The oculocerebral syndrome in association with generalised hypopigmentation

A case report

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Summary

A 14-year-old girl with generalised hypopigmentation, mental retardation, abnormal movements, and ocular anomalies is described. It is suggested that she represents a further case of oculocerebral albinism, a rare autosomal recessive condition. Reference is made to previous similar cases.

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The term 'oculocerebral albinism' has been applied to a heterogeneous group of patients who share the characteristics of generalised hypopigmentation, mental retardation, abnormal movements, and ocular anomalies. A further such case, representing the mildest form of this condition yet described, is reported. The possible relationship between hypopigmentation and mental retardation is discussed.

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Case report

The proband, a 14-year-old girl, is the second child of non-consanguineous parents who were born in the UK. The couple have one normal daughter. The mother has suffered two first- and one second-trimester miscarriages (the latter probably the result of cervical incompetence). Both parents are healthy and of above-average intelligence; both have dark hair and their normal daughter has ash-blonde hair. There is no significant family history.

The pregnancy with the proband was uncomplicated. Delivery was at term and was normal; birth weight was 2 500 g. There was physiological jaundice requiring no therapy.

Psychomotor development was markedly delayed. She sat unaided at 9 months and walked at 2 years. Single words were uttered at around 6 years of age. Her speech at 14 years is confined to 3 word sentences, often without apparent meaning; she exhibits marked echolalia. She has attended a training

centre since the age of 7 years and is now able to feed, wash and dress herself. She is hyperkinetic and has head-banging episodes, but has never experienced seizures. Secondary sexual development has been normal, with menarche at 13 years.

Examination revealed a girl of normal height and weight, and with a head circumference of 54 cm (50th percentile). She had generalised hypopigmentation with scattered pale freckles on the face and shoulders, pale yellow hair, and blue eyes, in keeping with tyrosinase-positive albinism. There were no specific dysmorphic features, and chest and abdominal examination revealed no abnormalities. Mental age was impossible to assess formally. The child was responsive to verbal stimulation but mostly responded inappropriately. Cranial nerves were intact except for myopia, non-paralytic strabismus, and persistent horizontal nystagmus. Range of ocular movements was full, and direct and consensual light reflexes were present. Photophobia was marked. Translucency of the irides was noted and ophthalmic examination under anaesthesia revealed hypopigmentation of the retina, with hypoplasia of the fovea and, notably, of the optic disc itself.

Muscle bulk and tone were normal, as were tendon reflexes. She exhibited a continual writhing movement of the neck and trunk, but gait was not ataxic. An electro-encephalogram was normal. Computed tomography (CT) of the head revealed no abnormalities; specifically there was no occipital hypoplasia. A full blood count and peripheral smear were within normal limits, as was routine serum chemical evaluation. Analyses of serum and urine for the inherited amino-acidopathies were normal, and on two occasions urinalysis failed to reveal any increase in levels of phenylpyruvate. The chromosome karyotype was normal.

Hair bulbs incubated overnight in a solution of tyrosine (80 g/dl in 0,1M potassium phosphate buffer) revealed a marked accumulation of pigment, which was not seen in hair bulbs incubated in a control buffer without tyrosine.

Discussion

There have been 4 reported cases of oculocerebral syndromes associated with hypopigmentation to date. Cross *et al.*[1] described 3 siblings (2 boys and 1 girl) in an inbred Amish family, with what they considered to be a 'new' genetic disorder. Features included generalised hypopigmentation, spastic diplegia, athetosis, severe mental retardation, and gross ocular anomalies (including microphthalmia, corneal opacification, and nystagmus). Passarge and Fuchs-Mecke[2] reported a severely retarded girl with albinism and an eczematous rash, who also had microphthalmia and nystagmus; she developed cataracts at 3 months of age. The parents were not consanguineous.

Two female offspring of a first-cousin marriage, both exhibiting hypopigmentation, mental retardation and ocular anomalies, have been reported.[3] Features included dolichocephaly, flat nasal root, microsomia, and cataracts. A male patient with hypopigmentation, mental retardation, ataxia, and myopia[4] was considered to be analogous to the case described by Preus *et al.*[3] This child also showed occipital atrophy on CT, a feature demonstrated at necropsy on one of the patients described.[3] The term 'neuro-ectodermal melanolysosomal disease' was coined to describe a condition of mental retardation and hypopigmentation in association with abnormal melanosomes and lysosomes.[5] These patients did not have ocular anomalies and probably represent a distinct condition.

The present patient may well represent a milder form of the disease noted in the previously reported cases (if indeed they represent a genetically homogeneous group, since it would appear that the cases described by Preus *et al.*[3] and Patton *et al.*[4] may represent a distinct condition). Specifically, the association of hypopigmentation, profound mental retardation, abnormal movements, and ocular anomalies, is common to all these patients, and to ours. It is possible that the differences in severity could be due to different alleles at the same locus.

The explanation for the association between cerebral dysfunction and hypopigmentation in these cases is speculative. That anomalous developmental organisation of visual and auditory pathways occurs in oculocutaneous albinism is well established,[6,7] and there is evidence that there are associated functional motor anomalies in these individuals.[8] An association between mental retardation and hypopigmentation has been noted in patients with the Prader-Willi syndrome[9] and these patients have been shown to have abnormalities of visual pathway decussation identical to those described in albinos.[10]

Whether the severe cerebral problems in patients with oculocerebral albinism can be considered a more severe expression of the developmental neural anomalies in mentally normal albinos is hypothetical. Unfortunately we were unable to perform monocular visual evoked potential testing on our patient because of lack of co-operation, but she does have strabismus, and this is probably indicative of an underlying visual pathway decussation anomaly. It may be, however, that all these patients represent the expression of a gene that in itself causes mental retardation, and the lack of pigment is incidental as a causal agent.

In conclusion, we have described a patient who would reasonably be classified along with the previously reported cases of oculocerebral albinism, sharing with them ocular anomalies, profound mental retardation, abnormal movements, and generalised hypopigmentation.

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