unevenness and gritty texture of scalp hair were noted [Figures 1 and 2]. Dermoscopy of the scalp revealed variation in pigmentation of hairs

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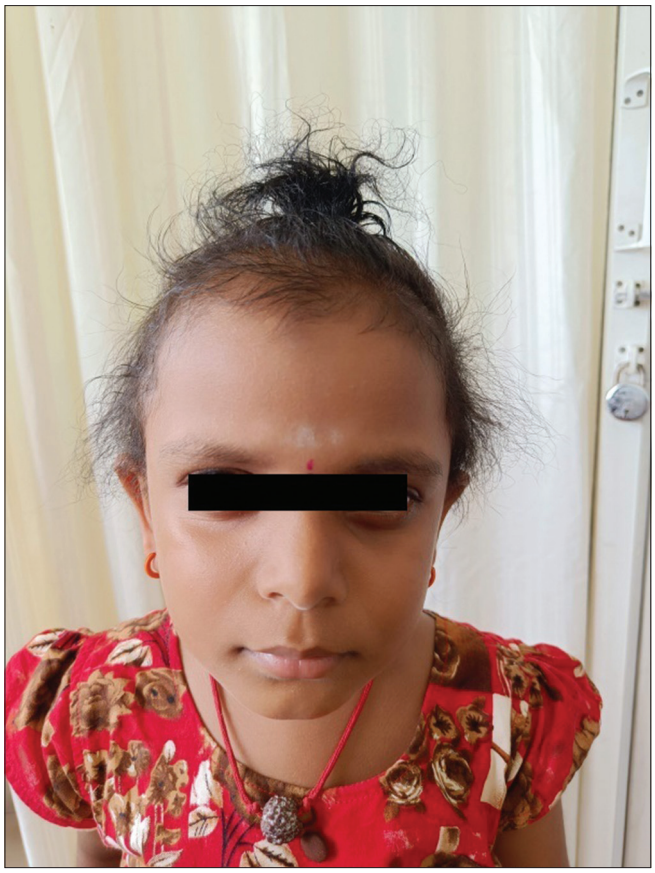

Figure 1: High forehead and regressing hairline

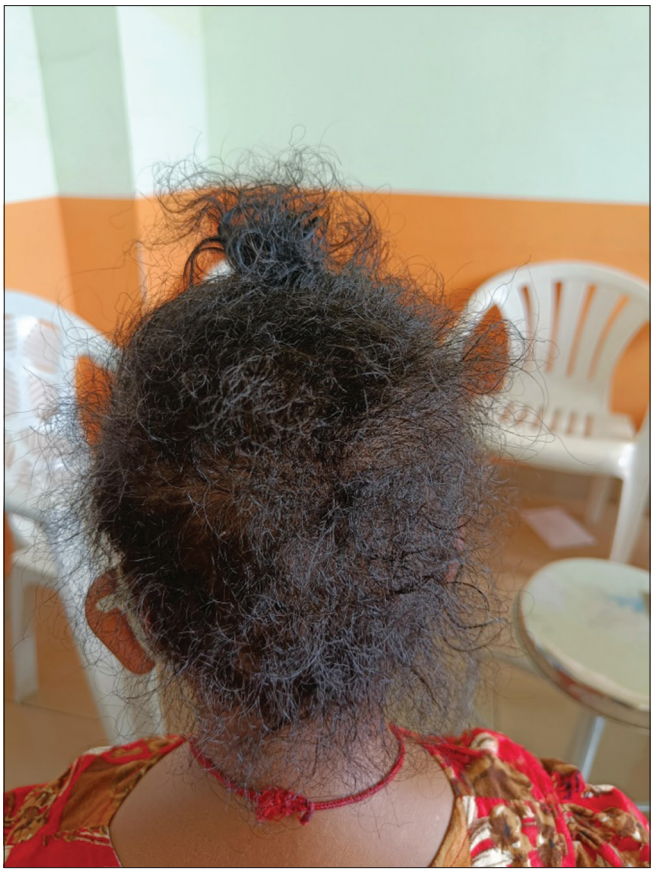

Figure 2: Unevenness and gritty texture of scalp hair

from grey to brown to jet black, few hairs with irregular narrowing, twisting, and few empty follicles [Derm lite DL4, (DermLite LLC, California, USA) Polarized mode, 10× magnification] [Figure 3]. Furthermore, hair examination was done under a scanning electron microscope (SEM) [JEOL IT800 Ultrahigh Resolution Field Emission SEM, USA], which revealed a triangular cross-section of hair and exposure of cortex at ×500 magnification [Figure 4a and b]. The other cutaneous and systemic (nervous system, ophthalmic, ear, nose, and throat (ENT), renal, and dental) findings were remarkably normal. The routine investigations done considering the current complaints demonstrated elevated levels of bilirubin and zinc, with normal copper and vitamin B12 levels.

The patient was diagnosed as a case of UHS with mild ZS. She was started on topical minoxidil 2% solution, hair moisturizer (having almond oil, shea butter, jojoba oil, and glycine soja oil), and oral biotin supplements (5 mg/day for 30 days). Also, the patient was noted to have a contracted right lobe of the liver with increased bilirubin. A comprehensive multidisciplinary approach with pediatric consults and regular monthly follow-ups was planned to rule out other systemic involvement. She is currently on follow-up for her hair issues, and has improved symptomatically from the time of the initial presentation.

