Ataxia-Pancytopenia Syndrome-Associated Ocular Albinism: A Clinical Vignette

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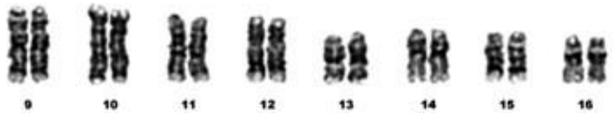
Objective

To explore the potential association of Ataxia-Pancytopenia Syndrome and oculocutaneous albinism by presenting a clinical vignette of a son as well as his father and siblings, each affected to various degrees by both pathologies.

Introduction

Oculocutaneous Albinism

Oculocutaneous Albinism (OCA) is a group of congenital heterogeneous disorders of melanin biosynthesis characterized by decreased or absent melanin pigment within the skin, hair, and eyes. At least four genes are responsible for the different types of OCA (OCA1-4). OCA1 is caused by mutations in the tyrosinase gene (TYR) on chromosome 11q14.3 and occurs in 1 out of every 40 thousand people. [1,5]



Portion of karyotype displaying chromosomes, including chromosome 11.
Source: NIH Image Gallery: https://ultrabem.com | Flickr

TYR plays a vital role in the process of melanogenesis, which significantly impacts the macular pigment processes derived from melanin that begins around week 17. At about week 25, cells begin to migrate and differentiate and begin to form the fovea.[2] The ciliary, iris and retinal pigment epithelial cells are developed from the neural ectoderm and the underlying cone photoreceptors elongate and become densely packed. The melanin additionally serves as a free radical stabilizer and absorber of visible light and UV radiation.

Ataxia-Pancytopenia Syndrome

Ataxia-Pancytopenia Syndrome (ATXPC) is a disease characterized by cerebellar ataxia, variable hematologic cytopenia's, and predisposition to marrow failure, myelodysplasia, and myeloid leukemia.[3] This is caused by alterations in SAMD9L gene. The majority of persons with a pathogenic variant in SAMD9L will manifest some feature of the syndrome.

SAMD9L serves as a multifunctional protein that has the potential to cause profound alterations in the cell cycle, cell proliferation, and protein translation in HSPCs. Expression of these genes, located on chromosome 7q21, and their mutations leads to a cellular environment that promotes DNA damage repair defects and ultimately apoptosis in hematopoietic cells.[4] Thus, a deletion of chromosome 7 can lead to myelodysplastic syndrome and predispose patients to malignancies.

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Case Presentation

4 y/o male, the oldest brother of three, presented to clinic after a failed vision screening. The parents reported photophobia and blurred vision. Past medical, surgical, & family history, as well as ROS was otherwise unremarkable at that time. His visual acuity exam was 20/40 in the right eye as well as 20/50 in the left eye (Snellen). The external exam was significant for esotropia, as well as horizontal pendular nystagmus. Notably, the patient and his two brothers had always had strikingly blonde hair with light complexions.

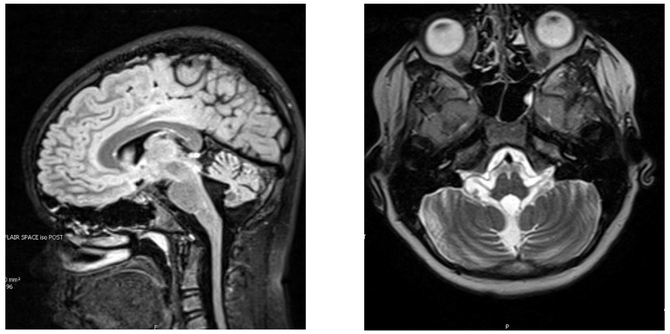
Optical coherence tomography (OCT) of the retina displayed foveal hypoplasia. Thus, the patient was monitored closely for changes in vision. His brothers were also examined with similar results, but the father did not show evidence of the disorder at that time.

Five years later, the parents reported changes; he seemed to be weaker. They also noticed that he was less coordinated and slower than his younger brothers. Additionally, he tended to walk on his toes and occasionally had a bilateral leg tremor. Neurologic physical exam revealed distal upper and lower extremity weakness. Truncal ataxia was present while appendicular coordination was well preserved. Brisk reflexes were present in bilateral lower extremities and sustained clonus at the ankles was present. Spontaneous clonus occurred during some physical movements.

The differential diagnosis included Chediak-Higashi & MIRAGE syndrome, Fanconi anemia, ataxia-telangiectasia, dyskeratosis congenita, X-linked sideroblastic anemia, and ataxia-pancytopenia syndrome.

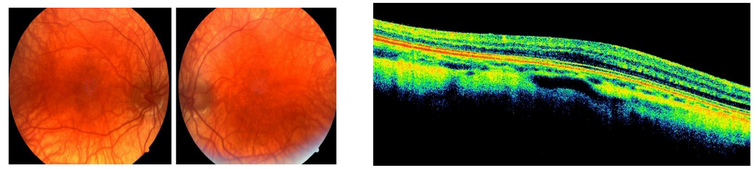
As a result of these findings, a brain MRI and cytogenetic studies were ordered. The brain MRI displayed mild-moderate cerebellar hypoplasia. The genetic studies revealed that the patient was heterozygous for TYR c, 1467 dup, p.(Ala490Cysfs*20), which is pathogenic., as well as heterozygous for TYR c.1205G>A, p. (Arg402Gln), which is risk factor. Pursuing this further, he had a mosaic heterozygous variant of uncertain significance in the SAMD9L gene, c.3127C>A., as did the father. Both younger brothers also completed genetic testing, revealing a chromosome 7 monosomy.

Diagnostic Findings



Sagittal & axial MRIs illustrating mild white matter disease and cerebellar hypoplasia.

Diagnostic Findings



Fundal imaging displaying albinoid fundus & OCT displaying foveal hypoplasia.

Discussion

We postulate that this is a demonstration of the association of SAMD9L mutations and additional chromosomal abnormalities such as within chromosome 11 where the TYR gene is located. Firstly, there have been documented reading and focusing difficulties with ATXPC. These patients exhibited marked retinal dysfunction, as evidenced by multifocal electroretinogram (mfERG). These findings are significant as SAMD9L mutations have been thought to be specifically harmful to cerebellar Purkinje cells and retinal cells.

Furthermore, it has been established that SAMD9L plays an intricate role in tumor suppression as well as key cellular regulatory functions. Thus, chromosome 7 abnormalities have been shown to predispose to malignancies. Chromosome 11 abnormalities have also been shown to have predisposition to myelodysplasia and myeloid malignancies.

Moreover, mutations involving chromosome 11 such as t(9;11)(p22;q23) and der(11q) have been associated with del(7q).[6,7] The literature has been unable to identify a specific mechanism underlying these abnormalities, although it is likely through multiple molecular events.

Conclusion

Ataxia-Pancytopenia Syndrome is a gradually progressive disease with significant detrimental effects including ataxia and nystagmus. As evidenced by the impact of SAMD9L mutations on retinal cells as well as cytogenetic associations, we hypothesize that this vignette serves as a display of the relationship between and chromosome 7 and 11 abnormalities.

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