Primary vitreoretinal dysplasia transmitted as an autosomal recessive disorder

NORIO OHBA, SHINOBU WATANABE, AND SHINGO FUJITA

From the Department of Ophthalmology, Kagoshima University Faculty of Medicine, Kagoshima, Japan 890

SUMMARY A sibship of a brother and sister with congenital bilateral pseudoglioma is described. The most prominent abnormality was a greyish-white vascularised mass in the retrolental spaces, which was noted as early as the first weeks of life. Corneal opacities, posterior synechiae, and complicated cataracts developed within 1 to 2 years age. The sibship showed normal chromosomes and had no systemic disorders, including mental and hearing impairment. The parents and other relatives were normal. Autosomal recessive disease, rather than Norrie's disease, was the most probable explanation for the dysplasia of the vitreous and retina in the sibship. This is probably the third report of familial occurrence with autosomal recessively inherited vitreoretinal dysplasia without systemic anomalies. The importance of the disease in genetic counselling is discussed.

Vitreoretinal dysplasia is induced by an arrest in the development of the vitreous and retina, and it typically presents as a 'pseudoglioma' due to opacities in the retrolental tissues. The causes of the condition are broadly divided into environmental and genetic.^{1,2} Among genetic factors chromosomal aberrations and Norrie's disease are relatively well known. The 13 trisomy syndrome is the most frequently found chromosomal abnormality, in which retinal dysplasia is associated with various systemic malformations.³ Norrie's disease is transmitted as an X-linked recessive 'disorder affecting only males, and mental and hearing defects are occasionally associated.'^{4,5} An autosomal recessive disease has been postulated as one of the genetically heterogeneous conditions,⁶ but its existence has not been fully appreciated because of the scarcity of reported cases.

This paper describes a sibship of a brother and sister who had congenital bilateral 'pseudoglioma' with a probable autosomal recessive gene. It is thought worthwhile to describe the cases in order to provide some evidence that congenital bilateral 'pseudoglioma' can be produced by an autosomal recessive gene and to draw attention to an important consideration in genetic counselling.

Case reports

The infants described here are a brother and sister who are the only children of nonconsanguineous parents. The parents were examined and found to be normal (the father had a questionable vascular anomaly in the far periphery of his left fundus, but it was assumed to be nonspecific and unrelated to the disease of his children). Family members of the patients have lived in the southwest region of the Kyushu Island of Japan. None of the accessible relatives were willing to come for examination, but according to the information obtained from the parents probably no other relatives had been affected with congenital ocular disease (Fig. 1).

Fig. 1 Pedigree of the family.

Correspondence to Norio Ohba, MD, Department of Ophthalmology, Kagoshima University Faculty of Medicine, Usuki-cho 1208-1, Kagoshima-shi, Japan 890.

BROTHER

A 3-month-old male infant was born at a full-term gestation with a birth weight of 2980 g. During pregnancy the mother had been healthy with negative serological tests for syphilis, toxoplasmosis, and rubella, and the delivery was uncomplicated; no supplemental oxygen was given. The parents noticed 'pupillary white reflexes' in the patient at the age of about 3 weeks, and any eye movement or fixation behaviour had not developed at the age of 2 months. The patient was referred to us at the age of 3 months.

On systemic examination the patient was seen to be a well-developed boy. Paediatric and neurological examinations were normal. Routine laboratory examinations, including urine analyses, blood chemistry, and serological tests, were all normal. Computerised tomography of the skull revealed slightly small eyeballs and dense opacities in the retrolental spaces, but the orbits and head were normal. A chromosomal study revealed a normal 46 XY male karyotype.

On ocular examination the patient appeared to have no light perception in either eye, and pupillary light reflexes were absent. The ocular adnexae and conjunctivae were normal. The eyeballs were not soft, but they appeared mildly microphthalmic, and the corneae measured 8×9 mm in diameter. The right cornea was a little hazy, and the anterior chamber was shallow, the iris diaphragm was displaced anteriorly, and the pupil dilated irregularly to 1% drops atropine; partial synechiae were present. The left anterior chamber was not very shallow, and the pupil dilated widely and regularly to atropine drops. The lenses were clear, and elongated ciliary processes were visible behind them. In the right retrolental space there was a fairly dense, greyish-white mass close to the posterior lens; a few aberrant vessels traversed in the mass, which seemed to originate from a disc-like structure lying deep in the mass. No details of the fundus could be visualised. In the left retro-

lental space there was a whitish opacity in the nasal portion of the vitreous, which originated from a malformed optic disc and extended in the vitreous toward the nasal equator of the lens. The opacity appeared as a severe form of falciform fold of retina and became wider as it coursed anteriorly. Through the relatively clear vitreous in its temporal portion posterior and temporal fundus could be seen, and it was observed that the retinochoroid had a diffuse pepper-and-salt-like appearance associated with scattered clumps of dense pigments, and the retinal vessels were scarce and narrow. A fluorescein angiogram of the left eye performed under a general anaesthesia revealed marked leakage of dyes from the poorly developed retinal and choroidal vessels. Electroretinographic responses were absent in both eyes (Fig. 2).

