SCIENTIFIC REPORT

Chiasmal misrouting and foveal hypoplasia without albinism

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Background/aims: To present the ophthalmological and electrophysiological characteristics of three darkly pigmented, female patients with misrouting and foveal hypoplasia. One of the patients had primary ciliary dyskinesia and situs inversus totalis (Kartagener syndrome).

Methods: Fundus photographs were taken and the angles at which the main temporal arterial branches leave the optic nerve head (ONH) were analysed. Optical coherence tomography (OCT) was performed through the presumed foveal region. Pattern onset visually evoked potentials (VEPs) (check sizes 60′, 40/400 ms) were recorded and the chiasmal coefficient was calculated to detect misrouting.

Results: Fundus photography showed normally pigmented fundi with absence of the usual foveal hyperpigmentation, foveal avascular zone, and macular and foveal reflexes. On OCT no foveal pit was found. The VEP recordings showed the largest positive CI component over the right hemisphere for the left eye, and over the left hemisphere for the right eye, with the CI almost absent over the ipsilateral hemispheres. The differential derivations showed opposite polarity for the recordings of the two eyes. The chiasmal coefficients of all three patients were significantly indicative of misrouting (−0.99, −0.91, and −0.99, respectively).

Conclusion: Based on the investigations in these patients the authors propose the hypothesis that foveal hypoplasia and misrouting exist as a distinct entity, and do not comprise the exclusive hallmark of albinism. The findings suggest that misrouting may exert a retrograde influence on foveal development.

Albinism is a heterogeneous genetically determined disorder of melanin synthesis in which either the eyes (ocular albinism (OA)), or the eyes, skin, and hair may be affected (oculocutaneous albinism (OCA)). Clinical signs show considerable variability in individual patients.[1] Ocular features include reduced visual acuity, nystagmus, iris translucency, and foveal hypoplasia. The optic discs show an abnormal course of retinal vessels consisting of an initial nasal deflection followed by an abrupt divergence and reversal of direction to form the temporal vascular arcades.[2]

In albinism, a far greater number of fibres from the temporal retina cross the midline and project contralaterally than in normal people. This chiasmal misrouting can be detected by recording multichannel visually evoked potentials (VEPs).[3] The general assumption is that if misrouting is detected, the diagnosis of albinism is proved unequivocally. Foveal hypoplasia in albino patients shows a strong correlation with misrouting[4] and is thought also to arise from defective melanin synthesis. To investigate whether conditions other than albinism may lead to misrouting and foveal hypoplasia, we examined three darkly pigmented patients with foveal hypoplasia; one of the patients had Kartagener syndrome.

PATIENTS AND METHODS

Patients

Patient 1 is a Dutch girl born in 1985 of healthy, unrelated parents; she has two healthy sisters. She has always been dark haired with dark brown eyes, and she tans normally. From an early age she had recurrent upper respiratory tract infections. In 1998 she had left sided appendicitis and was subsequently diagnosed with Kartagener syndrome. Kartagener syndrome consists of primary ciliary dyskinesia (PCD) with situs inversus totalis. PCD is caused by ultrastructural defects of respiratory cilia and sperm tails, leading to recurrent respiratory tract infections, sinusitis, bronchiectasis, and male subfertility. The disorder is autosomal recessively inherited with an incidence of between 1/30 000 and 1/120 000 live births.[5]

The patient was ophthalmologically examined regularly from the age of 3 months; we first saw her when she was 3 years of age. Her ophthalmological features are shown in table 1.

Patients 2 and 3 are sisters of Afghan origin, born in 1983 and 1989, respectively. Their parents and siblings have no ocular abnormalities. The patients have always been dark haired with dark brown eyes; their skin colour is similar to that of their parents and unaffected sibs. They were diagnosed with congenital idiopathic nystagmus in childhood. Their general health is good; they have no situs inversus. We first examined them when they were 16 years and 10 years, their ophthalmological features are shown in table 1.

After informed consent the patients underwent fundus photography, optical coherence tomography (OCT), and VEPs.

Methods

Fundus photographs were taken using a Zeiss fundus camera (FF 450) with a 50° field of view. The angles at which the main temporal arterial branches leave the optic nerve head (ONH) were analysed according to the method described by Neveu *et al*[2] (fig 1). In Neveu *et al*'s study, the exit angles of normal subjects were 66° (SD 11°), for albino patients they were 92° (8°).

