Prenatal Diagnosis of Oculocutaneous Albinism by Electron Microscopy of Fetal Skin


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Oculocutaneous albinism was diagnosed prenatally by electron microscopic examination of fetal skin samples taken during fetoscopy at 20 weeks of gestation. Melanosomes development in hair bulb melanocytes progressed no further than stage II, indicating a lack of melanin synthesis. In 4 age-matched control fetuses, numerous stage IV melanosomes, signifying active melanin synthesis, were identified. The diagnosis was confirmed after the pregnancy was terminated at 22 weeks. Examination of the fetal eye showed absence of pigment in the retinal epithelium and uvea at a stage when ocular melanogenesis would normally be active. This study shows that oculocutaneous albinism can be detected in the second trimester using similar techniques to those employed in the prenatal diagnosis of epidermolysis bullosa and ichthyosis.

Oculocutaneous albinism is an inherited disorder of the melanin pigmentedary system characterized by a congenital decrease or absence of melanin synthesis in the skin, hair, and eyes. The associated visual abnormalities include nystagmus, photophobia, and impaired acuity. The skin is poorly protected from the adverse effects of ultraviolet radiation, leading to severe sunburn, early aging changes including wrinkling and solar elastosis, and various malignancies such as basal and squamous cell carcinoma [1] and melanoma [2,3]. Additionally, albinos may suffer from severe social handicap, especially in Africa where their pale skin and hair may turn them into outcasts [4]. The disease can therefore be markedly disabling and in the absence of effective treatment there is a need for prenatal diagnosis, especially in communities located in tropical or subtropical climates.

There are at least 6 variants of oculocutaneous albinism inherited as autosomal recessive traits. The most common varieties are tyrosinase-positive and tyrosinase-negative albinism which are so designated according to whether or not there is evidence of tyrosinase activity in the melanocytes [5]. Tyrosinase-positive albinos will develop small amounts of melanin in their skin and eyes. Their melanocytes will contain stage III melanosomes [6] as demonstrable by electron microscopy, indicating early melanin synthesis. The melanocytes of tyrosinase-negative albinos possess only stage I and II melanosomes [6,7], pointing to a lack of melanin product.

We wish to report a successful attempt at prenatal diagnosis of oculocutaneous albinism by electron microscopic examination of fetal skin obtained in utero.

CASE HISTORY

The patient was a 36-year-old woman in her third pregnancy. Her first child, born in 1979, is an albino with platinum blond hair and light blue eyes. She also has nystagmus. The tyrosinase status is unknown. The patient and her husband come from the same tribe in the Middle East. She has mid-brown hair and blue-green eyes and he has black hair and dark brown eyes. They are not first cousins but may be distantly related. The husband has 2 albino nephews with white hair and his great-grandfather is said to have been an albino. The couple sought prenatal studies for albinism principally because they felt that in their community the disease caused considerable social and economic hardship. They decided to proceed with the present pregnancy only if prenatal testing revealed no evidence of albinism or other congenital abnormality.

METHODS

Fetoscopy and Fetal Skin Biopsy

Using techniques we have described previously [8], ultrasound examination, fetoscopy, and fetal skin biopsy were performed at an estimated gestational age of 20 weeks. The biparietal diameter was 48 mm, consistent with a gestational age of 20 weeks. The eyes could not be examined because the lids were fused. The skin was pink and the scalp hair sparse, unpigmented, and barely visible. Three samples (1.5 mm in maximum length) were taken with 20-gauge forceps from the back of the fetal scalp, under direct vision. Bleeding from the biopsy sites was minimal. The procedure lasted 20 min.

Processing for Light and Electron Microscopy

The biopsy samples were immediately flushed from the forceps with 0.9% NaCl solution. Two of these samples were then immersed in half-strength Karnovsky’s fixative in cacodylate buffer (pH 7.4) containing 5% sucrose and 0.05% CaCl2 for 1 h at 21°C. After several washes in buffer, the tissues were postfixed in 1.33% osmium tetroxide in cacodylate buffer (pH 7.4) on ice for 1 h. After dehydration in ethanol, the specimens were embedded in Epon. One-micrometer thick vertical sections were stained with methylene blue and azure II for light microscopy. Many serial sections needed to be cut from each block before adequate views of the lowest segments (hair bulbs) of the developing hair follicles could be obtained. Melanogenesis is more readily detectable in hair follicles than interfollicular epidermis of fetuses aged 20 weeks [9].

Test for Tyrosinase Activity

The third skin sample was immediately incubated at 37°C in a solution containing 0.1% 3,4-dihydroxyphenylalanine (dopa) in 0.1 M cacodylate buffer, pH 7.4. The dopa solution was changed after 30 min and the total incubation time was 4 h. The sample was then washed in distilled water, fixed in half-strength Karnovsky’s medium, and embedded in L.R. White resin (London Resin Company) for light and electron microscopy.

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Controls

Samples of scalp from 4 age-matched normal control fetuses, previously obtained after hysterotomy and processed for electron microscopy, were examined.

RESULTS

Light Microscopy

The appearances of the fetal skin were generally normal for 20 weeks of gestation [10]. The interfollicular epidermis contained 3-5 layers of nucleated cells which were covered by regressing periderm. There were numerous unpigmented hairs and the hair follicles were at different stages of development. Melanocytes were identified in the hair bulbs at the bases of the developing follicles. They could be distinguished from the surrounding epithelial cells by the relatively low density of their cytoplasm. Interfollicular melanocytes (clear cells) were rare. No melanin granules were detected in melanocytes, keratinocytes, or hairs.

