Eye (2009) 23, 966–974

www.nature.com/eye

LABORATORY STUDY

Pupil abnormalities in 131 cases of genetically defined inherited peripheral neuropathy

H Houlden, MM Reilly and S Smith

Abstract

Aim **To investigate and correlate the frequency and types of pupil abnormalities that are associated with hereditary peripheral neuropathy in a large cohort of patients prospectively examined.**

Methods **A prospective study between 1998 and 2007. Patients were enrolled and examined after being seen in the neurology clinic. Data were collected on demographics, family and medical history. Patients had eye and pupillography testing carried out as well as being neurologically and genetically investigated.**

Results **A consecutive series of 131 cases of inherited peripheral neuropathy were seen and categorized into five groups: familial amyloid polyneuropathy (FAP), Charcot Marie Tooth disease (CMT), hereditary neuropathywith liability to pressure palsies (HNPP), Refsum's disease, and hereditary sensory and autonomic neuropathy. A number of unreported mutations were identified in these patient groups. Pupil abnormalities were common in the Refsum's group, with frequent abnormally small pupils. The inherited neuropathies commonly associated with autonomic abnormalities were frequently found to have developed bilateral Horner's syndrome, which was particularly prevalent in our FAP series. Abnormalities were rare in HNPP and CMT type 1, but CMT type 2 showed frequent and varied pupil defects. The results describe the pupil abnormalities that were frequently associated with the particular group of inherited neuropathy patients, but we could not predict the genetic defect or the neuropathy severity.**

Conclusions **This is the first study of the pupil abnormalities found in the inherited neuropathies and provides an overview of the frequency and type of defects seen in a large number of cases. This series along with the detailed tables will act as an important diagnostic aid in assessing these patients.**

Eye (2009) **23,** 966–974; doi:10.1038/eye.2008.221; published online 18 July 2008

Keywords: pupil; neuropathy; genetics; inheritance

Departments of Molecular Neurosciences, Neuro-ophthalmology and MRC Centre for Neuromuscular diseases, The National Hospital for Neurology and Neurosurgery and The Institute of Neurology, Queen Square, London, UK

Correspondence:
H Houlden,
Department of Molecular Neuroscience,
The National Hospital for Neurology and Neurosurgery, Queen Square,
London WC1N 3BG, UK
Tel: +044 0207 837 3611;
Fax: +044 0207 278 5616.
E-mail: h.houlden@ion.ucl.ac.uk

Received: 30 April 2008
Accepted in revised form: 14 June 2008
Published online: 18 July 2008

There are no conflicts of interest and this work has not been previously presented or published

Professor Smith died in December 2007

Introduction

Inherited neuropathies are common disorders with a prevalence of at least 1 in 2500 individuals.[1] The classification is based on clinical features and electrophysiology, but over the last few years, genetic testing has shown that even clinically identical inherited neuropathies can be caused by different genetic defects.[2–8] Pupil abnormalities are an important aspect of the clinical characterization of patients with inherited neuropathy, but they have been investigated only in isolated cases or small groups.[9] Please refer to the Supplementary text, which has an extensive review of the literature on pupil abnormalities, as only brief background information is given here.

Familial amyloid polyneuropathy (FAP) is an inherited neuropathy with autonomic and systemic manifestations.[10] In FAP, there is deposition of amyloid material within the autonomic nerve supply of the ocular tissues, predominantly the vitreous body, conjunctivae, and ciliary ganglia,[11] with the development of scalloped pupils.[12,13] The pupil abnormalities in FAP have also been identified in immunoglobulin light-chain-associated amyloidosis,[14] but only a small number of the commonest Transthyretin FAP mutation types have been investigated.[14–16] Abnormal ocular signs are also an important feature of Refsum's

disease as in Refsum's original report[17] where the pupils were miotic and responded poorly to light, better to near, and dilated poorly in response to homatropine eyedrops. Similar observations have been made by subsequent authors,[18] but only in single cases or small series. The neurological phenotype of hereditary sensory and autonomic neuropathy (HSAN) is similar to FAP, but there have been no cases or families reported examined in detail.[19]

In Charcot Marie Tooth disease (CMT), pupil abnormalities have been reported over the years but mainly in single families,[9] and most cases were diagnosed with the clinically severe form of CMT called Déjérine–Sottas syndrome. Recently, pupil abnormalities have been shown to be particularly prevalent in certain myelin protein zero (*MPZ*) gene mutations,[20,21] and sluggish pupillary responses to light and near have been reported in a Gypsy family with HMSN-Lom.[22] No reports have analysed the pupils in hereditary neuropathy with liability to pressure palsies (HNPP).

In this study, we have analysed the genetic aetiology and the pupil abnormalities in a prospective series of 131 cases and cases presenting between 1998 and 2007 with inherited neuropathy. The patients seen formed five broad groups of inherited neuropathy: FAP, CMT, HNPP, HSAN, and Refsum's disease.