Linear scans of the retina with OCT were performed along four meridians through the presumed foveal region (horizontal, vertical, and diagonal). Standard OCT software was used to generate retinal topographic measurements.

Pattern onset VEPs (check sizes 60′, 40/400 ms) were recorded with five horizontal occipital electrodes referenced

Abbreviations: GCL, ganglion cell layer; OA, ocular albinism; OCA, oculocutaneous albinism; OCT, optical coherence tomography; ONH, optic nerve head; PCD, primary ciliary dyskinesia; VEP, visually evoked potential

Table 1 Ophthalmological features of patients 1, 2, and 3

Patient	Refraction RE/LE	VA RE	VA LE	Nystagmus	Stereo acuity	Iris	Fundus
1	+2.0 sph −2 cyl A 10°/+2.5 sph −2 cyl A 180°	0.2	0.2	+	Nil	Dark brown, no transillumination	Normal pigmentation, foveal hypoplasia
2	+2.0 sph −2 cyl A 180°/+2.5 sph −2 cyl A 180°	0.16	0.2	+	Nil	Dark brown, no transillumination	Normal (dark) pigmentation, foveal hypoplasia
3	+2.0 sph −5 cyl A 10°/+2.5 sph −5.5 cyl A 180°	0.1	0.16	+	Nil	Dark brown, no transillumination	Normal (dark) pigmentation, foveal hypoplasia

RE, right eye; LE, left eye; VA, visual acuity.

to a frontal midline electrode. The active midline electrode was placed 2 cm above the inion, with two lateral active electrodes on each side, at a spacing of 3 cm. These electrode positions are equivalent to T_5, O_1, O_z, O_2, and T_6 of the international 10–20 system. Misrouting was assessed from the differences of the recorded signals from the left and right

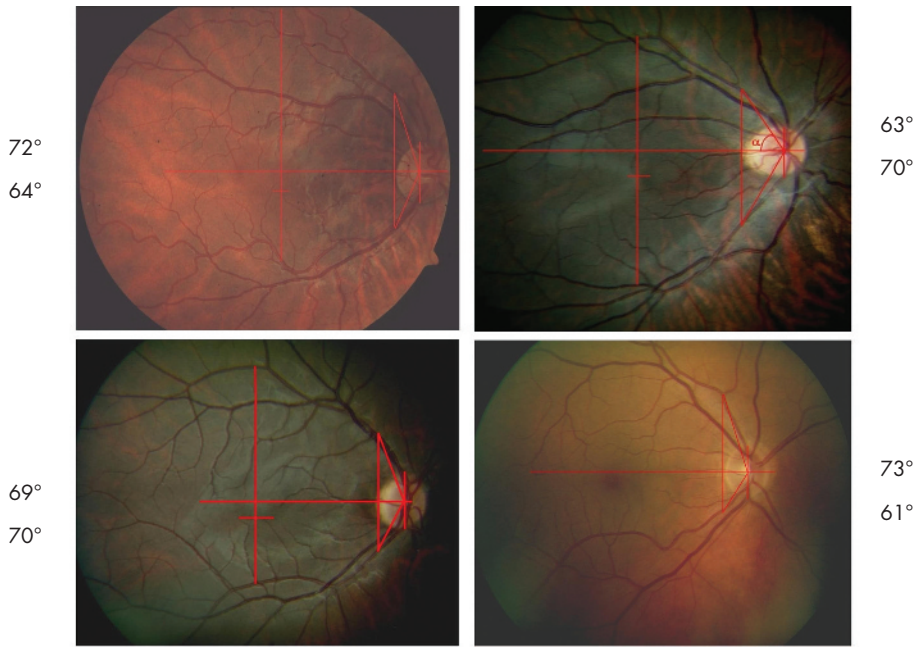


Figure 1 Fundus photographs of patient 1 (top left), patient 2 (bottom left), patient 3 (top right), and a normal subject (bottom right). The patients show absence of the usual foveal hyperpigmentation, foveal avascular zone, and macular and foveal reflexes. Small retinal vessels extend through the presumed macular area. In all subjects, measurement of the exit angle (α) of the main temporal arterial branches to the horizontal meridian is indicated, according to the method described by Neveu *et al*.[2] The horizontal meridian bisects the optic nerve head (ONH), the vertical meridian extends from the temporal edge of the ONH and intersects the inferior/superior temporal artery. The angle was measured between the horizontal meridian and the line between the projection on the horizontal meridian of the point where the artery exits the ONH, and the point where the vertical meridian intersects with the arterial vessel. The values are given next to the fundus photographs.

