Journal of Medical Genetics (1975). **12**, 94.

A family with apparently sex-linked optic atrophy

L. N. WENT, E. C. DE VRIES-DE MOL, and H. J. VÖLKER-DIEBEN

Departments of Human Genetics and Ophthalmology, Faculty of Medicine, University of Leiden, The Netherlands

Summary. A family is described in which a probable new form of sex-linked optic atrophy was found in eight individuals. Some additional neurological abnormalities were noted. Results of studies of the Xg blood group excluded close linkage between the optic atrophy and *Xg* genes. As a probable coincidence, Huntington's chorea was found in a side branch of the family.

Of the heterogeneous groups of optic atrophies only two inherited types occur with any appreciable frequency. These are the dominant optic atrophy (Kjer, 1972) and Leber's optic atrophy (Went, 1972). Dominant optic atrophy, which is probably present at birth, is usually a relatively mild disease with only slow progression. Leber's optic atrophy is characterized by an acute onset, frequently occurring between 10 and 30 years of age with little if any progression. The inheritance appears to be sex linked, although approximately 15% of patients are women. Transmission through affected males has never been recorded.

We report a family with optic atrophy characterized by an apparently sex-linked mode of inheritance but with very early onset (possibly present at birth) and slow progression which is clearly different from the above diseases.

Family studies and results

Figure 1 gives an abbreviated pedigree of the family. The index case (VI.35), a boy born in 1962 and 9 years old when first seen, presented with difficulties at school and was found to have a visual acuity of 0·1 in the right eye and 0·2 in the left with normal visual fields.

There was a history of poor vision combined with a neurological disorder in a maternal great-uncle (IV.8) of the index case; this was the main reason for an extended family study. In Table I the visual acuity is presented of the eight family members subsequently found to be suffering from optic atrophy. They were all reported to have had considerable difficulties at primary school; evidence points to impaired visual acuity having been at least partially responsible for this.

All the 60 other living family members indicated on the pedigree were personally seen at their homes and found ophthalmoscopically not to have optic atrophy. IV.4, IV.5, V.1, V.2, and V.3 all died very young. From the pedigree it is obvious that the females, IV.13, IV.16, V.7, V.16, and V.32 must have transmitted the optic atrophy. They were carefully studied from an ophthalmological point of view; no abnormal findings were found in any of them. All available offspring of the four sibs of III.2 were also studied, and although no optic atrophy was found, 13 patients with Huntington's chorea were detected. A complete linkage analysis of that part of the pedigree is presently being undertaken.

The neurological findings in the great-uncle (IV.8) of the index case were, apart from the optic atrophy: ataxic gait, ataxia, intention tremor and a coarse flapping tremor, dysdiadochokinesia, absence of ankle jerks, and mental retardation (IQ 65) and emotional lability. An electromyographic study revealed a single pattern in the right extensor digitor brevis muscle and a slightly decreased conduction velocity in the right peroneal nerve, while there was a decreased conduction velocity in peripheral nerves. Electro-diagnostic tests indicated a disturbance at the retinal level as well as involvement of the optic nerve. Neurological abnormalities were also found in other members with optic atrophy. These abnormalities included absent ankle jerks in all affected members, pathological plantar responses in some, and tremor of the hands and disturbances of gait. The detailed neurological and ophthalmological findings are reported elsewhere (Völker-Dieben *et al*, 1974).

Received 9 April 1974.

FIG. 1.

TABLE I

Patient	Age (yr)	Visual acuity		Anomaloscope		Ishihara	HRR	Farnsworth-15
		OD	OS	OD	OS			
IV.7	35*	1/60	0·1	—	—	—	—	—
IV.8	64	1/60	1/60	np	np	np	np	np
V.10	49	1/60	1½/60	np	40–50	Only 12 can be seen	np	np
V.28	25	0·16	0·4	np	25–55	Strong colour vision defect; the last four plates are read as by deuterans	Strong defect; no typing possible	Abnormal arrangement (non-specific)
VI.6	20	0·25	0·20	34–48	26–53			
VI.9	12	0·4	0·32	33–47	38–45			
VI.19	17	0·3	0·3	—	—			
VI.35	9	0·1	0·2	30–45	30–50			

* IV.7 had died at age 47 before the family was studied. The visual acuity was obtained from information of a previous hospital admission: np = not possible to test; —test not performed.