Materials and methods

Patients

Ethics approval was obtained from the joint medical and ethics committee at The National Hospital for Neurology and Neurosurgery to perform these clinical and genetic studies on hereditary neuropathy. Cases were ascertained through either the genetic peripheral nerve clinic run by one of the authors (MMR), the neurogenetics clinic (HH) (NHNN), and those patients with characterized neuropathies referred for slit lamp microscopy and pupillography. In addition to neurological examination, all patients were assessed for autonomic features in their history and cardiac examination and lying and standing blood pressure calculations were carried out. One hundred and thirty one patients (57 male/74 female patients, aged 7–85 years) were recruited to the study. In the patients studied, the ocular history was reviewed to exclude patients with a blind eye, trauma, iritis, and conditions that could also affect pupil size and function. The medication history was also reviewed to exclude patients on narcotics, anticholinergics, pilocarpine eyedrops, and other drugs that could affect the pupils. The clinical diagnoses, sex distribution, and age range are given in Table 1.

Genetic diagnoses

DNA was extracted from blood samples obtained with informed consent from patients. DNA analysis was carried out in 126 patients; in 5 patients analysis could not be completed. The chromosome 17 duplication and deletion analysis and genetic sequencing of other genes has been described previously, but primers and methods are available on request[23] (http://www.molgen.ua.ac.be/CMT).

Pupillography

Pupil diameters and their responses to light and accommodation (near) were recorded with a Whittaker/Applied Science Laboratories infrared television pupillometer as described previously.[24] Bilateral recordings were made wherever possible and darkness anisocoria and right–left diameter differences recorded. For clarity and statistical analysis, the remaining measurements for only one eye are presented (right if available) per patient. Reduced pupil diameters in darkness and bilateral Horner's syndrome were taken as indicators of sympathetic dysfunction, whereas reduced light reflexes and/or mydriasis in the light, bilateral pupillotonia, and light–near dissociation as indicators of parasympathetic dysfunction.

Statistics

All measurements were compared with those obtained under identical conditions in 315 healthy subjects (172 male/143 female subjects) aged 16–82 years as described and reported previously.[24]

All patients were subjected to multiple pupil function tests, seven of which define quantitative abnormality as a value lying outside one 97.5% confidence interval. Within this scenario, in the assessment of individual patients, single quantitative abnormalities have a probability value of 0.150 and they have been ignored. Two abnormalities with a value $P = 0.012$ and single abnormalities lying outside one 99.5% confidence interval ($P = 0.034$) have been included. Bilateral tonic pupils and bilateral Horner's syndrome do not occur in healthy subjects; such abnormalities have been included.

Results

The clinical diagnosis and the pupil abnormalities in the 131 patients are summarized in Table 1. The genetic defects identified along with the individual patient findings are given in detail in Tables 2 and 3. Table 4 shows a comparison of pupil abnormalities in the different groups. Refsum's disease was diagnosed in 11

Table 1 Clinical diagnoses and pupil abnormalities of patients studied

Clinical diagnosis	N	*M/F*	*Age range*	*Pupil abnormalities*				*Total abnormal*	*Total normal*
				Bilateral Horner	*Unilateral Horner*	*Bilateral tonic*	*Other*		
FAP	16	8/8	31–69	8	0	2	0	10	6
CMT all types	69	25/34	10–85	3	0	6	3	12	57
CMT 1a (*PMP22* duplication or mutation)	20	7/13	14–60	0	0	1	0	1	19
CMT 1b (*MPZ* mutations)	2	1/1	10–19	0	0	0	1	1	1
CMT 2 (one *MPZ*, one *MFN2* mutation)	19	7/12	18–85	3	0	3	2	8	11
DSS/CHN (one *PMP22* mutation)	2	1/1	33–47	0	0	0	0	0	2
CMT 4c (*KIAA1985* mutation)	1	0/1	56	0	0	1	0	1	0
HMSN-5	5	3/2	24–71	0	0	0	0	0	5
HMSN-6 (one *GAN* mutation)	2	1/1	18–22	0	0	0	0	0	2
CMT X (all have connexin 32 mutations)	18	5/13	22–70	0	0	1	0	1	17
HNPP	6	3/3	18–52	0	0	0	0	0	6
Refsum's disease	11	7/4	25–65	0	0	0	10	10	1
HSAN all types	29	14/15	7–74	4	2	4	3	13	16
HSAN-I (4 *SPTLC1* C133W mutations)	15	5/10	20–74	2	1	0	0	3	12
HSAN-II	8	4/4	7–45	0	1	2	1	4	4
HSAN-III	2	1/1	17–18	1	0	0	1	2	0
HSAN-IV (two *TRKA* mutations)	2	2/0	17–18	1	0	0	1	2	0
HSAN-V (two *TRKA* mutations)	2	2/0	11–42	0	0	2	0	2	0
All patients	131	57/74	7–85	15	2	12	16	45	86