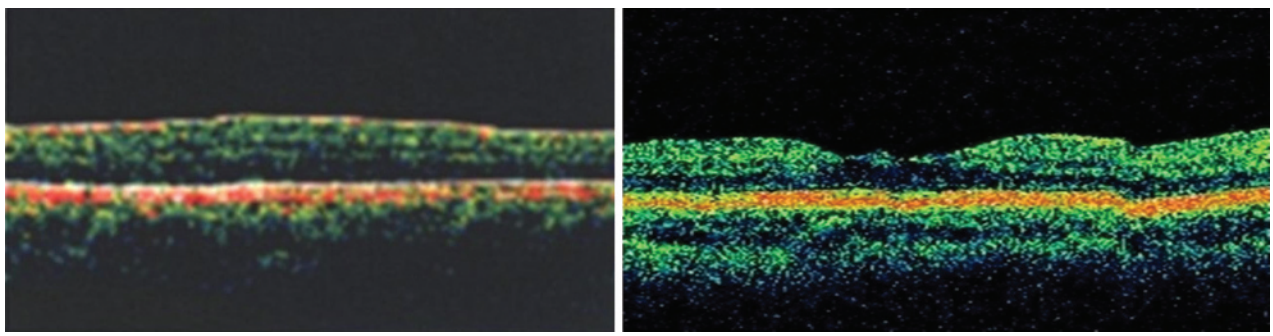
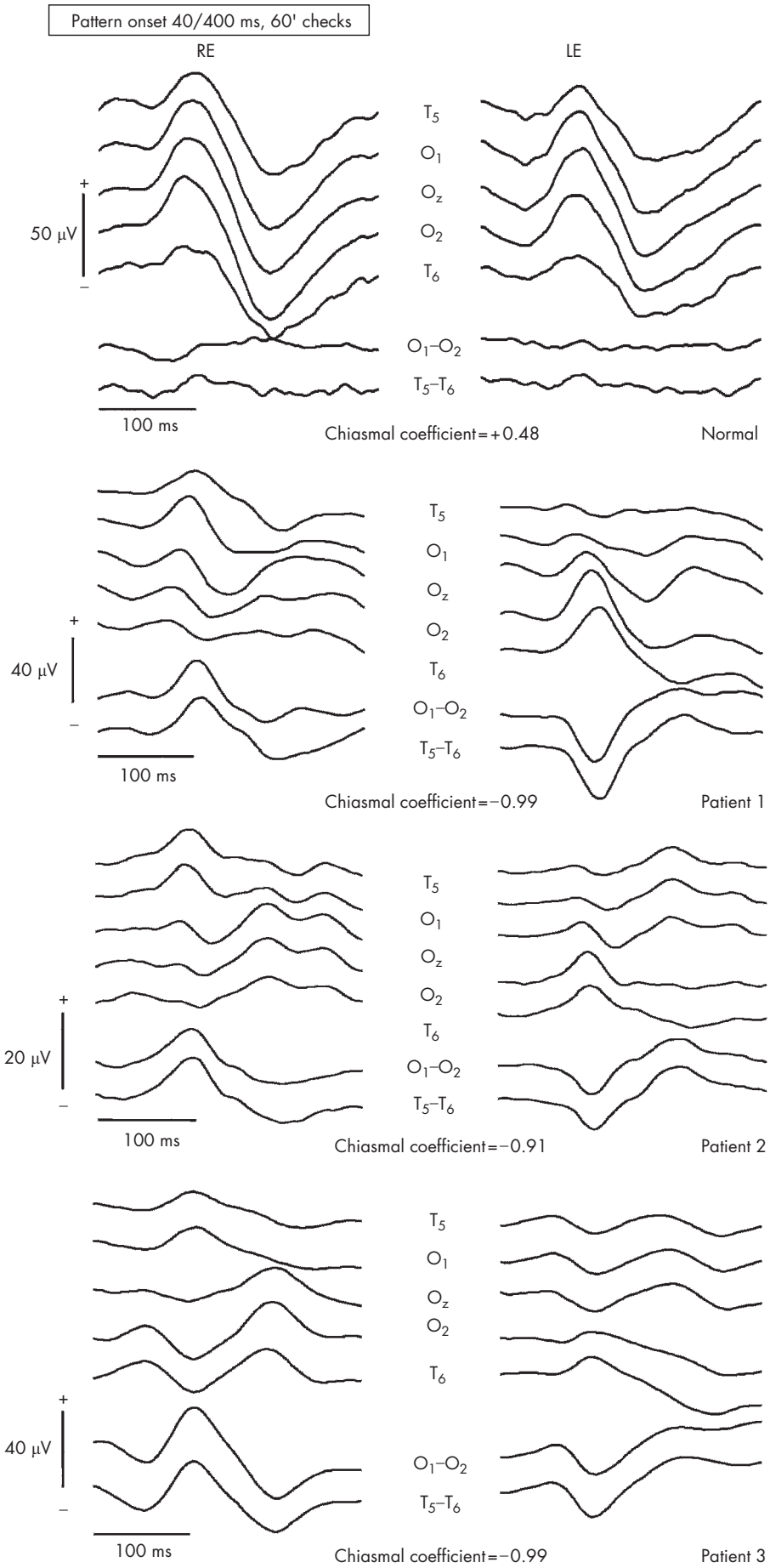


