Leopard spot retinal pigmentation in infancy indicating a peroxosomal disorder

C J Lyons, G Castano, A Q McCormick, D Applegarth

Background: Neonatal adrenoleucodystrophy (NALD) is a rare disorder resulting from abnormal peroxosomal biogenesis. Affected patients present in infancy with developmental delay, hypotonia, and seizures. Blindness and nystagmus are prominent features. The authors suggest a characteristic leopard spot pigmentary pattern in the peripheral retina to be diagnostic.

Methods: Three patients are reported with this presentation; the characteristic retinal appearance resulted in early diagnosis for one of these.

Conclusion: Leopard spot retinopathy in an infant with hypotonia, seizures, developmental delay, with or without dysmorphic features and hearing impairment, is a clue to the diagnosis of NALD.

Neonatal adrenoleucodystrophy (NALD), a rare autosomal recessively inherited disorder was first reported in 1978 by Ulrich et al. Visual loss is an early and prominent feature, often starting in infancy. Other clinical features include seizures, hypotonia, developmental delay, and deafness. Hepatomegaly and liver dysfunction occur early in life and mild craniofacial abnormalities may be present. Although adrenal insufficiency is clinically rare, adrenal cortical atrophy is a universal necropsy finding. Most present. Although adrenal insufficiency is clinically rare, adrenal cortical atrophy is a universal necropsy finding. Most.

Methods: Three patients are reported with this presentation; the characteristic retinal appearance resulted in early diagnosis for one of these.

Conclusion: Leopard spot retinopathy in an infant with hypotonia, seizures, developmental delay, with or without dysmorphic features and hearing impairment, is a clue to the diagnosis of NALD.

Computed tomography (CT) brain scan showed mild ventricular dilatation. The electroencephalogram (EEG) confirmed a seizure disorder with a structural abnormality. The ERGs and visual evoked potentials (VEP) were abnormal but not diagnostic. Brainstem auditory evoked responses were abnormal; pituitary and adrenal function were normal. Markedly elevated levels of very long chain fatty acids (VLCFA) were found in plasma and fibroblasts at the age of 8 months, and a liver biopsy showed absence of peroxisomes with micronodular cirrhosis. A diagnosis of neonatal adrenoleucodystrophy was made.

The patient developed progressive feeding problems and signs of portal hypertension. By the age of 4 years, he was blind with marked developmental delay and poor seizure control. Fundus examination showed extreme narrowing of the retinal blood vessels with bilateral optic atrophy. The retinal pigment epithelium was atrophic and the leopard spot pattern had disappeared. The patient and his family subsequently moved and were lost to follow up.

Patient 3 presented at 5 months of age with developmental delay and visual inattention. Ocular examination showed a visually inattentive boy with small amplitude horizontal nystagmus. A bilateral peripheral leopard spot pigmentary retinopathy was evident on funduscropy. Electroretinography

Patient 2 was born by spontaneous delivery at 34 weeks gestation. Mild dysmorphic features were noted including bilateral epicanthic folds and transverse palmar creases. Subtle clouding of the right cornea disappeared in the first week of life. A complete eye examination, including dilated indirect ophthalmoscopy, was otherwise normal. He was brought to the hospital at the age of 3 months with seizures. Clinical examination showed a hypotonic infant with poor head control, complete visual inattention and horizontal nystagmus, sluggish pupil reflexes, and peripheral leopard spot pigmentary retinopathy (fig 1). Hepatomegaly and hearing impairment were also evident.