CHN, congenital hypomyelinating neuropathy; CMT, Charcot Marie Tooth disease; CMT X, X-linked CMT due to Connexin 32 defects; DSS, Dejerine–Sottas syndrome; F, female; FAP, familial amyloid polyneuropathy; *GAN*, giant axonal neuropathy; HNPP, hereditary neuropathy with pressure palsies; HMSN, hereditary motor and sensory neuropathy; HSAN, hereditary sensory and motor neuropathy; *KIAA1985*, brain-expressed protein 1985; *MPZ*, myelin protein zero; M, male; *N*, number; *PMP22*, peripheral myelin protein 22; *PMP22* duplication, chromosome 17 duplication; *SPTLC1*, serine long-chain base subunit-1; *TRKA*, tyrosine kinase receptor A gene.

patients, based on raised phytanic acid. In the remaining 120 cases, 84 had a genetic diagnosis (70%). Overall, at least one significant pupil abnormality was found in 45/131 (34.4%) patients. We discuss only selected results as a great deal of information is given in the tables.

Familial amyloid polyneuropathy

In the FAP group, we have found a high prevalence of pupil abnormality in the 16 patients studied (Tables 1–3). Two had bilateral tonic pupils with anisocoria, reduced light reflexes, but normal near responses. Of the other 14 patients, 8 had bilateral Horner's syndrome with redilatation lag (Figure 1). The remaining six had normal pupils. Out of the 10 patients with pupil abnormality, 8 had signs of autonomic dysfunction elsewhere, mainly blood pressure and cardiac abnormalities (Tables 2 and 3).

Charcot Marie Tooth disease

In the CMT group, 12 of the 69 patients had abnormal pupils (Tables 2 and 3). Of the 12 pupil abnormalities, 8 were in the CMT2 group. The difference in occurrence of abnormality between clinical types is statistically significant ($\chi^2 = 20.09$, d.f. $= 7$, $P = 0.005$), with 42.1% of the CMT 2 patients having abnormal pupils. Three patients, all clinically CMT 2 (one in a recessive family), had bilateral Horner's syndrome. All were negative for Chromosome 17 duplication, two were negative for MPZ and Connexin mutations. In one patient, a mutation in the Mitofusin 2 gene was identified, case 13 (*MFN2* Arg94Gln). This young female patient had a mild axonal neuropathy along with marked physiological anisocoria, outside the normal range ($P < 0.01$), and the smaller pupil was abnormally small for her age. Unfortunately, no further *MFN2*

Table 2 Inherited neuropathy patients with abnormal pupils

No.	*Sex*	*Age*	*Clinical diagnosis*	*Genetic diagnosis*	*Pupil abnormality*		
					Bilateral tonic	*Bilateral Horner*	*Other*
1	F	32	Amyloidosis	*TTR* Pro52	1		
2	F	52	Amyloidosis	*TTR* Pro12	1		
3	M	69	Amyloidosis	*TTR* Ala60		1	
4	F	44	Amyloidosis	*TTR* Ala53		1	
5	F	69	Amyloidosis	*TTR* Ala60		1	
6	M	64	Amyloidosis	*TTR* Ala60		1	
7	M	47	Amyloidosis	*TTR* Lys47		1	
8	M	31	Amyloidosis	*TTR* Val33		1	
9	M	41	Amyloidosis	*TTR* Val47		1	
10	M	41	Amyloidosis	*TTR* Val48		1	
11	F	46	CMT 1a	Chromosome 17 duplication	1		
12	F	19	CMT 1b	*P0* mutation Gly137Ser			1
13	F	21	CMT 2	*Mitofusin* 2 Arg94Gln			1
14	F	75	CMT 2	Neg—Dup,*MPZ*,*PMP22*,*Cx32*, *MFN2*		1	
15	M	69	CMT 2	N/D	1		
16	M	24	CMT 2	Neg—Dup,*MPZ*,*PMP22*,*Cx32*, *MFN2*	1		
17	M	85	CMT 2	Neg—Dup		1	
18	M	31	CMT 2	Neg—Dup,*MPZ*,*PMP22*,*Cx32*, *MFN2*			1
19	F	34	CMT 2	Neg—Dup,*MPZ*,*PMP22*,*Cx32*, *MFN2*	1		
20	F	30	CMT 2 recessive	Neg—Dup,*MPZ*,*PMP22*,*Cx32*, *MFN2*		1	
21	F	56	CMT 4c	Compound heterozygous for *KIAA1985*	1		
22	F	70	CMT X	*Connexin 32* Ala 39 Val	1		
23	F	61	Refsum	Raised phytanic acid levels			1
24	F	30	Refsum	Raised phytanic acid levels			1
25	M	39	Refsum	Raised phytanic acid levels			1
26	M	31	Refsum	Raised phytanic acid levels			1
27	M	32	Refsum	Raised phytanic acid levels			1
28	M	27	Refsum	Raised phytanic acid levels			1
29	M	31	Refsum	Raised phytanic acid levels			1
30	M	35	Refsum	Raised phytanic acid levels			1
31	F	25	Refsum	Raised phytanic acid levels			1
32	F	65	Refsum	Raised phytanic acid levels			1
33	F	52	HSAN-I	*SPTLC1* C133W		1	
34	M	62	HSAN-I	*SPTLC1* C133W		1	
35	F	60	HSAN-I	*SPTLC1* C133W			1
36	M	37	HSAN-II	N/A	1		
37	M	25	HSAN-II	N/A	1		
38	F	36	HSAN-II	N/A			1
39	F	7	HSAN-II	N/A			1
40	F	17	HSAN-III	*SPTLC1*, *IKAP* negative		1	
41	M	25	HSAN-III	*SPTLC1* negative			1
42	M	18	HSAN-IV	*TRKA* Exon 15 del			1
43	M	17	HSAN-IV	*TRKA* Exon 15 del		1	
44	M	11	HSAN-V	*TRKA* Tyr 359 Cys homozygous	1		
45	M	42	HSAN-V	*TRKA* Tyr 359 Cys heterozygous	1		

