We have performed retinal fluorescein angiography and audiometry in 32 familial and 7 sporadic cases of facioscapulohumeral muscular dystrophy. A mild to moderate retinal vasculopathy, consisting of retinal teleangiectasis and microaneursyms, was present in 18 of 37 evaluable angiograms (49%); 5 patients had minimal changes and 14 angiograms (38%) were normal. High frequency hearing loss was found in 25 (64%) out of 39 patients. Retinal changes were absent in 5 of 18 families (6 cases examined), and after correction for age and sex, hearing function was normal in 5 of 19 families (7 cases examined). Age and severity of the myopathy did not have a clear relationship with the retinal vasculopathy or the hearing loss. There were no differences between families in which the myopathy was linked to chromosome 4q35 and families in which linkage could not be proven. Minimal retinal vascular changes and high tone hearing loss can be observed occasionally in the normal population. Therefore, although retinal vasculopathy and hearing loss are part of the clinical picture of FSHD, these signs cannot be accepted as decisive criteria for FSHD in clinically equivocal cases.
Key words: facioscapulohumeral muscular dystrophy • retinal vasculopathy • hearing loss

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ON THE SIGNIFICANCE OF RETINAL VASCULAR DISEASE AND HEARING LOSS IN FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

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Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal-dominant myopathy with a variable age of onset, and a variable rate of progression. The disease starts in the facial and shoulder girdle muscles and has a fairly uniform pattern of further spread of muscle involvement,[16,17] subsequently affecting the abdominal muscles, the foot extensors, and upper arm muscles, followed by the pelvic girdle and lower arm muscles. The gene for FSHD has been located on the tip of the long arm of chromosome 4 in the band 4q35 by linkage analysis.[23,24]

Extramuscular involvement in FSHD has been the subject of debate for many years. A retinal vasculopathy in association with sensorineural deafness and FSHD was originally described as an independent entity[18] (MIM 216350) and later as a special form of FSHD[7,10,15,21,27] until Fitzsimons et al. observed retinal vascular changes by fluorescein angiography in 48 of 64 patients with the common picture of FSHD.[5] Only one of these patients had visual loss, and the retinal vascular disease was visible by fundoscopy in 3 patients only. The vasculopathy seen on fluorescein angiography consisted of irregularities of the vascular wall, teleangiectasis, capillary microaneurysms with retinal edema and exudates, and capillary occlusions. The authors recognized a mild form of the vasculopathy as a simplification of the retinal bed with fewer, longer and wider capillaries than normal, visible in the peripheral retina only. Also, they found retinal

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vascular changes in 3 parents of 4 sporadic cases, suggesting that the retinopathy might serve to detect nonpenetrant gene carriers.

Sensorineural deafness has frequently been observed in association with FSHD,[22] but often unusual features such as a severe muscle disease, an autosomal-recessive pattern of inheritance, or mental retardation have been reported as well, supporting the idea of genetic heterogeneity of FSHD.[7,15,21,27,28] Recently, we demonstrated in a large patient population that high frequency hearing loss is part of the common picture of FSHD.[1]

As the extent and the significance of the retinal vascular changes and the sensorineural hearing loss were debated and the possibility of clinical, and therefore genetic heterogeneity was discussed, we tried to examine patients from a large number of families. After informed consent was obtained, we studied 32 familial and 7 sporadic cases, and 8 healthy parents of 4 sporadic cases.

PATIENTS AND METHODS

Eight healthy parents of 4 sporadic cases, and 39 patients, fulfilling all criteria of FSHD, including EMG and muscle biopsy in at least one patient per pedigree,[17] consented to routine ophthalmological examination, fluorescein angiography, and clinical audiometry. Among the 26 males (mean age 45.2 years) and 13 females (mean age 43.5 years) 32 cases were familial and 7 sporadic. The familial cases came from 19 families (Table 1). In three families (LE, U, VE) with 2 or more affected sibs in one sibship, autosomal-dominant inheritance could not be proven. In two of these families (LE, U) one parent could not be examined; in family VE both parents were healthy and nonpenetrance in one parent or germ-cell mosaicism was assumed. The remaining 16 families showed a clear autosomal-dominant pattern of inheritance. In 12 families, FSHD was linked to chromosome 4 markers[23,24] and associated with specific fragments recognized by p13E-11.[25,26] In seven families, a chromosome 4 association could not be proven. For various reasons, DNA was not available from families N, U, VI, and VE. Family R has been discussed before,[24] and in two other small families (KL and LU) linkage could not be proven, but could not be excluded either (Table 1). In the sporadic cases one to five chromosome 4–associated DNA rearrangements were found.[25,26] DNA was not available from sporadic cases 6 and 7.

Patients were questioned about symptoms of diseases with possible retinal vascular pathology and about hereditary ophthalmological diseases. They all underwent stereoscopic direct and indirect fundoscopy. Black and white photographs and color slides were made to distinguish drusen, exudates, hemorrhages, and pigment spots. If abnormalities were observed, the abnormal eye was photographed first during the fluorescein angiography. In the other cases, the eye to be photographed first was chosen at random. One patient underwent angiography of both eyes separately. In all other patients both eyes were studied in one examination. The routine fluorescein angiography was performed with a 30° angle camera, photographing the early phase of the macula of one eye first, moving to the lateral peripheral retina of the same eye (Fig. 1), and then to the other eye in the same sequence.