Figure 2 OCT of patient 1 (left), and of a patient with congenital nystagmus but normally developed fovea (right). In patient 1, there is extension of all neurosensory retinal layers through the area in which the fovea would normally be located. No clivus, anticlivus, or foveal pit can be seen. In the subject with congenital nystagmus a foveal pit can clearly be seen.


Pattern onset 40/400 ms, 60' checks
RE
LE
T5
O1
Oz
O2
T6
O1–O2
T5–T6
50 µV
100 ms
Chiasmal coefficient=+0.48
Normal
40 µV
Chiasmal coefficient=−0.99
Patient 1
20 µV
Chiasmal coefficient=−0.91
Patient 2
Chiasmal coefficient=−0.99
Patient 3

hemisphere (O_1–O_2 and T_5–T_6). We furthermore calculated the chiasmal coefficient, which is the cross correlation between the differential signals for the right and left eye.[6] By definition, the chiasmal coefficient can have a value between −1 and +1; it is negative in misrouting, and positive in normal subjects. The normative criterion value for our department is M −2SD = −0.17.

RESULTS

Fundus photography showed normally pigmented fundi with absence of the usual foveal hyperpigmentation, foveal avascular zone, and macular and foveal reflexes (see fig 1). The exit angles of the main temporal arteries lay below the mean −2 SD of the angles of the albino group ($p<0.05$) and were well within the range of the angles in normal subjects.

On OCT no foveal pit was found[7] (fig 2).

The VEP recordings showed the largest positive CI component[8] over the right hemisphere for the left eye, and over the left hemisphere for the right eye, with the CI almost absent over the ipsilateral hemispheres (fig 3). The differential derivations showed opposite polarity for the recordings of the two eyes. The chiasmal coefficients of all three patients were significantly indicative of misrouting (−0.99, −0.91, and −0.99, respectively).

DISCUSSION

We demonstrated the combined occurrence of misrouting and foveal hypoplasia in two darkly pigmented sisters, and in an unrelated female patient with Kartagener syndrome. There are no previous reports of ocular abnormalities in Kartagener syndrome, but, as in our patient, the syndrome may go unnoticed: she was only diagnosed with situs inversus by coincidence because of a perforated appendix.

It is unlikely that these patients have albinism. Because they are females with unaffected parents, they will not have (X linked inherited) OA. Autosomal recessive OA does not exist as a distinct entity but is considered to be a mild form of OCA type II.[9] Although in OCA type II patients may acquire some pigmentation later in life, at a young age patients are more lightly pigmented than their parents and unaffected sibs. The patients in this study, however, did not show any form of hypopigmentation, patient 1 even being the most darkly pigmented of her family. They were examined ophthalmologically regularly from a young age, and iris transillumination or fundus hypopigmentation was not noticed. We furthermore found that the exit angles of their retinal arteries lay below the mean −2 SD of the angles of the albino group.