CHN, congenital childhood neuropathy; CMT, Charcot Marie Tooth disease; CMT X, CMT due to Connexin 32 defects; *Cx32*, Connexin 32; DSS, Dejerine–Sottas syndrome; F, female; FAP, familial amyloid polyneuropathy; HSAN, hereditary sensory and motor neuropathy; M, male; *MPZ*, myelin protein zero; *MFN2*, Mitofusin 2; N/D, not done; neg, negative; *SPTLC1*, serine long-chain base subunit-1; *TRKA*, tyrosine kinase receptor A gene; *TTR*, transthyretin gene.

mutations have been identified to compare the pupil abnormalities. Fifty-seven patients had normal pupils. All six HNPP patients studied had normal pupils.

Refsum's disease

In Refsum's disease, 9 patients out of 11 had abnormally small pupils, 7 being below the 0.5% confidence limit

Table 3 Patients with inherited neuropathy and normal pupils

Number	*Sex*	*Age*	*Clinical diagnosis*	*Genetic diagnosis*
46	F	51	Amyloidosis	*TTR* Met30
47	F	40	Amyloidosis	*TTR* Met30
48	F	49	Amyloidosis	*TTR* Ala60
49	F	49	Amyloidosis	*Apolipoprotein AI*, deletion70–72
50	M	32	Amyloidosis	*TTR* Gly54
51	M	51	Amyloidosis	*TTR* Tyr77
52–68	10F, 7M	14–60	CMT 1a	Chromosome 17 duplication cases
69	F	26	CMT 1a	Chromosome 17 small duplication
70	F	59	CMT 1a	Chromosome 17 small duplication
71–78	6F, 2M	18–63	CMT 2	Neg—Dup,*MPZ*,*PMP22*,*Cx32*, *MFN2*
79	M	10	CMT 1b	*P0* mutation Asp128Gly
80	F	58	CMT 2	*P0* mutation Arg36Trp
81	M	13	CMT 2 recessive	Neg—Dup,*MPZ*,*PMP22*,*Cx32*, *MFN2*
82	F	28	CMT 2 recessive	Neg—Dup,*MPZ*, *PMP22*, *Cx32*, *MFN2*
83	F	47	DSS/CHN	*PMP22*, Ser71Iie
84	M	33	DSS/CHN	*PMP22*, *MPZ*, Ch17 dup neg
85–89	2, 3MF	24–71	HMSN-V	Neg—Dup,*MPZ*, *PMP22*, *Cx32*, *MFN2*
90	F	18	HMSN-VI	Neg—Dup,*MPZ*,*PMP22*,*Cx32*, *MFN2*
91	M	22	Giant axonal neuropathy	Homozygous mutation in *Gigaxonin* gene
92	M	54	CMT X	*Connexin 32* Val 95 Met
93	F	33	CMT X	*Connexin 32* Arg 22 Gln
94	F	60	CMT X	*Connexin 32* Gly 21 Asp
95	F	58	CMT X	*Connexin 32* Arg 142 Trp
96	M	28	CMT X	*Connexin 32* Arg 142 Trp
97	F	47	CMT X	*Connexin 32* Arg 142 Trp
98	F	65	CMT X	*Connexin 32* Arg 220 Stop
99	F	48	CMT X	*Connexin 32* Ala 39 Gly
100	F	30	CMT X	*Connexin 32* Pro 70 Ser
101	F	46	CMT X	*Connexin 32* Ala 39 Val
102	M	39	CMT X	*Connexin 32* Ala 39 Val
103	M	22	CMT 1a	Chromosome 17 duplication
104	F	49	CMT 1a	Chromosome 17 duplication
105	M	56	CMT X	*Connexin 32* Phe 153 Ser
106	F	31	CMT X	*Connexin 32* Phe 153 Ser
107	F	27	CMT X	*Connexin 32* Phe 153 Ser
108	F	32	CMT X	*Connexin 32* Cys 60 Phe
109–114	3F, 3M	19–52	HNPP	Ch17 deletion cases
115	M	45	Refsum	Raised Phytanic acid levels
116	F	46	HSAN-I	Negative for HSAN-I gene
117	F	38	HSAN-I	Negative for HSAN-I gene
118	F	74	HSAN-I + marfan	Negative for HSAN-I gene
119–127	5F, 4M	20–69	HSAN-I	*SPTLC1* C133W cases
128	F	15	HSAN-II	*SPTLC1* negative
129	F	16	HSAN-II	N/A
130	M	15	HSAN-II	N/A
131	M	45	HSAN-II	N/A