All angiograms were reviewed by four experienced ophthalmologists who were familiar with the expected abnormalities. When judged technically sufficient, each angiogram was given a final score based on the most abnormal fundus. The score was labeled "negative" if an angiogram was considered to be without abnormalities; "minimally and equivocally abnormal" if some teleangiectasis and a few hyperfluorescent patches, possibly microaneurysms, were present such as in Figure 4; "mildly abnormal" if central or perifoveal teleangiectasis were present, with a mild coarse pattern of the capillaries and some isolated hemorrhages; and "moderately abnormal" if prominent teleangiecta-

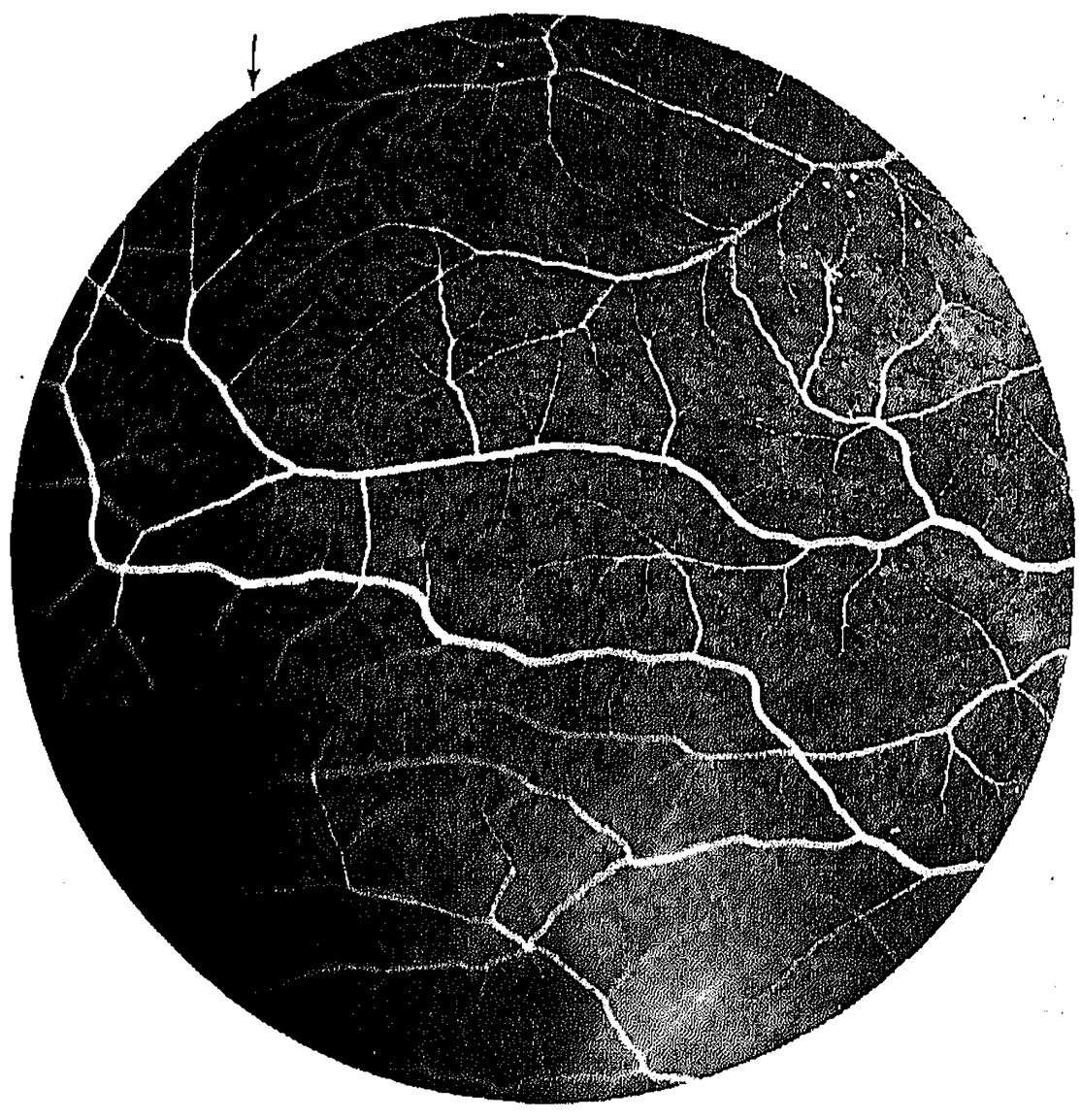

FIGURE 1. Case AV14. Fluorescein angiogram of retinal periphery showing hyperfluorescence of a rather coarse (simplified) capillary bed (*) and some microaneurysms.

sis or beading of the capillaries, capillary occlusions with fields of occlusion, and microaneurysms with isolated exudates were found (Figs. 2 and 3). The designation "severely abnormal" was reserved for the Coats-like picture with large exudates and hemorrhages and capillary occlusions as reported by Fitzsimons et al.[5] Our coding of mild and moderate changes is comparable to the light and mild changes in the series of Caswell et al.[2] A consecutive control series of 130 fluorescein angiograms made for other reasons than a clinical suspicion of retinal vascular disease was scored in a similar fashion.

All patients were asked about noise trauma and the use of ototoxic drugs and they all underwent otoscopic examination. Audiograms were obtained in sound-proof facilities. Tone audiograms were corrected for age and sex using standardized tables.[19]

RESULTS

None of the patients suffered from a disease that could lead to retinal vascular and capillary pathology except patient JIV3 who had late onset diabetes mellitus. His angiogram was judged minimally abnormal (Table 1).

