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Oculocutaneous albinism in a set of triplets

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A 30-year-old Sri Lankan G2/P1 conceived triplets (trichorial, triamniotic) following hormone stimulation. Prophylactic lung maturation with steroids was carried out in the 27th week of gestation. Premature rupture of membranes in triplet B occurred at 29 2/7 weeks of gestation. Tocolysis and erythromycin were started. The contractions persisted and the triplets (two males and one female) were delivered by cesarean section at 30 3/7 weeks of gestation. Anthropometric measurements for all three infants were within normal limits. All three had mild respiratory distress and required nasal CPAP and oxygen on the first day of life.

Already at birth, it was noted that the skin color of triplet A (male) and triplet C (female) was very light in comparison to that of triplet B. Both babies had blond hair and eyelashes. During the following weeks, this phenomenon became increasingly apparent so that the diagnosis of albinism was suspected (Fig. 1). The parents, both Sri Lankan, had dark hair and were non-consanguineous. The mother had normally pigmented skin, the father was fair. The family pedigree especially on the paternal side consisted of several generations with blue eyes and white hair (Fig. 2). On the maternal side, an aunt and an uncle have blue eyes and light skin. The clinical course of the babies was uneventful and they were transferred to a neighboring hospital on day 17 of life.

An ophthalmological examination carried out in the 4th week of life revealed blue irises, pale pigment epithelium, small, pale papillae, and an absent macular reflex consistent with macular hypoplasia in the case of triplet A and C thereby confirming the diagnosis of oculocutaneous albinism. Triplet B had a normally pigmented and vascularized retina with a positive macular reflex (Fig. 3).

Cerebral ultrasound showed mild dilatation of the lateral ventricles in the case of triplet A and C and a small right-sided subependymal bleed in the case of triplet B. All three babies had mild neutropenia, with absolute neutrophil counts ranging between 1160 and 1300 per µL. Platelet counts were normal. The babies were discharged at the age of 8 weeks (38 5/7 weeks post menstrual age) with normal weight, length and head circumference for age. The neurological examination was normal and there was no evidence of nystagmus in triplet A or C.

At follow-up at a corrected age of 3 months (Fig. 4), both triplets A and C showed a pendular nystagmus which was more prominent in the female triplet C (movie). The male triplet showed some darkening of the hair, the female infant remained blond. In order to reduce photophobia and to correct for a refractive error (extensive hyperopia), special dark glasses were recommended at this time. The parents were advised to prevent exposure to sun with the use of clothing, hats and

sunscreens with physical filters and SPF 50. Genetic counseling of the family was carried out. Chromosome and molecular genetic analyses in the affected babies and parents were recommended but have not been performed until now.

Triplets A-C (from left to right) at the age of 3 weeks.

Fig. 1

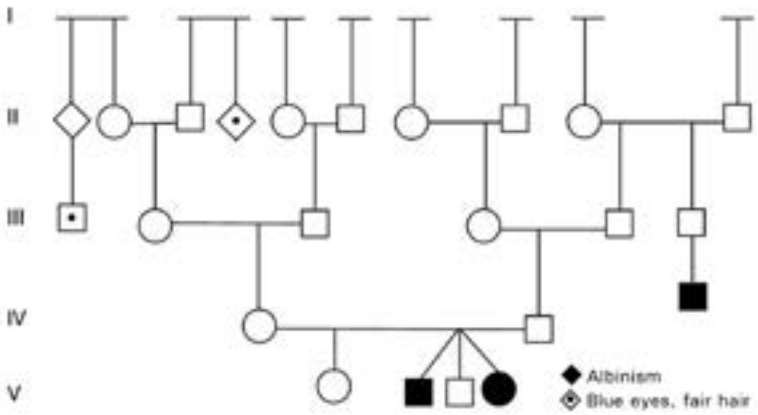

Fig. 2

Family pedigree.

Ophthalmological examination at 4 weeks of age: note color of eye lashes and increased translucency of the iris.

Fig. 3

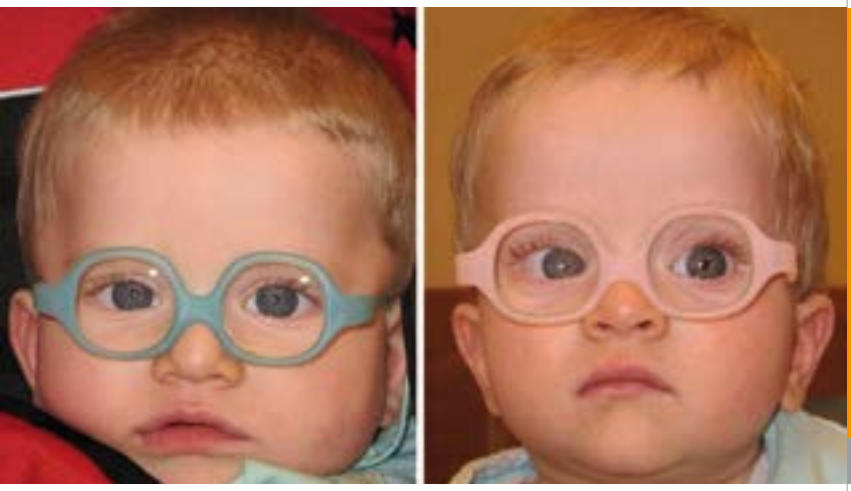

Fig. 4

Affected infants at the age of 3 months
(triplet A: left, triplet C: right).