Figure 1 Fundus photograph of patient 1. The mid-peripheral retina shows a classic leopard spot pigmentary retinopathy.
almost always abnormal; these and plasma VLCFA assay adrenal glands, and liver. Microscopy. These inclusions can also be present in the brain, layer neurons, ganglion cells, and macrophages by electron receptors. A typical bileaflet inclusion is evident in the Macrophages may contain pigment and degenerated photoreceptor outer segment/retinal pigment epithelium relation decreased plasmalogen levels may also affect the photo-receptor outer segment-retinal pigment epithelium relation since they are cell membrane constituents. peroxisomes such as hepatocytes, oligodendrocytes, and neurons in the first weeks of life. Tissue VLCFA accumulation causes the neurological and ocular findings; decreased plasmalogen levels may also affect the photo-receptor outer segment-retinal pigment epithelium relation with areas of photoreceptor degeneration with patchy hypertrophy, nodular hyperplasia, and atrophy of the pigment epithelium. Pigmented cells can be found in the subretinal space and in other layers in the retina. Macrophages may contain pigment and degenerated photoreceptors. A typical bileaflet inclusion is evident in the photoreceptor cells, pigmented epithelium, inner nuclear layer neurons, ganglion cells, and macrophages by electron microscopy. These inclusions can also be present in the brain, adrenal glands, and liver. The ERG, VEP, and brain auditory evoked responses are almost always abnormal; these and plasma VLCFA assay should confirm this diagnosis. In atypical cases, other tests like plasma/urine bile acid intermediates, plasma piperocilic acid, and peroxisomal enzymatic activity in cultured skin fibroblasts may be necessary. Peroxisome pathology may be evident on liver biopsy. A skin biopsy to establish cultured fibroblasts is required to confirm and investigate the absence or near absence of liver peroxisomes.

DISCUSSION
The cause of neonatal adrenoleucodystrophy is the absence or near absence of peroxisomes, intracellular organelles exclusively responsible for the catabolism of long chain fatty acids (16 or more carbon atoms), very long chain fatty acids (22 or more carbon atoms), and piperocilic acid. Peroxisomes are also important in plasmalogen and bile acid synthesis; their absence therefore results in increased levels of plasma VLCFAs, bile acid intermediates and piperocilic acid, and decreased red blood cell plasmalogen levels. These metabolic disturbances are particularly important in cells which are normally rich in peroxisomes such as hepatocytes, oligodendrocytes, and neurons in the first weeks of life. Tissue VLCFA accumulation causes the neurological and ocular findings; decreased plasmalogen levels may also affect the photo-receptor outer segment-retinal pigment epithelium relation with areas of photoreceptor degeneration with patchy hypertrophy, nodular hyperplasia, and atrophy of the pigment epithelium. Pigmented cells can be found in the subretinal space and in other layers in the retina. Macrophages may contain pigment and degenerated photoreceptors. A typical bileaflet inclusion is evident in the photoreceptor cells, pigmented epithelium, inner nuclear layer neurons, ganglion cells, and macrophages by electron microscopy. These inclusions can also be present in the brain, adrenal glands, and liver. The ERG, VEP, and brain auditory evoked responses are almost always abnormal; these and plasma VLCFA assay should confirm this diagnosis. In atypical cases, other tests like plasma/urine bile acid intermediates, plasma piperocilic acid, and peroxisomal enzymatic activity in cultured skin fibroblasts may be necessary. Peroxisome

CONCLUSION
Leopard spot retinopathy has not been reported with NALD in the scientific literature. Although there is no treatment, early diagnosis avoids unnecessarily invasive, distressing, time-consuming and expensive tests. This may help an affected family to come to terms with the prognostic implications and provide an opportunity for immediate genetic counselling.

Authors’ affiliations
C J Lyons, G Castano, A Q McCormick, Department of Ophthalmology, British Columbia Children’s Hospital, 4480 Oak Street, Vancouver, BC, Canada V6H 3V4
D Applegarth, Department of Pediatrics, British Columbia Children’s Hospital, 4480 Oak Street, Vancouver, BC, Canada V6H 3V4

Correspondence to: Christopher Lyons, Department of Ophthalmology, A136 BC Children’s Hospital 4480 Oak Street, Vancouver, BC, Canada V6H3V4; cjlyons@telus.net

Accepted for publication 4 April 2003

REFERENCES