CHN, congenital childhood neuropathy; CMT, Charcot Marie Tooth disease; ; CMT X, CMT due to Connexin 32 defects; *Cx32*, Connexin 32; DSS, Dejerine–Sottas syndrome; F, female; FAP, familial amyloid polyneuropathy; *GAN*, giant axonal neuropathy; HSAN, hereditary sensory and motor neuropathy; M, male; *MFN2*, Mitofusin 2; *MPZ*, myelin protein zero; N/D, not done; neg, negative; *SPTLC1*, serine long-chain base subunit-1; *TRKA*, tyrosine kinase receptor A gene; *TTR*, transthyretin gene.

(Figure 1). A total of 3/7 showed reduced light reflexes, 2/6 showed exaggerated near responses, and 3/6 showed light–near dissociation. None of the reflexes, although abnormal, was truly tonic. One patient had normal pupils. Tropicamide 0.5%, followed 30 min later by phenylephrine 10% eye drops, was instilled into one eye of 10 of these 11 patients. The final diameter reached was 6.00 ± 0.64 mm (range 2.8–8.4 mm).

Hereditary sensory and autonomic neuropathy

The HSAN patients consisted of 13 (44.8%) out of 29 with abnormal pupils. In patients with the *SPTLC1* C133W mutation, three out of four had abnormal pupils, and in the non-HSAN-I cases, there was a much higher incidence of pupil abnormalities. Both patients with HSAN-IV had abnormal pupils; both of these patients

Table 4 Pupil differences between inherited neuropathy diagnostic groups

Miosis in dark	***Groups***					
	Normal	*HNPP*	*FAP*	*CMT*	*HSAN*	*Refsum*
N	11/315	0/6	1/16	5/69	7/29	9/11
%	3.5	0	6.2	7.2	24.1	81.8
Mydriasis in light	*Normal*	*FAP*	*HNPP*	*Refsum*	*CMT*	*HSAN*
N	8/176	0/14	0/6	0/2	5/67	4/25
%	4.6	0	0	0	7.5	16.0
Dark anisocoria	*Normal*	*Refsum*	*HNPP*	*CMT*	*HSAN*	*FAP*
N	5/168	0/7	0/6	4/66	5/28	4/16
%	3.6	0	0	6.1	18.0	25.0
Reduced light reflex	*Normal*	*HNPP*	*CMT*	*HSAN*	*FAP*	*Refsum*
N	5/246	0/6	4/69	2/27	2/16	3/7
%	2.0	0	5.8	7.4	12.5	42.9
Reduced near reflex	*Normal*	*FAP*	*HNPP*	*CMT*	*HSAN*	*Refsum*
N	2/117	0/14	0/6	2/65	1/22	2/6
%	1.7	0	0	3.1	4.5	33.3
Bilateral tonic pupils	*Normal*	*Refsum*	*HNPP*	*CMT*	*FAP*	*HSAN*
N	0/241	0/6	0/6	6/67	2/16	4/27
%	0	0	0	9.0	12.5	14.8
Unilateral tonic pupils	*Normal*	*CMT*	*HSAN*	*FAP*	*HNPP*	*Refsum*
N	0/241	0/67	0/27	0/16	0/6	0/6
%	0	0	0	0	0	0
Bilateral Horner's syndrome	*Normal*	*HNPP*	*Refsum*	*CMT*	*HSAN*	*FAP*
N	0/241	0/6	0/5	3/56	4/23	8/14
%	0	0	0	5.4	17.4	57.1
Unilateral Horner's syndrome	*Normal*	*CMT*	*FAP*	*HNPP*	*Refsum*	*HSAN*
N	8/225	0/56	0/14	0/6	0/5	2/23
%	3.6	0	0	0	0	8.7
Light–near dissociation	*Normal*	*HNPP*	*CMT*	*FAP*	*HSAN*	*Refsum*
N	2/91	0/6	2/65	1/14	2/22	3/6
%	2.2	0	3.1	7.1	9.1	50.0
Any abnormality	*Normal*	*HNPP*	*CMT*	*HSAN*	*FAP*	*Refsum*
N	14/315	0/6	12/69	13/29	10/16	10/11
%	4.6	0	17.4	44.8	62.5	90.9

CMT, Charcot Marie Tooth disease; FAP, familial amyloid polyneuropathy; HNPP, hereditary neuropathy with pressure palsies; HSAN, hereditary sensory and motor neuropathy.
The normal group is placed in the left hand column. The patient groups are arranged in the order of percentage abnormality.