No patient had visual complaints other than refraction-related symptoms. Seven of the first 10 patients who underwent specific corneal examination showed mild corneal lesions, which were attributed to orbicularis oculi weakness. All patients underwent careful fundoscopy which revealed vascular irregularities in 4 patients. Three patients had one or two small exudates, and 2 patients had a small hemorrhage. No patient showed the severe picture reported by Fitzsimons et al.[5]

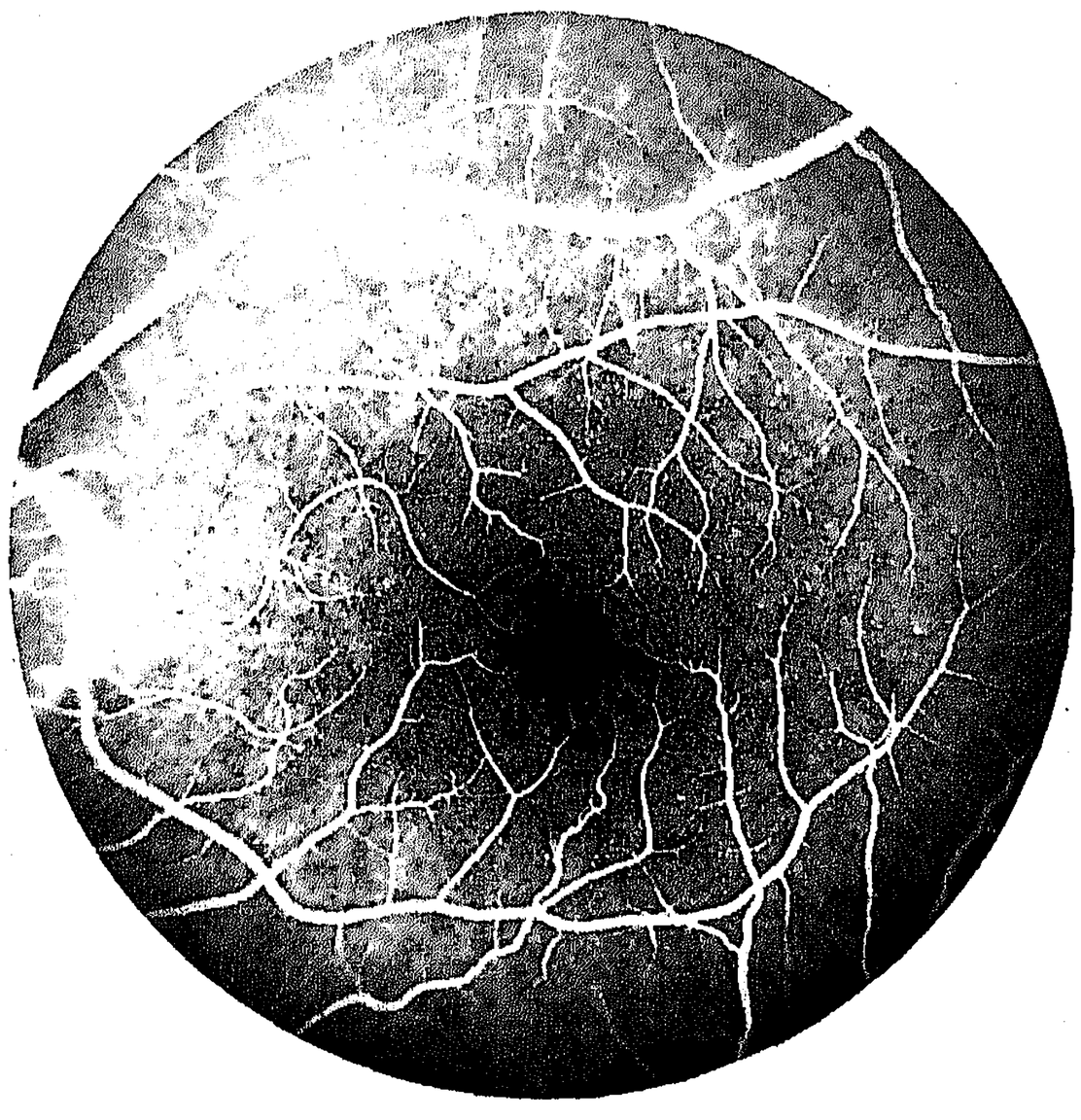

FIGURE 2. Case GIII20. Fluorescein angiogram of the left eye showing perimacular teleangiectasis, microaneurysms, and patchy capillary hyperfluorescence.