TABLE II

Pedigree	Sex	Age	ABO	MN	Rh	K	Xg[a]
IV.6	F	72	A_1	M	R_1r	–	–
IV.8	M	64	A_1	M	R_1r	–	+*
IV.9	M	63	A_1	MN	R_1r	–	+
IV.10	F	62	B	M	rr	–	+
IV.11	F	60	A_1	M	R_1r	–	+
IV.13	F	59	A_1	M	R_1r	–	+†
IV.14	M	65	A_2	MN	R_1r	–	+
IV.16	F	55	A_2B	M	R_1r	–	+†
IV.18	F	53	B	M	R_1r	–	+
V.7	F	54	O	MM	R_1r	–	+†
V.10	M	49	A_1	MM	rr	–	+*
V.11	F	47	A_1	MM	rr	–	+
V.15	M	47	A_2	MN	R_1R_1	–	+
V.16	F	41	A_1	M	rr	–	–†
V.17	M	49	O	MN	rr	–	–
V.18	M	43	O	MN	R_1r	–	+
V.19	F	40	O	M	R_1r	–	+
V.20	M	30	O	MN	R_1r	–	+
V.21	M	28	A_1	MN	R_1r	–	+
V.22	M	36	A_1	M	R_1r	–	+
V.23	M	34	A_1	M	R_1r	–	+
V.25	M	36	A_1	M	R_1r	–	+
V.26	F	35	A_1	M	R_1r	–	–
V.28	M	25	O	M	R_1r	–	–*
V.31	M	41	A_1	MN	R_1R_2	–	+
V.32	F	33	A_1B	MN	R_1R_2	–	+†
V.33	M	32	A_1	MN	R_1R_2	+	+
V.35	F	29	A_1	MN	R_2r	–	+
V.36	M	24	B	MN	R_1r	–	+
V.37	M	17	B	M	rr	–	+
V.38	F	27	A_2B	M	rr	–	+
VI.6	M	20	O	MM	R_1r	–	+*
VI.7	M	16	O	MM	R_1r	–	+
VI.8	M	14	O	MN	R_1r	–	+
VI.9	M	12	O	MM	R_1R_2	–	+*
VI.14	M	20	A_1	MM	R_2r	–	+
VI.17	M	13	A_1	MM	R_1r	–	+
VI.18	F	13	O	MN	R_1r	–	+
VI.19	M	17	A_1	M	R_1r	–	–*
VI.20	M	16	A_1	MN	R_1r	–	–
VI.21	F	12	A_1	MN	R_1r	–	+
VI.30	M	15	O	M	R_1r	–	–
VI.31	M	7	O	M	R_1r	–	–
VI.32	M	5	A_1	M	rr	–	–
VI.34	F	12	A_1B	M	R_1R_2	–	+
VI.35	M	9	A_1B	MN	R_1R_2	–	+

* Optic atrophy.
† Obligatory carrier optic atrophy.

In view of a likely sex-linked inheritance in this family a search was made for the presence of other X-linked markers. As expected, no G6PD deficiency for electrophoretic variants were found, and all but one of the 60 relatives tested for colour vision gave an entirely normal response. (Only the husband of V.26 proved to have a protan defect.) Colour vision defects did occur in the patients with optic atrophy; these were obviously secondary to the optic atrophy. The results obtained in patients with pseudoisochromatic plates are indicated in Table I. The results with the H.R.R. and Farnsworth 15 tests were grossly abnormal, but unspecific for any type of colour defect.

The results of the Xg blood group, together with some further blood group studies are presented in Table II.