The patient has been followed up until the age of 3 years. Physical and mental development was normal for a blind child, and there was no hearing impairment. The abnormalities of the right anterior segments had gradually progressed. At the age of 7 months the cornea had increased its diffuse haziness, and the posterior synechiae developed totally, making the pupil secloded. Thereafter the right anterior chamber became more shallow and the iris atrophy and lens opacity progressed, while the blood vessels became extinct. At the age of 12 months the right complicated cataract became so dense that the retrolental mass and elongated ciliary processes were no longer visible.

In contrast the left eye showed little change during the follow-up period, and a part of the fundus was still visible at the age of 3 years. However, the patient never showed any sign of vision.

SISTER

A 4-week-old female infant, she was the only sibling of the brother described above. After the first affected son the parents had been seriously concerned with a recurrence of the disease in the second child, and they

Fig. 2 The brother case. Left: Retrolental mass in the right eye. Centre: Mass in the nasal retrolental space in the left eye. Right: Elongated ciliary processes are visible in the temporal vitreous in the left eye.

Fig. 3 The sister case.
Left: Retroental mass in the right eye. Right: Retroental mass in the left eye.

had been told of a relatively high risk if the child were a boy, because the first child was possibly affected with Norrie's disease, which is transmitted in an X-linked recessive manner. No prenatal sexual diagnosis was attempted, and the second child proved to be a girl. She was born at a full-term gestation, with a birth weight of 2550 g. The mother had been well during pregnancy, the delivery was uneventful, and no supplemental oxygen was given. As soon as a week after her birth, contrary to prediction, the parents noticed 'pupillary white reflexes' very similar to those in the first child. The patient was first seen by us at the age of 29 days.

On systemic examination the patient was found to be well developed, and paediatric examinations were normal. Routine laboratory examinations were normal. A chromosomal study revealed a normal 46 XX female karyotype.

On ocular examination the patient appeared to have no light perception in either eye. There were no pupillary light reactions, and a sign of 'pseudoglioma' was noted in both eyes. The lids and conjunctivae were normal, and the eyeballs appeared normal in size and tension. The corneae were clear and measured 10×10 mm in diameter. The anterior chambers were clear but moderately shallow. The right pupil was round and dilated well to 1% drops of atropine. There were no anterior or posterior synechiae, but persistent pupillary membranes were noticeable. The lenses were clear, and elongated ciliary processes were visible peripherally behind them. The retroental spaces were filled with a greyish-white soft mass, and some aberrant vessels traversed its surface. Details of the vitreous and fundus posterior to the mass could not be visualised in either eye (Fig. 3).

The patient has been followed up until the age of 1 year 8 months. She showed normal physical and mental development for a blind child, and no hearing impairment occurred. At the age of 5 months

the anterior chambers had become shallower, and the degree of the posterior synechiae progressed, resulting in an irregular pupil in the right and extremely small one in the left. The vessels traversing the retroental mass gradually became extinct. At the age of 8 months the cornea became opaque, and rubeosis iridis developed in both eyes. After the age of 1 year the lenses gradually became cataractous, so that the retroental opacities were barely visible.

Discussion

The brother and sister described here had congenital bilateral blindness due to maldevelopment of the vitreous and retina. A vascularised opaque mass in the retroental space was responsible for a prominent clinical sign, that is, 'pseudoglioma,' noted as early as the first week of life. The fundal structures were invisible because of the extensive retroental opacities, except for one eye in the brother, whose partially clear vitreous permitted us to observe a diffuse retinal dysplasia. Absence of pupillary light reflexes and nonrecordable electroretinograms suggest extensive retinal malformations in both eyes of each sibship.

The developmental anomalies in the present sibship are consistent with 'congenital pseudoglioma,' 'total congenital retinal detachment,' or 'congenital nonattachment of retina,' which are no more than descriptive terms.¹²⁵⁷ But their clinical features are compatible with a severe form of 'persistent hyperplastic primary vitreous' or 'congenital falciform of retina (falciform detachment of retina).'⁵⁸ For simple description we use the term 'vitreoretinal dysplasia,' which includes a diverse group of diseases caused by an arrest in the development of the vitreous and retina and manifests typically as 'congenital pseudoglioma.'

Vitreoretinal dysplasia is classified into primary and secondary forms. The secondary form may be

induced by environmental factors, such as fetal irradiation, pre- and perinatal inflammations, and the results of prematurity or oxygen administration. It is often clinically indistinguishable from the primary form, but it is more frequently unilateral and lacks a hereditary factor. The fact that the present sibship showed bilateral and familial occurrence strongly suggests that the condition was primary rather than secondary.