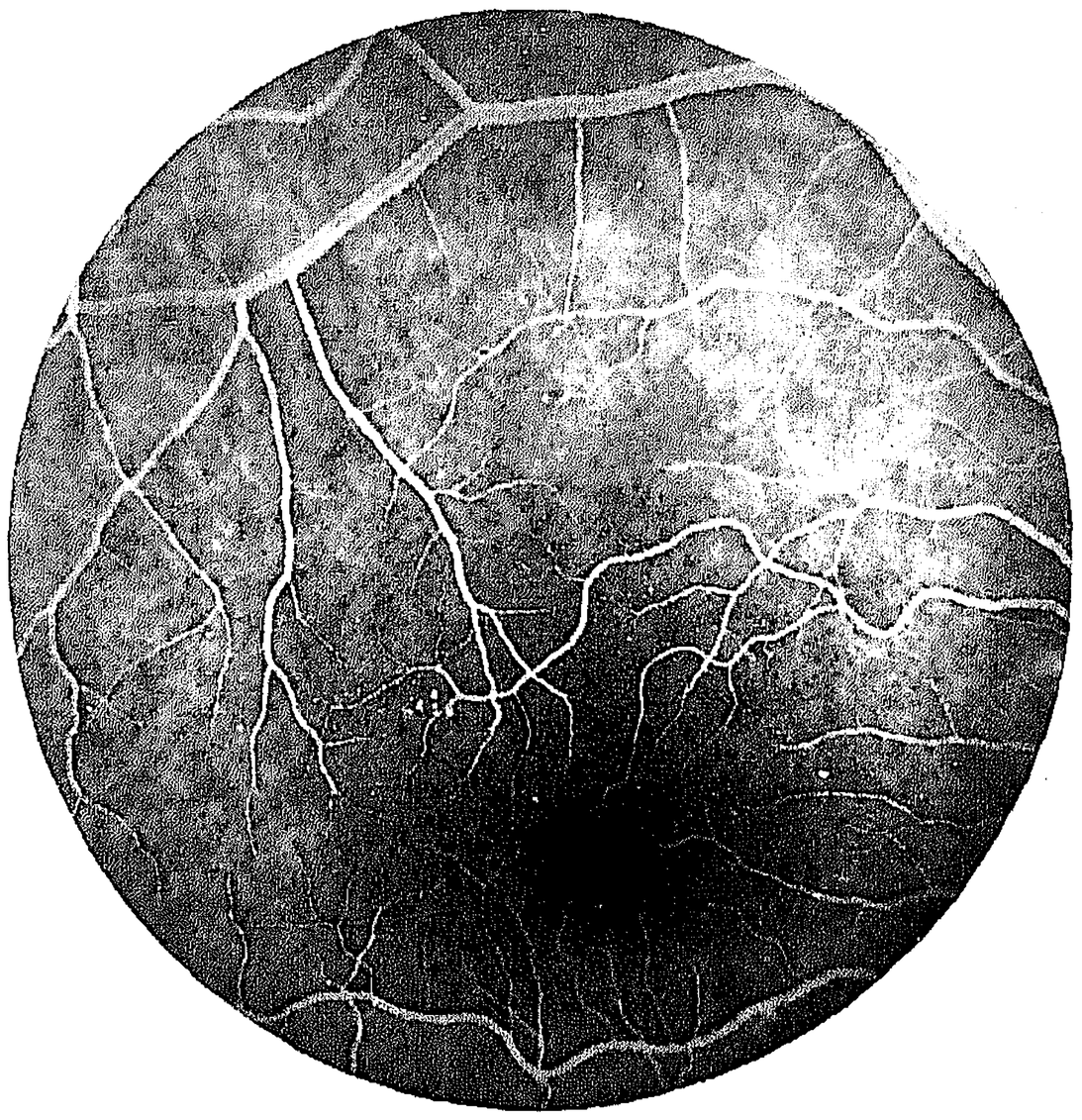

FIGURE 3. Sporadic case 6. Fluorescein angiogram of the right eye showing solitary microaneurysms and groups of aneurysms in the area bordered by the temporal vessels.

From the 32 familial cases, two angiograms (HV16, LEII7) were judged technically insufficient. Therefore, 30 angiograms from 18 families could be scored (Table 2). The five families (C, I, L, R, and U) with normal angiograms contributed six angiograms; six other normal angiograms were observed in sibs from families with abnormal angiograms. A normal angiogram was seen in patient JIV10, while the family was scored equivocally abnormal because of the angiogram in JIV3. Fourteen patients (47%), coming from 10 families (56%), revealed a mildly or moderately abnormal fluorescein angiogram (Figs. 1–4). We did not observe the severe, Coats-like picture. There were differences in the extent of involvement between the two eyes. This might be due to the technical problem of making early photographs of both eyes after a single injection of fluorescein. Vascular changes were observed in the parafoveal and perimacular field in 7 cases, in the periphery in 4 cases, and in both areas in 3 patients. Capillary microaneurysms were present perimacularly in 7 patients, and peripherally in only 1. Six patients had vascular occlusions; only 4 showed small exudates.

Table 1. Retinal vascular pathology and hearing loss in facioscapulohumeral muscular dystrophy.

Patient	Sex	Age	Onset*	Retinal vasculopathy†	Hearing loss‡
Chromosome 4 relation proven					
AV9	F	34	21	−	—
AV10	M	33	15	+	—
AV14	M	40	14	+ +	L
BIII1	M	68	20	+	RL
BIII6	F	53	16	−	RL
BIV4	M	34	24	−	RL
CIII1	M	44	21	−	L
EIV1	M	46	16	±	L
EV1	M	24	14	+	—
GIII17	M	49	19	+ +	—
GIII20	M	40	20	+ +	RL
HV7	M	54	14	+	RL
HV8	M	47	35	+ +	RL
HV16	M	48	8	TI§	L
IV7	M	69	20	−	—
IVI11	F	32	6	−	—
JIV3	M	62	18	±	RL
JIV10	F	61	24	−	R
LIV44	F	53	19	−	RL
VSII5	M	38	35	+	RL
OJII4	M	44	10	±	—
LEII7	F	53	16	TI	RL
Chromosome 4 relation not proven					
NIII10	M	66	20	+	—
NIII12	F	63	6	−	RL
RII6	M	54	16	−	—
UII3	M	43	5	−	RL
KLIII5	F	69	55	+ +	RL
KLIV18	F	32	29	+	RL
VIIII1	M	27	14	+	RL
VEII5	M	43	¶	−	—
VEII7	M	40	19	+	—
LUIII19	F	30	¶	±	—
Sporadic cases of FSHD and 4 parent pairs					
1	F	19	2	+	RL
2	F	31	10	+ +	L
3	M	39	18	±	—
4	F	35	10	−	—
5	M	31	16	−	RL
6	M	62	17	+ +	RL
7	M	31	16	+	L
P1¶	M	46		−	RL
M1	F	46		−	RL
P2	M	58		+	RL
M2	F	57		−	—
P3	M	66		+	RL
M3	F	63		+	L
P4	M	68		+	RL
M4	F	65		+	—

**Onset of symptoms of FSHD by history.*
†Grading of the retinal vasculopathy: −, normal; ±, equivocal; +, mildly abnormal; + +, moderately abnormal.
‡R = right ear deficit; L = left ear deficit.
§Technically insufficient.
‖Denotes an asymptomatic case.
¶P1 father of sporadic case 1.