had a novel frameshift mutation in exon 15 of the *TRKA* gene (Table 2). In one patient with the *TRKA* mutation, pupillometry was impossible but photography revealed miosis below the 0.5% confidence interval of normal. The other had bilateral Horner's syndrome, also with severe miosis. The proband with HSAN-V (homozygous point

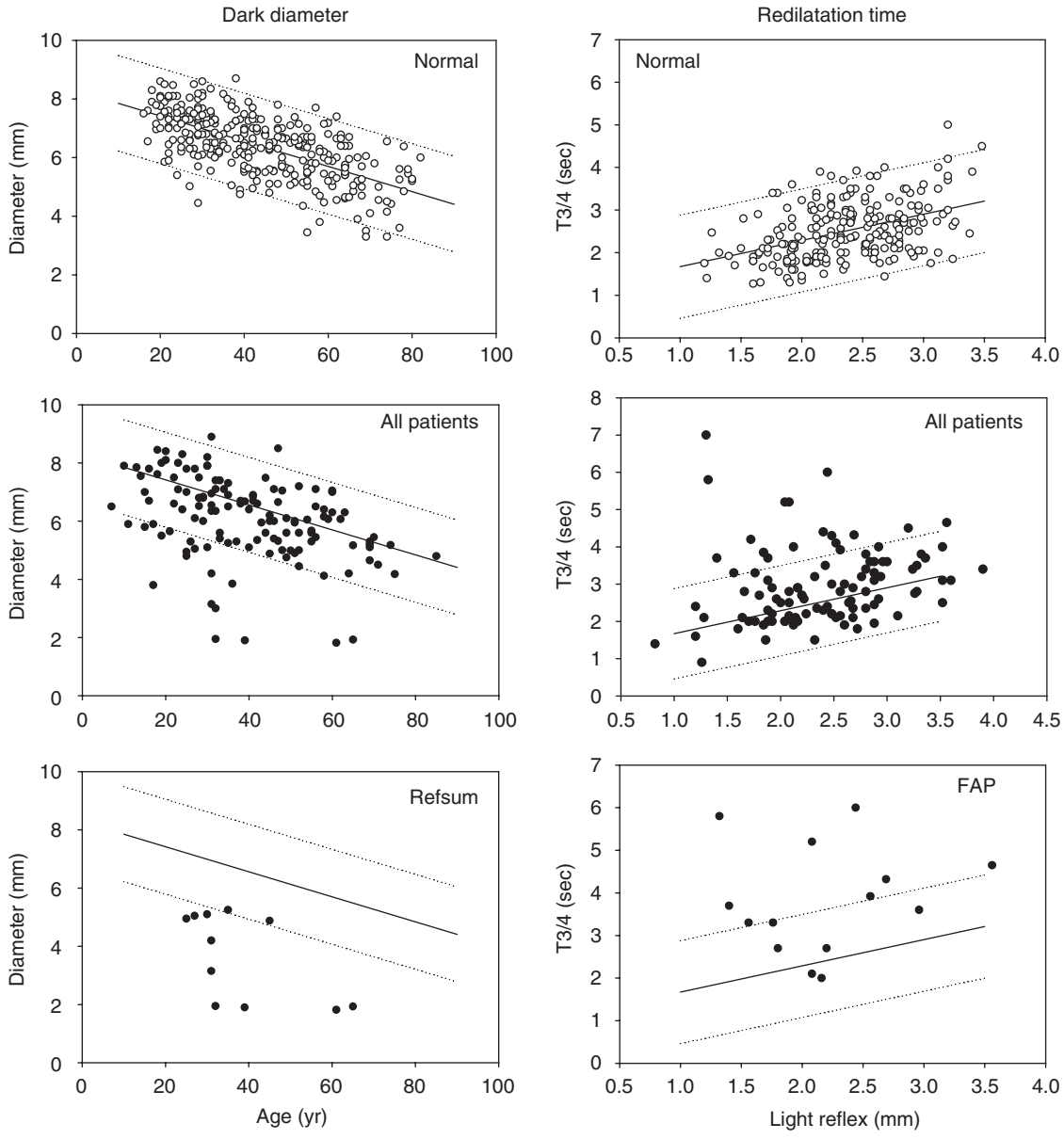

Figure 1 Dark diameter (graphs on the left), the relationship between age and pupil dark diameter in healthy control subjects (top—normals), all patients with inherited neuropathy included in this study (middle—all patients), and patients with Refsum's disease (bottom—Refsum). Redilatation, relationship between light reflex amplitude, and redilatation time in healthy control subjects (top), all patients with inherited neuropathy (middle), and patients with familial amyloid neuropathy (bottom—FAP).

mutation in exon 8 of the *TRKA* gene) had tonic pupils as did his father, who was a heterozygous carrier and was clinically normal otherwise.