The pathogenesis of misrouting in the three patients is unknown, but may possibly be caused by a defect in one of the genes involved in regulating optic chiasm development.[10] To explain the combination of Kartagener syndrome with misrouting, we searched the literature for currently known genes and candidate genes of PCD[5] and compared them to those of chiasm development,[10] but we did not find a gene implicated in both. However, *ZIC3,* a candidate gene for left-right asymmetry,[5] and *ZIC2*, a gene involved in chiasm development,[11] show some broad similarities in their expression domains.[12] Further molecular studies are needed to determine if these genes are responsible for the combination of Kartagener syndrome with misrouting.

In addition to misrouting, foveal hypoplasia is a striking feature of our patients. In albinos both features are strongly correlated[4] and misrouting as well as foveal hypoplasia are thought to arise because of defective retinal melanin synthesis.[13] A correlation between the levels of ocular melanin and the degree of misrouting has indeed been demonstrated,[14] but the role of melanin in foveal development is much more uncertain.

It has been suggested that critical densities of the central ganglion cell layer (GCL) are required for normal development of the foveal pit.[15] Some studies have demonstrated a reduced GCL density in the area centralis of albino mammals,[16] which may provide an explanation for the foveal hypoplasia in albinism. However, the reason for this reduced GCL density remains unclear. Albino animals show a significant deficit in rod numbers, while cone numbers and mosaic are normal.[17] A correlation has therefore been suggested between rod numbers and ganglion cell density,[17] but such a correlation does not explain why a reduced GCL density occurs only centrally, while the total number of retinal ganglion cells in adult albino retina is normal.[18] Furthermore, in contrast with the correlation found between pigmentation and degree of misrouting,[14] there does not seem to exist a correlation between levels of pigmentation and deficits in the central ganglion cell layer.[19]

The combined occurrence of foveal hypoplasia and misrouting in albinos as well as in non-albinotic patients therefore suggests a mutual influence: foveal hypoplasia causing misrouting, or vice versa. Because it has been shown in patients with aniridia that foveal hypoplasia does not lead to misrouting,[2] we propose the hypothesis that misrouting may exert a retrograde influence on foveal development.

The development of the foveal pit occurs from 24 weeks' gestation to 45 months postpartum,[20 21] which means that foveal pit formation occurs at a time when chiasmal decussation is already established. Retrograde influences originate from the visual cortex or optic nerves and tracts. Humans with misrouting caused by albinism show reorganisation of the normal cortical topographic representation.[22] They also have smaller optic nerves, tracts, and chiasms than normal subjects.[23] Abnormalities of the striate cortex have been shown to influence developing ganglion cells, with the period of maximal retrograde influence occurring in the first months of life, thus overlapping with the period of foveal development.[24] The finding of foveal hypoplasia in cases of severe optic nerve hypoplasia and colobomata[25] may be an additional indication of the existence of retrograde influences.

In conclusion, this study shows for the first time misrouting and foveal hypoplasia in three patients without albinism, and proposes an alternative mechanism for the development of foveal hypoplasia. Further studies are needed in patients with foveal hypoplasia, caused by a variety of

Figure 3 From top to bottom; responses to pattern onset-offset stimulation of a normal subject, patient 1, patient 2, and patient 3. In the three patients, the differential recordings O_1–O_2 and T_5–T_6 show a positive peak with stimulation of the right eye, which means that the response is found in the left hemisphere. For the left eye, this peak is negative, caused by a response of the right hemisphere. The chiasmal coefficient is given by[6]:

$$cc = \frac{\int_{t1}^{t2} [V_{RH,RE}(t) - V_{LH,RE}(t)] \cdot [V_{RH,LE}(t) - V_{LH,LE}(t)]\, dt}{\int_{t1}^{t2} |[V_{RH,RE}(t) - V_{LH,RE}(t)] \cdot [V_{RH,LE}(t) - V_{LH,LE}(t)]|\, dt}$$

where $V_{RH,RE}$ and $V_{LH,RE}$ are the signals recorded from the right and left hemisphere while stimulating the right eye; $V_{RH,LE}$ and $V_{LH,LE}$ the signals from the right and left hemisphere when stimulating the left eye. The three chiasmal coefficients of the patients were significantly indicative of misrouting.

conditions, to understand the precise association between the optic chiasm and foveal development.

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