When chromosome 4–associated FSHD patients were compared with patients in whom chromosome 4 association was not proven, no significant difference in the numbers of abnormal angiograms was observed (Table 2). A similar tendency was present in the sporadic cases. Sporadic cases 1–5 had shown the rearranged DNA fragments,[25,26] while no DNA was available from cases 6 and 7, demonstrating again that the clinical picture is the same in chromosome 4 proven and not-proven FSHD patients.

Both parents from sporadic cases 1–4 underwent fluorescein angiography. In the 4 parents of 2 sporadic patients without an abnormal angiogram, all angiograms were abnormal, while in both parents of another sporadic case both angiograms were judged normal (Table 1). The genetic studies had proven that the parents were not gene carriers and their children were new mutations for FSHD.[26]

Among the 130 control fluorescein angiograms in which a retinal vasculopathy was not suspected, 16 were considered technically insufficient to score vascular changes; 83 (73%) were found to be without abnormalities; 22 (19%) were graded equivocally abnormal; and 9 (8%) were considered mildly abnormal, i.e., vessel wall irregularities but no capillary aneurysms. These figures are difficult to interpret as these angiograms were made because of other ophthalmological pathology. The mean age of the control group (44 years) was similar to that of the FSHD patients. An age-dependent factor relating to the onset of retinal changes in FSHD appears unlikely (Table 3), as in all age groups approximately half of the FSHD patients reveal retinal vascular pathology.

Only patient JIV3 suffered noise trauma at his job; no one could recall having been exposed to ototoxic drugs. Otoscopic examination showed tympanic membrane scarring related to otitis media in 2 cases (BIII1 and NIII12). After corrections for age and sex[19] five families (12 patients) proved to have a normal audiogram (Table 4). Twenty familial FSHD patients (62.5%) proved to have an abnormal audiogram, which in a similar rate of occurrence could be observed in the sporadic cases (Table 1). Of all 25 (64%) abnormal audiograms, 2 patients (EIV1 and LEII7) showed a low tone deficit only, 2 patients (UII3 and HV8) had a low and high tone deficit, and 3 patients (BIII1, BIII6, and sporadic case 2) had low and midtone deficit in addition to a high tone hearing loss. Of all patients, 7 had an unilateral hearing loss which was in the left ear in 6. The high tone hearing loss was either a dip at 4000–6000 Hz or a steady decline after 2000 Hz.[1] The hearing loss in the 8 parents of the sporadic cases revealed a mild high tone hearing loss in all but 2 parents examined. Parent P3 had a history of repeated noise trauma.

Table 2. Retinal fluorescein angiography in 30 familial FSHD patients.

	Chromosome 4 relation proven			Chromosome 4 relation not proven			
	Abnormal	±	Normal	Abnormal	±	Normal	Total
Males	9	3	3	3	0	3	21
Females	0	0	5	2	1	1	9
Patients	9	3	8	5	1	4	30
Families	6	2	3	4	1	2	18

DISCUSSION

Retinal vascular changes and sensorineural deafness in association with a myopathy was originally described by Small and interpreted as an independent genetic entity (MIM 216350).[27] Subsequent observations recognized the myopathy as FSHD. The retinal vascular changes were interpreted initially as bilateral Coats' disease, but Coats' disease is defined as a usually unilateral, nonhereditary exudative vascular retinopathy.[13] Reports of extreme tortuositas and a retinal vascular disease without marked exudates in FSHD patients led to the noncommittal term "retinal vascular abnormalities."[21] Different modes of inheritance, i.e., autosomal-recessive,[18,28] autosomal-dominant,[7,21] and sporadic[15,27] cases have been suggested, and various associated findings such as mental retardation,[15,18] extensive muscle infiltrates,[27] or respiratory failure,[28] have been described that contributed to the speculation about genetic heterogeneity of FSHD. Fitzsimons et al. demonstrated retinal vascular changes in 75% of their autosomal-dominant FSHD patients.[5] The discussion on the significance of the retinal changes were complicated by the finding of a retinal vasculopathy in 8 of 30 first degree relatives without signs of muscle involvement. Two sibs were obligatory gene carriers according to the pedigree; 3 sibs were young, and it was suggested that they might develop muscle signs later in life; and 3 were one of the parents of sporadic cases. These results led to the suggestion that the retinopathy could be a sensitive way to detect a gene carrier.[5]

Our results demonstrating retinal vascular pathology in 18 of 37 FSHD patients (49%), in whom