Discussion

ZS, also known as cerebro-hepato-renal syndrome, is a rare inherited peroxisomal biogenesis disorder.[1] Survival beyond the first year of life is rare due to the array of symptoms and organ involvement in severe ZS.[2] The milder phenotypes may have a better prognosis and present into adulthood with associated defects such as sensorineural hearing loss, retinal diseases, leukodystrophy, and cognitive delay.[5,6] UHS or spun glass hair is a rare structural anomaly of the hair shaft.[7] Both sporadic and inherited forms are described.[8] Microscopy of the hair shaft may be normal or with a longitudinal groove.[7] Cut-section viewed under SEM reveals a triangular shape, replacing the normal oval cross-section.

It may be highlighted that medical literature does not point out a direct correlation of ZS/peroxisomal biogenesis disorder (PBD) with that of UHS. However, ZS is caused by mutations in the *PEX* genes, which are needed for peroxisome biogenesis. Peroxisomes, on the other hand, are cell organelles needed for lipid metabolism.[9] Hair lipids influence the shine, feel, manageability, and strength of the hair. Lipid metabolism plays a crucial role in the formation of the lipid envelope of hair.[10] Integral hair lipids in the inner root sheath of hair follicles play a key role in maintaining the stiffness and structural integrity

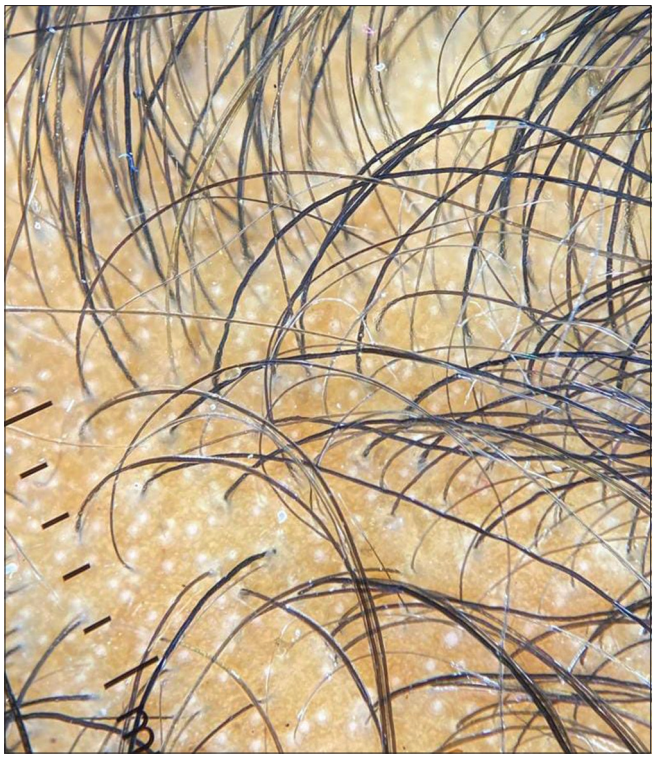

Figure 3: Dermoscopy showing irregular twisting, narrowing, empty follicles, decreased pigmentation of a few hairs [Derm lite DL4, (DermLite LLC, California, USA) Polarized mode, 10× magnification]

of the hair.[10,11] According to studies, genetic errors in lipid metabolism have been found to show abnormal hair morphogenesis and growth.[10,11] Expression of different peroxisome proliferator-activated receptors (PPARs) is noted in both dermal and epithelial human hair follicle cells and PPARα (one of the PPARs) was shown to be involved in hair growth.[12,13] Therefore, impaired lipid metabolism in ZS to some extent may contribute to hair abnormality in UHS.

Previously reported cases of ZS with *PEX* 1 and *PEX* 6 gene mutations had dermatological findings of Beau's lines, leukonychia, and hair abnormalities like pili annulati.[5] Another case report diagnosed with *PEX* 12 mutation and milder ZS, had cognitive impairment, visual and hearing loss.[5] In our case, the patient has liver and hair abnormalities (UHS) alone. The definitive diagnosis of ZS may be achieved by genetic testing, which was done in this case. UHS is diagnosed by SEM, which revealed a triangular cross-section of hair. The use of minoxidil for hair growth in females is well documented.[14] Although it is not an approved treatment for instances as in this case, topical minoxidil is routinely employed with the goal of improving blood circulation to the hair follicles. A child with UHS and loose anagen syndrome was successfully treated with minoxidil, as per a case report.[15] Also, recent literature has shown the beneficial effects of oral supplements (oral biotin) in UHS.[7] Thus, the same was used for the current case with satisfactory improvement.

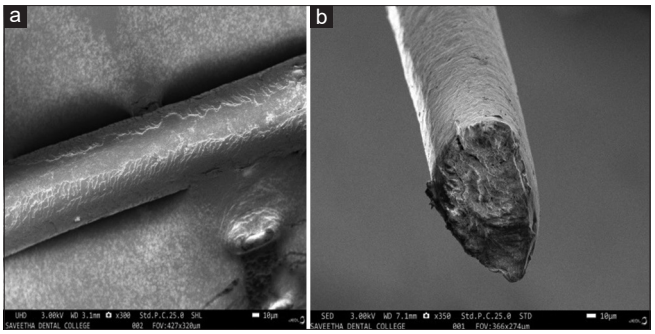

Figure 4: (a) SEM x 500 showing exposure of cortex. (b) SEM x 500 showing triangular cross-section of hair

Conclusion

ZS with a homozygous mutation of the *PEX* 12 gene may present as a mild form with liver abnormalities alone, without any other systemic involvement. This rare association of UHS with ZS is probably the first to be reported. Treatment with topical minoxidil and oral supplements for the primary complaint of decreased hair growth was the only needed intervention, as shown by the improved patient satisfaction.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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