Discussion

In this series of 131 patients with hereditary neuropathies, we provide an overview of the frequency and type of pupil defects. The neuropathy types were split into five groups, with the Refsum's disease and the autonomic neuropathies (FAP and HSAN) having the greatest frequency of defects. The severity of the autonomic neuropathy in the cases of FAP and those with HSAN was associated with a greater likelihood of having abnormal pupils, but this was not in all cases or all mutation types. This was most consistent in the patients with HSAN-III, -IV, and -V who all had pupil abnormalities and a severe neuropathy with autonomic features. There were cases of HSAN-I, HSAN-II, and FAP with moderate autonomic neuropathy but no pupil

abnormalities. This is consistent with previous data on the small group of FAP and Refsum's patients but unreported in HSAN. In the parents available from recessive families with HSAN-II and HSAN-V, abnormal pupils were also recognized, suggesting that they were mild manifesting carriers.

The most frequent FAP group observed was the Ala60 *TTR* mutation (Irish type) seen in four cases. The main pupil abnormality seen was bilateral Horner's syndrome, reported also in light-chain-associated amyloidosis.[25] The two cases with Met30 mutations did not have abnormal pupils, which was unexpected, as a previous study by Ando *et al*[26] reported that 81% of Met30 patients had abnormal pupils early in their diagnosis.

The frequency of pupil abnormalities in CMT and HNPP was low and not associated with severity or mutation type, although one unexpected finding was the frequency of pupil abnormalities in CMT 2, especially as only one of the CMT 2 group with pupil abnormalities had an *MPZ* mutation. It is well recognized that MPZ mutations are a frequent cause of abnormal pupils in CMT 2 as in one of our cases.[20,23] It is, however, apparent that not all *MPZ* mutations cause pupil abnormalities, because we found normal pupils in cases with CMT1B and CMT2 and *MPZ* mutations. The majority of our CMT2 cases were also screened for the Mitofusin 2 gene, a frequent cause of CMT2A (Table 2). Only one case was found to have an *MFN2* mutation and she had marked anisocoria. The phenotype spectrum of *MFN2* mutations includes axonal neuropathy with optic atrophy, but there are no previous reports of pupil abnormalities.[27] To confirm the association of abnormal pupils with MFN2 mutations, further cases need to be identified and examined. The frequency of pupil abnormalities in the CMT 2 group negative for *MPZ* and *MFN2* suggests that the axonal neuropathy present in this form of CMT may in itself be associated with pupil abnormality or the unknown genetic defect(s) lead to abnormal deposits in the iris.

In the group with Refsum's disease, only one patient did not have a pupil abnormality. This case had an extremely strict diet and undetectable phytanic acid levels at the time of pupillography. The main abnormality found in the other patients was miosis.[28,29] The relative failure of the pupils of Refsum's disesase patients to dilate to phenylephrine suggests that in this condition, miosis is not due to an autonomic defect, but it is more likely due to a structural abnormality within the iris. This is consistent with previous pathological and electron microscopy examinations of the irides which have shown high concentrations of the phytanic acid lipid deposits in both sphincter and dilator muscles.[30,31] Any structural abnormality would correlate with the severity of the Refsum's disease and respond to diet restriction if started early enough. There are unfortunately no neuropathological studies on the irides of the other forms of inherited neuropathies in our cohort.

In summary, this is the first study of the pupil abnormalities found in a large group of inherited peripheral neuropathies and provides an overview of the frequency and type of defects seen but analysing this data we could not predict the genetic defect. In the FAP and HSAN (non-HSAN-I) groups, abnormal pupils were associated with a more severe neuropathy, but not in the other inherited neuropathy groups. This series along with the detailed tables will act as an important diagnostic aid in assessing these patients.

Acknowledgements

We are grateful to the patients, without whom the study would not have been possible. We also thank the MRC, HH holds an MRC clinician scientist fellowship. Professor Smith died in December 2007 during the final preparation of this manuscript. He made an enormous contribution to this paper and to the investigation of pupil abnormalities throughout his life.

References

1 Skre H. Genetic and clinical aspects of Charcot–Marie–Tooth's disease. Proceedings of the Third International Congress on Muscle Diseases. Excerpta Med Int. Cong. Series, No 334. Amsterdam, Excepta Medica, 1974. 1974.
2 Zuchner S, Vance JM. Molecular genetics of autosomal-dominant axonal Charcot–Marie–Tooth disease. *Neuromolecular Med* 2006; **8**: 63–74.
3 Szigeti K, Nelis E, Lupski JR. Molecular diagnostics of Charcot–Marie–Tooth disease and related peripheral neuropathies. *Neuromolecular Med* 2006; **8**: 243–254.
4 Pareyson D, Scaioli V, Laura M. Clinical and electrophysiological aspects of Charcot–Marie–Tooth disease. *Neuromolecular Med* 2006; **8**: 3–22.
5 Nicholson G, Myers S. Intermediate forms of Charcot–Marie–Tooth neuropathy: a review. *Neuromolecular Med* 2006; **8**: 123–130.
6 Kleopa KA, Scherer SS. Molecular genetics of X-linked Charcot–Marie–Tooth disease. *Neuromolecular Med* 2006; **8**: 107–122.
7 Houlden H, Reilly MM. Molecular genetics of autosomal-dominant demyelinating Charcot–Marie–Tooth disease. *Neuromolecular Med* 2006; **8**: 43–62.
8 Dubourg O, Azzedine H, Verny C, Durosier G, Birouk N, Gouider R *et al*. Autosomal-recessive forms of demyelinating Charcot–Marie–Tooth disease. *Neuromolecular Med* 2006; **8**: 75–86.
9 Dyck P, Chance P, Lebo R, Carney J. *Hereditary Motor and Sensory Neuropathies*. W.B. Saunders: Philadelphia, 1993.
10 Lipton L, Tomlinson I. The genetics of FAP and FAP-like syndromes. *Fam Cancer* 2006; **5**: 221–226.