Discussion

Sex-linked inheritance seems the most plausible explanation for the optic atrophy in our family. Only males are affected, seven of whom are living and were investigated. Five of the females (IV.13, IV.16, V.7, V.16, and V.32) who must have transmitted the gene, were living and found to be opthalmologically normal. The other two obligatory carrier females who were deceased were reported to have had normal visual acuity. None of the affected males had children, but only two of the four older affected males (IV.8 and V.10) had been married long enough potentially to have produced offspring. In its mode of inheritance the optic atrophy in our family is not different from that seen in Leber's optic atrophy (Went, 1972). In this latter disease one in eight affected individuals is a female, but the disease has never been shown to be transmitted through affected males. There is, however, one marked difference between Leber's optic atrophy

and the optic atrophy in our family; the age and mode of onset. The optic atrophy in our family has been present from earliest childhood in all patients. In two patients (VI.9 and VI.35) an advanced stage of optic atrophy was observed at the age of 12 and 8 years, respectively. There is no evidence of an acute onset or deterioration in any of the patients. In contrast to this, in Leber's optic atrophy the mean age of onset is 24 years, and the onset is acute. Before this acute onset no abnormalities of vision have ever been reported.

A further difference from Leber's optic atrophy is that in the patients of our family the visual fields have been essentially normal, whereas in Leber's optic atrophy all patients have central scotomas.

The defect of colour vision in this family and in families with Leber's optic atrophy, seems to involve mainly the red/green mechanism. The defect of colour vision occurring in this family is, however, less classifiable than that of patients with Leber's optic atrophy, which seems to be a deuteran-like defect (Grützner, 1966).

We know of only one other report in the literature of a possibly sex-linked optic atrophy. Lysen and Oliver (1947) reported upon a family in which eight males over four generations were partially or totally blind, involving in one instance transmission from an affected man through his non-affected daughter to a grandson. The age of onset, however, is uncertain. In two patients vision became poor at the ages of 16 and 14, while in two others the poor vision was probably present at birth and at the age of 3 years, respectively. The presence of choroiditis, chorioretinitis, and cataract has been noted (Lysen and Oliver, 1947) in some affected individuals and in view of this and of the uncertainty of the presence of optic atrophy the condition occurring in this family appears to be different from that observed in our family.

In view of the presence of neurological abnormalities in at least some of our patients with optic atrophy the presence of a sex-linked heredodegenerative neurological disorder accompanied by optic atrophy has to be considered. The presence of optic atrophy secondary to a heredo-degenerative neurological disorder is frequently encountered; a good discussion of this has been presented by André-van Leeuwen (1948). Sex-linked heredodegenerative disorders are, however, very rare. The only report known to us being that of Johnston and McKusick (1962) concerning a family with spastic paraplegia. This family was restudied, together with a second family, by Thurmon *et al* (1971). In the second family no optic atrophy appeared to be present, but in the first family optic atrophy occurred in a number of patients in combination with the spastic paraplegia. The involvement of the optic nerves has not been well documented but they appear to be absent in four of the 10 patients and unilateral in two. The disorder is clearly different from the one seen in our family, where the optic atrophy is always bilateral and present from early childhood, while it may be accompanied by neurological abnormalities at a later age. Only in one patient (IV.8), aged 64, has this led to marked physical disability, while the neurological findings in his case are clearly different from those described by Johnston and McKusick (1962).

A study of the Xg blood group gave some linkage information. The results are indicated on the pedigree and presented in detail in Table II. The Xg genotypes of III.1 and III.2 are inferred from the genotypes of IV.6 and IV.8, the genotype of IV.2 has been derived from V.10 and V.16. The genotype of IV.2 is therefore unambiguous, she must have had one X chromosome with both the optic atrophy and Xg^a from her mother, III.2. Thus, V.10 is a non-recombinant and V.16, who carries the gene for optic atrophy because she has an affected son, must be a recombinant. Furthermore, V.11 and V.13, who both can be inferred to be Xg^a/Xg heterozygotes must have received the Xg^a gene from their mother (who has this gene in coupling with the gene for optic atrophy) since their father must have had an Xg gene as his daughter V.16 is Xg(a−).