DISCUSSION

Albinism can affect people of all ethnic backgrounds. Approximately 1 in 17'000 people has one of the types of albinism, ocular or oculocutaneous (1,2).

Oculocutaneous albinism (OCA) describes a group of congenital heterogeneous disorders of melanin biosynthesis. The structure and number of melanocytes are normal. At least four genes are responsible for the different types of OCA (3).

OCA1 is caused by mutations in the tyrosinase gene (TYR) on chromosome 11q14.3. Tyrosinase catalyzes the first two steps in the melanin biosynthesis pathway. Mutations completely abolishing tyrosinase activity result in OCA1A, while mutations maintaining some enzyme activity result in OCA1B allowing some accumulation of melanin pigment over time. Mutations in the OCA2 gene in the region of chromosome 15q11.2-q12 cause the OCA2 phenotype. The OCA2 protein is important for normal biogenesis of melanosomes and for normal processing and transport of melanosomal proteins. OCA3 is caused by mutations in the tyrosinase-related protein 1 (TYRP1), another enzyme in the melanin biosynthesis pathway. Finally, mutations in the membrane-associated transporter protein gene (MATP) is responsible for OCA4. The MATP protein plays an important role in pigmentation and functions as a membrane transporter in melanosomes.

The degree of skin and hair hypopigmentation varies with the type of albinism. In OCA1A, hair, eyelashes and eyebrows are white, skin is white and does not tan. Irises are light blue to pink and translucent. Pigment does not develop. Visual acuity is 1/10 or less and photophobia is intense. In OCA1B, the hair and skin may develop some pigment with time (1-3 years), blue irises may change to green/brown. Visual acuity can reach 2/10. In OCA2, the amount of cutaneous pigment may vary, and newborns almost always have pigmented hair. Nevi and ephilids are common. Iris color varies and the pink eyes seen in OCA1 are absent. Visual acuity is better than in OCA1 and can reach 3/10. OCA3 results in red OCA in Africans who have red hair and reddish brown skin. Visual anomalies are not always detectable. OCA4 is clinically similar to OCA2.

All types of OCA and ocular albinism have similar ocular findings including varying degrees of congenital nystagmus, iris hypopigmentation leading to iris translucency, reduced pigmentation of the retinal pigment epithelium, foveal hypoplasia, reduced visual acuity in the range of 20/60 to 20/400, refractive errors and sometimes color vision impairment. Photophobia may be prominent. Iris translucency is demonstrated by slit lamp examination. A characteristic finding is misrouting of the optic nerves, consisting of an excessive crossing of fibers in the optic chiasma which can result in strabismus and reduced

stereoscopic vision. This can be demonstrated by monocular visual evoked potentials.

Diagnosis of OCA is based on clinical findings of hypopigmentation of the skin and hair in addition to characteristic ocular symptoms. However, due to the clinical overlap between the OCA subtypes, molecular diagnosis is necessary to establish the gene defect and thus the OCA subtype.

All 4 types of OCA are inherited as autosomal recessive disorders. The parents of an affected child are obligate carriers, the recurrence risk for another affected child is 25% and healthy siblings are at a 67% risk of being carriers. Offspring of an affected person are obligate carriers. In most cases, there is no family history of albinism. The condition does occur in individuals of 2 successive generations of a family, so called "pseudodominance" if an affected person has children with a carrier. Carrier detection and prenatal diagnosis are possible. In African populations, there is a high frequency of the OCA2 mutant alleles, hence affected patients in several generations may be seen.

Albinism may be part of an underlying syndrome (2), e.g., Hermansky-Pudlak syndrome (severe immunologic deficiency, interstitial lung fibrosis, granulomatous colitis and mild bleeding problems), Chediak-Higashi syndrome (increased susceptibility to bacterial infections, prolonged bleeding time, peripheral neuropathy), Griscelli syndrome

(immune impairment or neurological deficit, hypopigmentation of skin and hair), or Wardenburg syndrome Type ll (sensory deafness and partial albinism).
The management of OCA includes management of eye and skin problems (2). Reduced visual acuity can be helped with glasses, possibly bifocals and dark glasses or photochromic lenses for photophobia. Nystagmus may be helped with contact lenses or surgery of the eye muscles. Children require special attention at school. Regarding the skin, most people with severe forms of OCA do not tan and get easily sunburned. Those forms with a little pigment development with age may be less affected by the sun. Sunscreens with a sun protection factor of at least 30 and ideally containing physical filters are recommended (3).

Lifespan for patients with OCA is normal (2). General medical problems are not increased compared to the general population, but the incidence of skin cancer, squamous cell carcinoma and basal cell carcinoma in particular, is higher inaffected patients (23% to 34%) so that regular skin checkups are necessary (3). Development and intelligence are normal (4).

The type of OCA in our patients remains unclear. The family history and the investigations carried out suggest that the OCA in this family is an isolated entity without association with a syndrome. Molecular genetic analysis would help to determine the type of OCA and therefore the prognosis in this family..

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