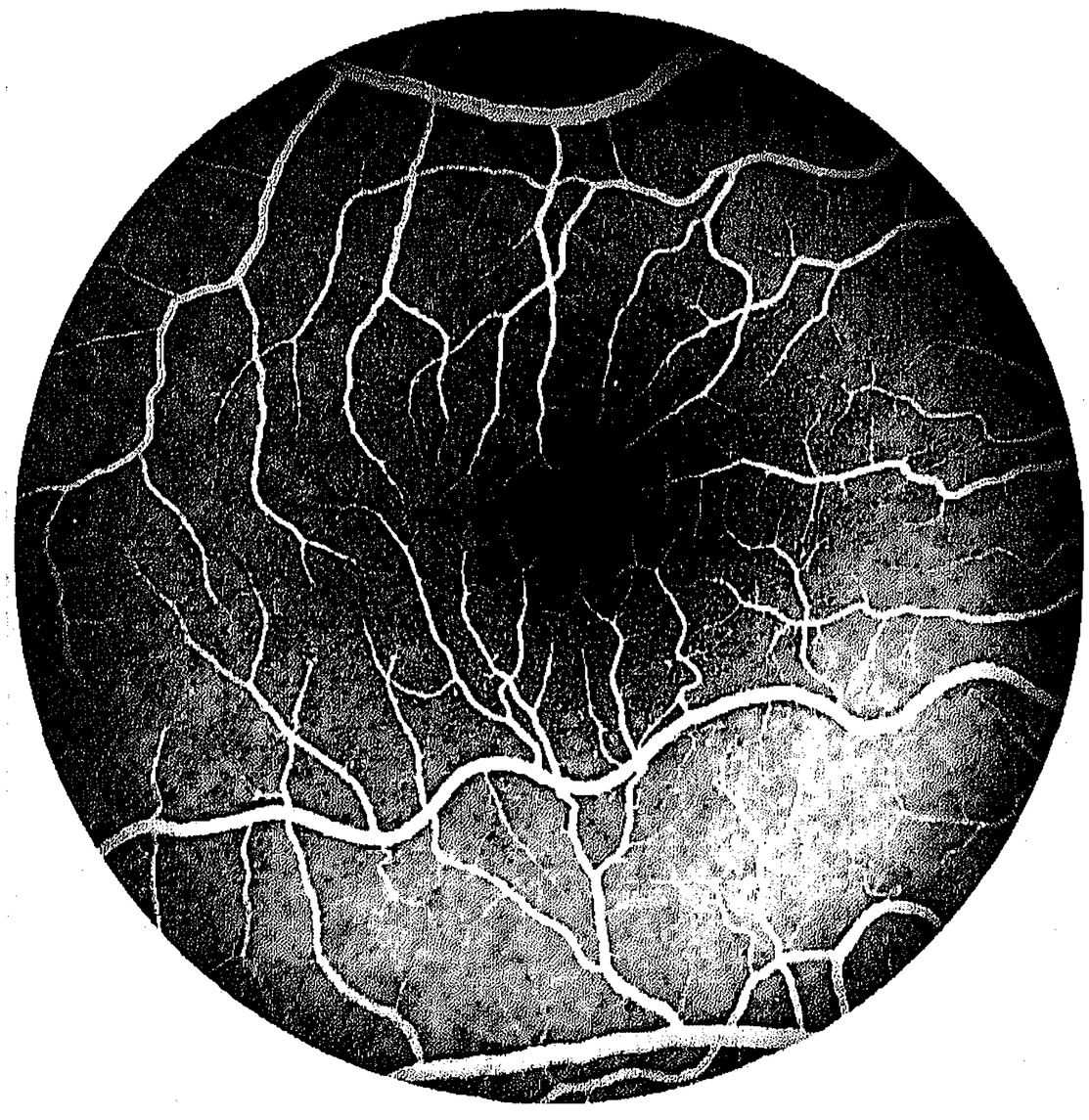

FIGURE 4. Sporadic case 2. Fluorescein angiogram showing the posterior pole with a diffusely hyperfluorescent capillary bed.