An analysis of the further possible genotypes which might give information on recombinants and non-recombinants in this family leaves only a small number of variables.

The genotype of III.2 may have been either Xg^a and optic atrophy in coupling or in repulsion, since she was heterozygous at both loci. The Xg genotype of III.3 could have been Xg^a or Xg. Furthermore, V.11 and V.13 may be heterozygotes for the optic atrophy, in which case they are non-recombinants and two of their three non-affected sons who were tested are recombinants while the third is a non-recombinant. Alternatively, V.11 and/or V.13 are not carrying the optic atrophy gene in which case they are recombinants. As an exercise, analysis of the 16 different combinations resulting from the possible genotypes gives a minimum of four recombinants with eight non-recombinants (III.2 Xg^a and optic atrophy in coupling; III.3 Xg^a; V.II and V.13 carriers of optic atrophy) and a maximum of six recombinants with three non-recombinants (III.2 Xg^a and optic atrophy in repulsion; III.3 Xg; V.11 and V.13 non-carriers of optic atrophy).

If we suppose sex-linked inheritance to be responsible for the optic atrophy, we must conclude that the gene for optic atrophy is not at a measurable distance from Xg, as is also the case for the genes of protan and deuteran colour vision defects, haemophilia A, and G6PD deficiency. Autosomal dominant sex-limited inheritance cannot be excluded, however.

The simultaneous presence of Huntington's chorea in the pedigree must be considered as a coincidence. The presence of this disease has been well established in generations I, II, and III and has been studied by ourselves in offspring of III.6 and III.9. No optic atrophy was found in any of the offspring of sibs of III.2. That III.2, who died at the age of 70, has also carrried the Huntington gene seems, on the basis of extensive questioning of living relatives, to be extremely unlikely.

Drs R. Sanger and P. Tippett graciously performed the blood group studies. Drs A. Staal and J. W. Klawer analysed the patients from a neurological point of view, while Dr G. H. M. van Lith did the electro-ophthalmological studies. Miss A. Gelderblom and Mrs L. Sutikno have given valuable additional help.

References

André-van Leeuwen, M. (1948). Hérédo-ataxies par dégénérescence spino-ponto-cérébelleuse. II. Les manifestations optiques. *Revue d'Oto-Neuro-Ophtalmologie*, **20**, 43–108.

Grützner, P. (1966). Ueber erworbene Farbensinnstörungen bei Sehnervenerkrankungen. *Albrecht v. Graefes Archiv für Ophthalmologie*, **169**, 366–384.

Johnston, A. W. and McKusick, V. A. (1962). A sex-linked recessive form of spastic paraplegia. *American Journal of Human Genetics*, **14**, 83–94.

Kjer, P. (1972). Infantile optic atrophy with dominant mode of inheritance. In *Handbook of Clinical Neurology*, ed. P. J. Vinken and G. W. Bruyn, vol. 13, pp. 111–123. North Holland, Amsterdam.

Lysen, J. C. and Oliver, A. P. (1947). Four generations of blindness. *Bulletin of the Dight Institute*, **5**, 20–25.

Thurmon, T. F., Walker, B. A., Scott, C. I., and Abbott, M. H. (1971). Two kindreds with a sex-linked recessive form of spastic paraplegia. *Birth Defects: Original Article Series*, **7**, pt. 6, 219–221. National Foundation—March of Dimes, New York.

Völker-Dieben, H. J., Van Lith, G. H. M., Went, L. N., Klawer, J. W., Staal, A., and De Vries-de Mol, E. C. (1974). A family with sex-linked optic atrophy (ophthalmological and neurological aspects). *Documenta Ophthalmologica*, **37** (2), 307–326.

Went, L. N. (1972). Leber disease and variants. *Handbook of Clinical Neurology*, vol. 13, ed. by P. J. Vinken and G. W. Bruyn, pp. 94–110. North Holland, Amsterdam.