Primary vitreoretinal dysplasia is a hereditary disorder and consists of genetically heterogeneous diseases.^{2,6} Chromosomal aberrations, the trisomy 13 syndrome being the one most frequently found, may induce retinal dysplasia as a part of systemic defects in heart, kidney, and skeleton.³ Many cases of 'retinal dysplasia' described by Reese and Blodi⁹ might have been examples of chromosomal aberrations in view of the associated systemic malformations. Since the present sibship had normal chromosomes without any systemic defect, a chromosome-induced ocular disease can safely be ruled out. Vitreoretinal dysplasia is also induced by a Mendelian pattern of inheritance, and an X-linked recessive disease has been well documented as Norrie's disease.^{4,5} The disease affects only males, and the heterozygous female does not show any clinical symptoms.

The clinical appearance of the present sibship is very similar to Norrie's disease except for absence of extraocular symptoms, as illustrated in Table 1, and

differentiation seems almost impossible. The absence of mental and hearing impairment does not provide convincing evidence against Norrie's disease, since those symptoms occur in about 30% of cases.⁵ However, Norrie's disease is most unlikely in the present sibship because a girl was affected and the father was normal; if the present sibship were affected with Norrie's disease, not only must the father have been affected but the mother must have been heterozygous for the gene. An autosomal recessive mode of inheritance is the most probable in accounting for the present sibship, though the possibility of a gene mutation in either of the parents for autosomal dominant disease cannot be entirely excluded. No definite case with the latter disease has been recorded previously.

In contrast to Norrie's disease, over 200 cases of which have been recorded, including those by us,^{5,10} less attention has been drawn to autosomal recessive disease. So far as we know only 2 familial cases have been previously reported. Franceschetti¹¹ described a sibship of a brother and sister with congenital bilateral 'pseudoglioma' whose parents were first cousins and healthy. They had greyish lesions in pupils, and rubeosis iridis, and iris bombé, and corneal opacities developed later. Philips *et al.*¹² described a sibship of a brother and sister with congenital bilateral nonattachment of retina whose parents were healthy and nonconsanguineous. The sibship had in the anterior vitreous a white mass like cotton-wool with some blood vessels; bilateral microphthalmos, degenerative corneal opacities, and shallow anterior chambers developed later. It is noticeable that the present sibship had very similar clinical features to those in the cases described by Franceschetti and Philips *et al.*

The following 2 families may possibly represent the same disease, but Norrie's disease cannot convincingly be ruled out. Clarke¹³ described a family in which a man who was blind from bilateral congenital cataract married his first cousin. A boy and 2 girls of the 6 children had congenital bilateral 'pseudoglioma.' Since the father was supposedly affected with the same disease as the children in view of the unsuccessful operation for the 'congenital cataract,' 2 alternative genetic patterns are equally plausible, namely, autosomal recessive and X-linked recessive, and in either case the mother might have been heterozygous. Weve¹⁴ described a family in which 3 males were affected with either 'pseudoglioma' or 'falciform fold of retina,' and the mode of inheritance might have been more probably X-linked recessive, that is, Norrie's disease.

The present sibship may thus represent the third family on record as having autosomal recessive vitreoretinal dysplasia, and it provides some

Table 1 Clinical picture of the present sibship in comparison with Norrie's disease*

	Present sibship		Norrie's disease
	Brother	Sister	
Sex	M	F	M
Familial	+	+	+
Sex-linked	-	-	+
Disease in pregnancy	-	-	-
Age at onset	cong.	cong.	cong.
Binocular	+	+	+
Microphthalmia	+	(+)	-
Buphthalmia	-	-	(+)
Phthisis	-	-	+
Blindness	+	+	+
Tyndall	-	-	(-)
Shallow anterior chamber	+	+	+
Ant. synechia	-	+	+
Post. synechia	+	+	+
Cataract	+	+	+
Elongated ciliary processes	+	+	+
Retrolental mass	+	+	+
Vitreous opacities	?	-	(+)
Retinal vascular aberrations	?	+	-
Retinal detachment	+	±	+
Focal retinal lesions	-	-	(-)
Oligophrenia	-	-	+
Hypacusis	-	-	+
Other serious malformations	-	-	-
Prematurity	-	-	-

*From Warburg M (Table 8).⁴

+ = Frequently. (+) = Occasionally. (-) = Infrequently. - = Rarely.

supportive evidence for the existence of this genetically distinct entity. The disease may be rare, but in our opinion other cases might have been unrecognised because of difficulty in the genetic diagnosis, particularly in sporadic cases. Its clinical picture is not necessarily specific, being more or less indistinguishable from Norrie's disease as well as from various secondary dysplasias. We assume, however, that knowledge of the disease will help in detecting more cases and provide information of value in genetic counselling.

The clinical appearance of vitreoretinal dysplasia is variable. In this connection, the coexistence in one member of the present sibship of a severe form of persistent hyperplastic primary vitreous and falciform fold of retina gives support to the view¹⁴ that differently described symptoms can be the result of essentially the same causative factor.

This study was supported by a grant-in-aid for scientific research from Japanese Ministry of Education, project number: 448331.

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