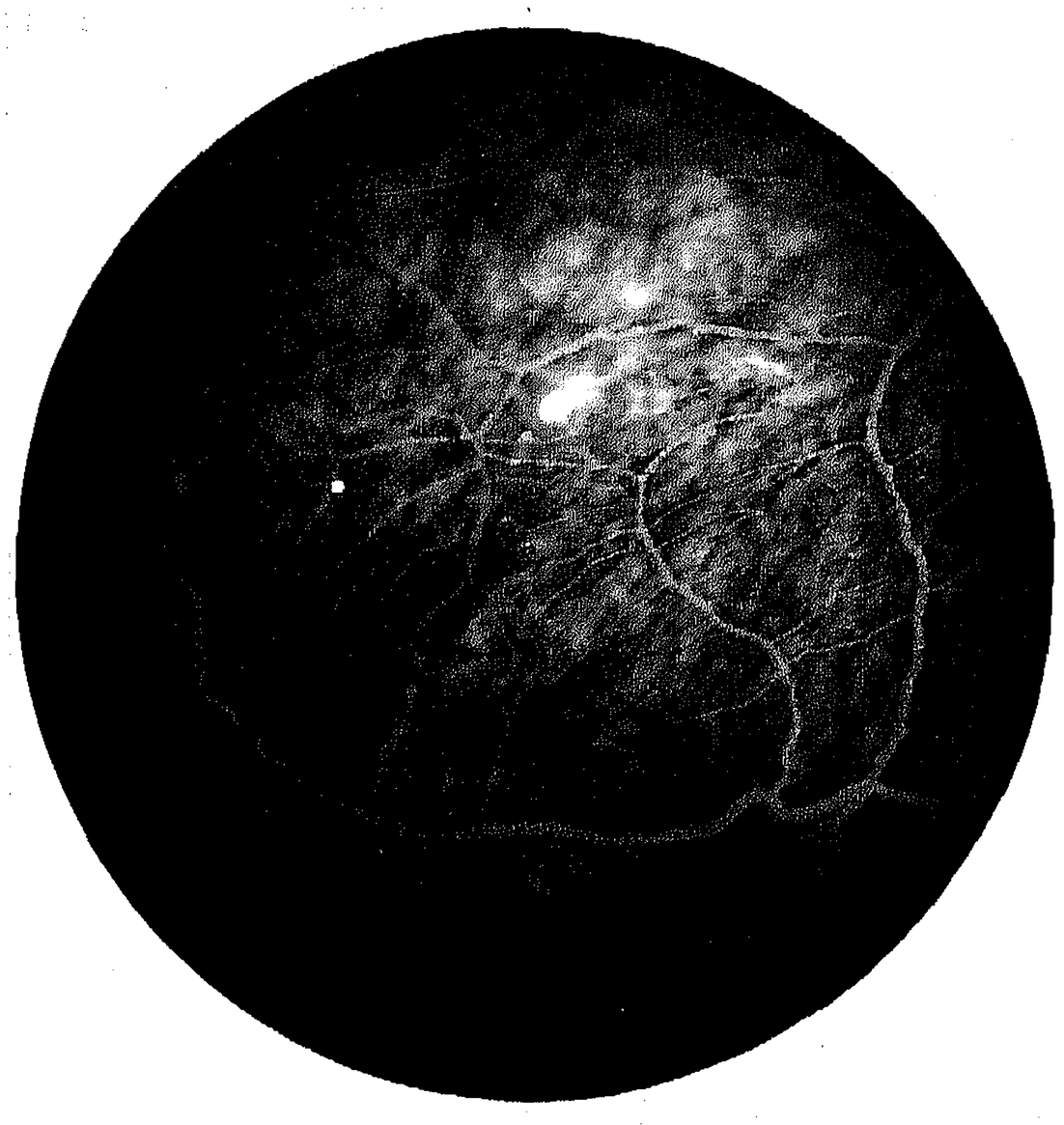

FIGURE 5. Sporadic case 2. Fluorescein angiogram showing abnormal vascular structures in the temporal inferior periphery of the right eye and small and larger microaneurysms with capillary occlusion. Note the irregular caliber of the large retinal vessels.

Table 3. Retinal fluorescein angiography in 37 FSHD patients according to age.

Years	Abnormal	±	Normal	Total
10–19	1	0	0	1
20–29	2	0	0	2
30–39	5	2	5	12
40–49	5	2	3	10
50–59	1	0	3	4
60–69	4	1	3	8
	18	5	14	37

we could evaluate a retinal angiogram (Table 3), support the observations of Fitzsimons et al.[5] As the vascular pathology can be observed by fluorescein angiography only in the majority of patients, and as the extent of the vascular changes can vary considerably between the two eyes while the pathology often can be seen in the early phase of the fluorescein passage only, it is possible that the observed frequency of abnormalities is lower than the true presence of vascular changes.

We did not observe the severe abnormalities as reported by Fitzsimons et al.[5] Our overall impression was the general tendency of mild abnormalities in our patients, compared to cases published.[5,13] Also, we could not substantiate the retinal vasculopathy as a reliable means to detect nonpenetrant gene carriers. The observation of retinal vascular changes in a population not studied because of a suspicion of vasculopathy, and in the healthy parents of genetically proven FSHD mutations, casts doubts on the specificity of the retinal changes in FSHD. Yet its frequency in FSHD suggests it represents a specific entity that can be separated from familial retinal vasculopathy with tortuositas (MIM 180,000)[8] by the absence of massive retinal hemorrhages and the presence of the myopathy. In idiopathic juxtafoveolar retinal teleangiectasis the vasculopathy resembles the situation in FSHD, but the latter is milder and lacks visual loss.[6] SLE[12] and diabetes mellitus might resemble the findings in FSHD; the additional clinical and laboratory features should point to the correct diagnosis. The retinal changes in the family reported by Storimans et al.[20] resemble those of FSHD. We ruled out linkage with chromosome 4q markers in that family (data not shown). Other syndromes with retinal and cerebral vascular lesions are so distinct, because of the CNS involvement, that they do not resemble FSHD.[3,4,9,11,14]

The same reasoning for the retinal changes applies to the sensorineural hearing loss. Brouwer et al.[1] have already demonstrated, by comparing hearing function in affected and nonaffected sibs, that high-tone hearing loss is part of FSHD. Eighteen of the present patients (family A–J) took part in that study. Not all patients showed a hearing deficit after correction for age and sex, and when present, there was no correlation between the severity of the disease and the severity of the hearing loss. Also there were no systemic differences between the families.[1] Our results support the thesis that there is no clinical difference between the chromosome 4–related FSHD cases and those in whom chromosome 4 linkage could not be proven. The presence of hearing loss is not an argument for genetic heterogeneity. In addition, the observations in our sporadic cases support the genetic arguments that these cases constitute new mutations of the FSHD gene. However, our present results cannot decide between a contiguous gene syndrome or a pleiotropic effect of one gene, as we did not study many large families in their entirety. Even then, conclusions might not be definitive since the audiologic changes could have many causes, and the minimal findings of retinal vasculopathy might create an interpretation problem. The final answer will depend on the demonstration of the molecular defect in FSHD.

