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ABCD syndrome (Albinism-black lock-cell migration disorder of the neurocytes of the gut-sensorineural deafness syndrome)

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Abstract
An autosomal recessive syndrome characterized by albinism, black lock at temporal occipital region, bilateral deafness, aganglionosis of the large intestine and total absence of neurocytes and nerve fibers in the small intestine.

Keywords: aganglionosis, temporo-occipital, nystagmus, hirschsprung's disease, blepharophimosis, hypertrichosis

Introduction
ABCD syndrome is the acronym for albinism, black lock, cell migration disorder of the neurocytes of the gut, and sensorineural deafness. It has been found to be caused by mutation in the endothelin B receptor gene (EDNRB).
ABCD syndrome is defined as albinism, black lock, cell migration disorder of the neurocytes of the gut, and deafness. It was initially misdiagnosed and later discovered that a homozygous mutation in the EDNRB gene causes ABCD syndrome.
This helped scientists discover that it is the same as type IV Waardenburg syndrome, also known as Shah-Waardenburg syndrome.

Fig 1

Fig 2

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Risk Factors
As long as the ABCD is a genetic disorder anyone with a family history of the Waardenburg syndrome, albinism, congenital intestines' dysfunction, inherited deafness or blindness is at risk. The main method to prevent the disease is a genetic counseling that enables couples to prepare for pregnancy; helps provide information about the genetic diseases and raising an affected child, disease's administration and future pregnancies.

Characteristics
In the beginning, medical officials defined ABCD syndrome by the four key characteristics of the syndrome.
In the first case study of the Kurdish girl, researches described her as having "albinism and a black lock at the right temporo-occipital region along Blaschko lines, her eyelashes and brows were white, the irises in her eyes appeared to be blue, she had spots of retinal depigmentation, and she did not react to noise.
"The albinism is interesting in this diagnosis because the skin of an affected individual is albino pale besides the brown patches of mispigmented skin. The "black locks" described and seen in clinical pictures of the infants are thick patches of black hair above the ears that form a half circle reaching to the other ear to make a crest shape.
As identified in this first case study and stated in a dictionary of dermatologic syndromes, ABCD syndrome has many notable features, including

- Snow white hair in patches,
- Distinct black locks of hair,
- Skin white except brown macules,
- Deafness,
- Irises gray to blue,
- Nystagmus,
- Photophobia,
- Poor visual activity,
- Normal melanocytes in pigmented hair and skin, and
- Absent melanocytes in areas of leukoderma.
- Individuals have the blue/gray irises typical of people affected by blindness.

The C of ABCD syndrome is what distinguishes this genetic disorder from BADS and it involves cell migration disorder of the neurocytes of the gut. This characteristic occurs when nerve cells do not function correctly in the gut, which results in aganglionosis

The intestines' failure to move food along the digestive tract. Deafness or being unresponsive to noise due to very low quality of hearing was reported in every case of ABCD syndrome. The characteristics of ABCD syndrome are clearly evident in an inflicted individual.

No longer considered a separate syndrome, ABCD syndrome is today considered to be a variation of Shah-Waardenburg type IV. Waardenburg syndrome (WS) is described as "the combination of sensorineural hearing loss, hypo pigmentation of skin and hair, and pigmentary disturbances of the irides."

Hearing loss and deafness, skin dyspigmentation and albinism, and pigmentary changes in irises are the similarities between WS and ABCD.

According to a dictionary of dermatologic syndromes, Waardenburg syndrome has many notable features, including "depigmentation of hair and skin – white forelock and premature graying of hair, confluent thick eyebrows, heterochromic irides or hypopigmentation of iris, laterally displaced inner canthi, congenital sensorineural deafness, broad nasal root, autosomal dominant disorder, and other associated findings, including black forelocks."

Fig 3

Causes

Researchers in the past 20 years have determined that a gene mutation, specifically a homozygous mutation in the EDNRB gene, is the cause of ABCD syndrome. The advancement of technology led to new DNA material testing methods and this discovery changed the view of ABCD syndrome completely.