Enzyme Histochemistry

No reaction product was observed in the epidermis or appendages by light microscopy. For technical reasons it was not possible to examine the material by electron microscopy.

Electron Microscopy

The tissue preservation was moderately good although there was variable damage, probably caused by the biopsy procedure. A total of 8 melanocytes was examined. All melanocytes (Fig 1A) contained stage I and II melanosomes which varied in number between cells. Stage I melanosomes were round mem-

![Fig 1. Electron micrographs of hair-follicle melanocytes and melanosomes from albino and normal fetuses. A. Melanocyte in fetoscopy specimen from albino fetus aged 20 weeks. Melanosomes (m) are lacking in melanin. Bar = 1 μm. B. Melanocyte from normal fetus aged 19 weeks. Melanosomes (m) are heavily pigmented. Bar = 1 μm. C and D, Stage II melanosomes in affected fetus (fetoscopy specimen). Bars = 100 nm. E, Stage II melanosomes with characteristic beaded filaments in affected fetus (postmortem specimen). Bar = 200 nm. F, Stage II-IV melanosomes in normal fetus. Bar = 200 nm.](image)
brane-bound vesicles usually with an amorphous content. Stage II melanosomes were oval and about 0.3 μm in length and 0.1 μm in width. Often there was a matrix consisting of parallel filaments or sheets traversing the long axis of the organelle [11]. The filaments exhibited a periodic beading which appeared as cross-striations in a few sections (Fig 1C, D). No stage III or IV melanosomes were seen. The findings suggested a diagnosis of albinism.

Controls

In sections from the 4 control samples, melanin deposition could readily be identified by light microscopy in hair bulb melanocytes as well as surrounding cortical cells and hair cortex. Electron microscopy revealed many stage III and IV melanosomes (Fig 1B, F) in a total of 18 melanocytes examined. The stage IV melanosomes were about 0.65 μm long and 0.2 μm wide.

Termination of Pregnancy and Postmortem Examination

The patient and her husband chose to terminate the pregnancy. Prostaglandin F2α, and hypertonic urea solution was instilled intra-amniotically at 22 weeks and she aborted after 15 h.

At postmortem examination the crown–rump length was 18 cm, the fetal skin was light pink, the eyelids were fused, and the scalp hair and eyebrows were very scanty and white. No gross congenital abnormality was noted. Samples of eyebrow and scalp were taken for microscopical examination. A test for tyrosinase activity performed on cryostat sections was negative. Ultrastructural studies revealed moderately severe autolytic changes. It was, however, possible to identify numerous stage I and II melanosomes (Fig 1E) inside follicular melanocytes. Absence of complete melanosome development was confirmed.

Ocular Findings

The left eye, together with eyelids which were fused at the margins, was removed for histologic examination; with an anterior-posterior diameter of 13 mm it was commensurate with normal development for a gestation of 22 weeks. On opening the eye, the retina was found to be detached as a result of postmortem autolysis and the exposed choroid, as well as the ciliary body and iris, were seen to be devoid of pigment. Light microscopy revealed no structural abnormality but nowhere, including the "pigment" epithelia of the retina, ciliary body, and iris, was there any detectable melanin and Masson-Fontana stains were negative. The eyelash follicles in separate sections of the eyelids were also lacking in pigment. The tissue was too severely affected by autolysis for adequate ultrastructural examination. However, no stage IV melanosomes could be identified in either the uvea or retinal epithelium.

DISCUSSION

This study shows that oculocutaneous albinism can be detected prenatally using similar techniques to those employed in the prenatal diagnosis of epidermolysis bullosa [8,12] and bullous ichthyosiform erythroderma (epidermolytic hyperkeratosis) [13], in which electron microscopy is used to examine fetal skin samples obtained under fetoscopy. Harlequin ichthyosis has also been diagnosed prenatally by light microscopy of fetal skin [14]. In fetuses at risk from epidermolysis bullosa or ichthyosis, samples can be taken from the trunk or limbs at 18 weeks of gestation. In excluding albinism it is necessary to examine samples of scalp, preferably removed at a later age (20 weeks) when melanogenesis in hair follicles is normally active.

In this study the fetal scalp hair and eyebrows were barely visible through the fetoscope, and we were unable to predict the diagnosis before electron microscopical examination. Since fetal hair development is variable at 20 weeks it might be possible in other cases to see pigmented hair, thereby lessening or removing the need for skin biopsies.

It was not known previously whether the ultrastructural features of albinism, namely arrested melanosome development, would be readily evident prenatally, although other workers have predicted that the disease could be detected at 20 weeks of gestation [9]. The histologic findings in the fetal eye showed a total lack of pigment at a stage when ocular melanogenesis should be nearing completion since the process is normally well established as early as the 7th week of gestation and virtually complete by the 27th week [15]. For technical reasons it was not possible to examine melanosomes from the uveal or retinal pigment cells, but the light microscopical findings are considered sufficient to confirm the diagnosis.

The apparent lack of tyrosinase activity in the albino fetus cannot be assumed to indicate a tyrosinase-negative phenotype until more information is available in normal fetuses. The amount of enzyme normally present at 20 weeks of fetal age may be too low to convert the exogenous dopa into melanin.

It is unlikely that prenatal diagnosis of oculocutaneous albinism would be indicated in communities located in a temperate climate such as that in Northern Europe. Our patient comes from the Middle East where the outlook for albinos may be very different.

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REFERENCES