The ophthalmologic and audiologic results in the sporadic cases suggest that they are similar to the autosomal-dominant cases. Based on the neuromuscular findings these sporadic cases represent new mutations of FSHD. These results are supported by the genetic studies, which show DNA rearrangements, i.e., smaller fragments, in most of the sporadic FSHD patients that cannot be found in the healthy parents.[25,26] The retinal and audiologic changes that were found in the parents of the sporadic cases are difficult to explain in genetic terms, since the genetic studies strongly suggest that the parents are not nonpenetrant gene carriers, and the sporadic cases are truly new mutations. These findings underline the relative nature of the audiologic and retinal changes that have

Table 4. Audiometry in 32 familial FSHD patients.

	Chromosome 4 relation proven		Chromosome 4 relation not proven		
	Abnormal	Normal	Abnormal	Normal	Total
Males	11	5	2	4	22
Females	4	2	3	1	10
Patients	15	7	5	5	32
Families	10	2	4	3	19

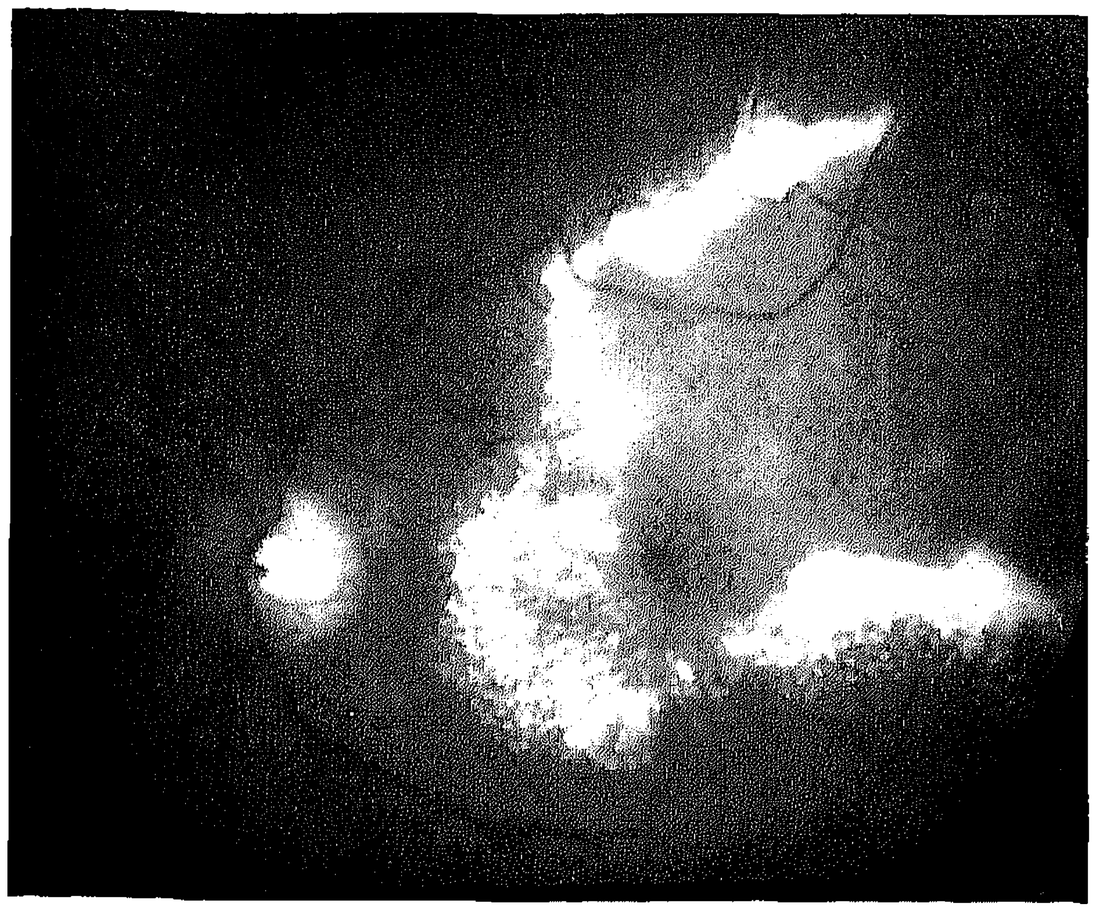

FIGURE 6. Autosomal-dominant case 3 (see Addendum). Large retinal exudate.

been studied, and support the general conclusion that these changes cannot serve as diagnostic criteria in questionable cases of FSHD.

ADDENDUM

After this study was completed, a survey of FSHD patients in The Netherlands revealed 3 cases of Coats' disease among 256 patients studied (1.7%). Assuming a bias in reporting such cases, the true prevalence of a severe retinal vasculopathy in FSHD is probably lower as it is assumed that 500 symptomatic FSHD patients are alive in The Netherlands. The cases we know of include a mentally retarded 32-year-old male (IQ 70–80) with bilateral severe hearing loss, end-stage Coats disease in the blind left eye and vascular tortuosity and retinal hemorrhages in the right eye.

The second patient was an 11-year-old mentally retarded boy (IQ 60–80) with an early onset sporadic FSH myopathy, bilateral high tone perception deafness, and a bilateral Coats syndrome, which had left him a vision of 0.5 in his right eye and no vision in his left eye. DNA studies had not been performed. The third patient was a 36-year-old female with infantile onset of facial weakness, shoulder girdle and pelvic girdle weakness at the age of 8, and wheelchair dependency since the age 15. Her father had suffered from FSHD but no other family members were known to be affected. At the age of 35 she developed in a couple of hours a poor vision of her left eye. Fundoscopy revealed a large exudate (Fig. 6). Fluorescein angiography was not performed at that time.

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