A homozygous mutation means that there was an identical mutation on both the maternal and paternal genes.

The identifying clinical report stated the test was done by scanning the Kurdish family for mutations in the EDNRB gene and the EDN3 gene by using a test called denaturing gradient gel electrophoresis.

Diagnosis

- The electrophoresis test takes advantage of electrical currents and differences in melting points of fragments of DNA or RNA to move them based on their molecular weight
- The differences in mobility of the fragments then can be analyzed to determine different sequences and to detect individual alleles.
- Different nucleotides in DNA are codes for certain proteins, which are formed by different patterns of the base pairs adenine, thymine, guanine, and cytosine.
- The combination of adenine and thymine and guanine and cytosine align on the double strands of DNA.
- The test results found "an aberrant DGGE pattern of exon 3 of the EDNRB gene. The mutation was determined to be a homozygous C to T base pair transition at the amino acid level, causing a premature stop in gene translation."
- This specialized testing enables geneticists to recognize the gene mutation that is the cause of ABCD syndrome.

New findings introduced an important break in the beliefs about ABCD syndrome because the endothelin B gene is a gene involved in Shah-Waardenburg syndrome. The endothelin receptor B produces Waardenburg syndrome type IV. Researchers began discussing the possibility that ABCD syndrome was in fact not a syndrome; rather it was a type of another syndrome known as Waardenburg. Discovering that the same gene is involved in ABCD and Waardenburg syndrome is important because researchers can now look further into ways to fix this crucial gene.

The occurrence of WS has been reported to be one in 45,000 in Europe. The diagnosis can be made prenatally by ultrasound due to the phenotype displaying pigmentary disturbances, facial abnormalities, and other developmental defects. After birth, the diagnosis is initially made symptomatically and can be confirmed through genetic testing. If the diagnosis is not made early enough, complications can arise from Hirschsprung's disease.

Diagnosis is determined by the presence of major and minor characteristic clinical features according to the Waardenburg Consortium criteria, as well as history and physical examination for Hirschsprung disease utilizing plain abdominal X-ray, barium enema, anorectal manometry and rectal biopsy. Genetic molecular analysis confirms the diagnosis.

Screening

Screening generally only takes place among those displaying several of the symptoms of ABCD, but a study on a large group of institutionalized deaf people in Columbia revealed that 5.38% of them were Waardenburg patients. Because of its rarity, none of the patients were diagnosed with ABCD (Waardenburg Type IV). Nothing can be done to prevent the disease.

Treatment

Treatment for the disease itself is nonexistent, but there are options for most of the symptoms. For example, one suffering from hearing loss would be given hearing aids, and those with Hirschsprung's disorder can be treated with a colostomy.

Prognosis

If the Hirschsprung's disease is treated in time, ABCD sufferers live otherwise healthy lives.

If it is not found soon enough, death often occurs in infancy.

For those suffering hearing loss, it is generally regressive and the damage to hearing increases over time. Digestive problems from the colostomy and reattachment may exist, but most cases can be treated with laxatives.

The only other debilitating symptom is hearing loss, which is usually degenerative and can only be treated with surgery or hearing aids.

Conclusion

ABCD syndrome is an autosomal recessive syndrome characterized by albinism, black lock, cell migration disorder of the neurocytes of the gut (Hirschsprung disease [HSCR]), and deafness. This phenotype clearly overlaps with the features of the Shah-Waardenburg syndrome, comprising sensorineural deafness; hypopigmentation of skin, hair, and irides; and HSCR. Therefore, we screened DNA of the index patient of the ABCD syndrome family for mutations in the endothelin B receptor (EDNRB) gene, a gene known to be involved in Shah-Waardenburg syndrome. A homozygous nonsense mutation in exon 3 (R201X) of the EDNRB gene was found. We therefore suggest that ABCD syndrome is not a separate entity, but an expression of Shah-Waardenburg syndrome.

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