11 Duke JR, Paton D. Primary familial amyloidosis: ocular manifestations with histopathologic observations. *Trans Am Ophthalmol Soc* 1965; **63**: 146–167.
12 Wong VG, McFarlin DE. Primary familial amyloidosis. *Arch Ophthalmol* 1967; **78**: 208–213.
13 Lessell S, Wolf PA, Benson MD, Cohen AS. Scalloped pupils in familial amyloidosis. *N Engl J Med* 1975; **293**: 914–915.
14 Davies DR, Smith SE. Pupil abnormality in amyloidosis with autonomic neuropathy. *J Neurol Neurosurg Psychiatry* 1999; **67**: 819–822.
15 Murakami A, Fujiki K, Hasegawa S, Imamura S, Kawano H, Kanai A *et al*. Transthyretin Ser-44 mutation in a case with vitreous amyloidosis. *Am J Ophthalmol* 2002; **133**: 272–273.
16 Murakami T, Atsumi T, Maeda S, Tanase S, Ishikawa K, Mita S *et al*. A novel transthyretin mutation at position 30 (Leu for Val) associated with familial amyloidotic polyneuropathy. *Biochem Biophys Res Commun* 1992; **187**: 397–403.
17 Refsum S. Heredoataxia hemeralopica polyneuritiformis—ettidligere ikke beskrevet familiaert syndrom? *Nord Med* 1945; **28**: 2682.
18 Clarke D, Critchley M. Heredopathia atactica polyneuritiformis (Refsum's syndrome). *Proc Roy Soc Med* 1951; **44**: 689–690.
19 Dyck PJ, Schaid DJ. Genetic heterogeneity in hereditary sensory and autonomic neuropathies: the need for improved ascertainment. *Muscle Nerve* 2000; **23**: 1453–1455.
20 Kurihara S, Adachi Y, Wada K, Adachi A, Ohama E, Nakashima K. Axonal and demyelinating forms of the MPZ Thr124Met mutation. *Acta Neurol Scand* 2003; **108**: 157–160.
21 Reilly M, Greenwood RJ. Disorders of the peripheral nerves. In: Greenwood RJ, Barnes MP, McMillan TM, Ward CD (eds). *Handbook of Neurological Rehabilitation*. Psychology Press, Taylor and Francis Group: Hove and New York, 2003, vol 1, pp 725.
22 Leonardis L, Zidar J, Popovic M, Timmerman V, Löfgren A, Van Broeckhoven C *et al*. Hereditary motor and sensory neuropathy associated with auditory neuropathy in a Gypsy family. *Pflugers Arch* 2000; **439**: R208–R210.
23 Reilly MM. Sorting out the inherited neuropathies. *Pract Neurol* 2007; **7**: 93–105.
24 Bremner F, Smith S. Pupil findings in a consecutive series of 150 patients with generalised autonomic neuropathy. *J Neurol Neurosurg Psychiatry* 2006; **77**: 1163–1168.
25 Bremner FD, Smith SE. Pupil abnormalities in selected autonomic neuropathies. *J Neuroophthalmol* 2006; **26**: 209–219.
26 Ando E, Ando Y, Okamura R, Uchino M, Ando M, Negi A. Ocular manifestations of familial amyloidotic polyneuropathy type I: long-term follow up. *Br J Ophthalmol* 1997; **81**: 295–298.
27 Zuchner S, De Jonghe P, Jordanova A, Claeys KG, Guergueltcheva V, Cherninkova S *et al*. Axonal neuropathy with optic atrophy is caused by mutations in mitofusin 2. *Ann Neurol* 2006; **59**: 276–281.
28 Folz SJ, Trobe JD. The peroxisome and the eye. *Surv Ophthalmol* 1991; **35**: 353–368.
29 Claridge KG, Gibberd FB, Sidey MC. Refsum disease: the presentation and ophthalmic aspects of Refsum disease in a series of 23 patients. *Eye* 1992; **6**(Part 4): 371–375.
30 Toussaint D, Danis P. An ocular pathologic study of Refsum's syndrome. *Am J Ophthalmol* 1971; **72**: 342–347.
31 Dick AD, Jagger J, McCartney AC. Refsum's disease: electron microscopy of an iris biopsy. *Br J Ophthalmol* 1990; **74**: 370–372.

Supplementary Information accompanies the paper on Eye website (http://www.nature.com/eye)