FAMILIAL NEUROPATHIES: A CLINICAL AND ELECTROPHYSIOLOGICAL STUDY AT GROOTE SCHUUR HOSPITAL

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A thesis presented in fulfilment of the degree of

Master of Medicine (Neurology) of the University if Cape Town.

November 1993

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This dissertation reports on the clinical, electrophysiological and genetic results of different neurologic disorders characterized by progressive weakness and wasting of the legs in South African kinships.

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1. Introduction:

Inherited neuropathies can presently be divided into categories dependant on their clinical characteristics and include the Hereditary sensori-motor neuropathies (HSMN), Hereditary motor neuropathies (HMN) and Hereditary sensory and autonomic neuropathies (1). This study has focused on the familial neuropathies presenting with "peroneal muscular atrophy" which may be the result of disease in the peripheral nerve or anterior horn cell and therefore includes HSMN and HMN.

Charcot, Marie and Tooth simultaneously described the first cases of "peroneal muscular atrophy" in 1886 (2, 3). The disorder which commonly presents in childhood was defined as slow progressive weakness and muscle wasting affecting predominantly the feet, with distal upper limb involvement occurring years later. With the introduction of nerve conduction studies Henrikson (1956) and Gilliatt and Thomas (1957), found slowed nerve conduction speeds in some of these patients (4, 5). Dyck and Lambert later recognised two common variants with consistent electrophysiological features in families (6). They subdivided the latter into HSMN type I (demyelinating/ Charcot-Marie-Tooth (CMT)-1) and HSMN type II (axonal/CMT-2) based on their electrophysiological evaluations.

Less commonly encountered variants of HSMN which are all characterised by electrophysiological sensory and motor nerve involvement include (1);

type III- Dejerine Sottas;
IV - Refsum's disease (excess phytanic acid);
V - HSMN with spastic paraplegia;
VI - HSMN with optic atrophy;
VII- HSMN with retinitis pigmentosa
(normal phytanic acid)

Although mental retardation (7) and sensori-neural deafness (8) have been described with familial neuropathies, inadequate reporting or absent documentation of neurophysiological testing precludes these from the current classification. Involvement of the peripheral motor, sensory and possibly autonomic nerves may be associated with the spinocerebellar and olivopontocerebellar degenerations (1), but these are not included in the familial neuropathy classification.

Roussy and Levy described cases in 1926 that had pes cavus, tendon areflexia, ataxia of gait and distal limb weakness and sensory loss with tremor in the upper limbs and claimed their phenotype represented a distinct entity (9). Over the next decades many authors questioned the validity of their assumption, and Dyck and Lambert showed in 1968 that these individuals only represented a clinical variant of HSMN I (6).

A subgroup of familial "peroneal muscular atrophy" have been found to show electrophysiological involvement of only the peripheral *motor* system. The aforementioned has been classified in recent years as subcategories of hereditary spinal muscular atrophy (SMA) using descriptive labels dependant on the distribution of weakness. These include the proximal, distal, bulbospinal, scapuloperoneal, fascioscapulohumeral, oculopharyngeal and

bulbar "varieties of SMA" (10). SMA however refers to the particular phenotype of progressive proximal weakness most commonly with onset in childhood, and the gene locus has recently been mapped to the long arm of chromosome 5 (11).

Classifying the pure *motor* component of the "peroneal muscular atrophy" group as SMA variants is confusing and uninformative and I have therefore considered them as hereditary motor neuropathies (HMN). This group like HSMN, is also clinically heterogeneous.

Reviewing the literature in 1935, Bell concluded that the "peroneal muscular atrophies" may be inherited in an autosomal dominant, recessive or X-linked manner but may also occur in a sporadic fashion in families (12). Recent molecular genetic advances have shown that both HSMN I and II are genetically heterogeneous. HSMN Ia which is the commonest, is due to "segmental trisomy" of band p11.2 on chromosome 17 which is also the locus for peripheral myelin protein-22 (PMP-22), the candidate gene for type Ia (13,14,15,16). HSMN Ib has been linked to the Duffy blood group marker located on chromosome 1q (17), and the X-linked families to the long arm of the X chromosome (18,19).

HSMN IIa has recently been linked to markers on chromosome 1p36 (Vance J et al. In Press). Type II has been classified further into IIb and IIc where the gene is unknown in both instances, but the latter is associated with vocal cord paralysis (personal communication, Harding AE; 1993).

Apart from the familial motor neurone disease subcategory, no chromosomal linkage has been established in HMN. The former has been linked to chromosome 21 in certain families and mutations in the Cu/Zn-binding superoxide dismutase gene on chromosome 21 has recently been demonstrated in these families (20).

2 Objectives:

1. The primary aim of this prospective study was to determine the phenotypic spectrum of the inherited neuropathies seen in individuals at Groote Schuur Hospital between May 1990 and January 1993. The patients were classified according to their clinical and neurophysiological phenotypes, as well as inheritance patterns within their respective families.

The phenotypic groups have been examined for common or characteristic clinical features such as symptoms and their time of onset, dysmorphic features and the degree of functional disability. Racial and gender differences have also be delineated. These features have not been documented before in our population, and are not only essential for neurologists providing clinical counselling for such families, but will provide an accurate clinical database for further genetic studies.

2. Secondly, with respect to the HSMN group, I intended to asses linkage to the Duffy blood group locus on chromosome 1 by determining LOD scores in large families where individuals from at least 2 generations were examined and found to be affected. It was my intention to then compare the phenotypic expression of these families to non-linked families. The families that do not display linkage to chromosome 1 will be examined at a later date by the Department of Genetics with the use of DNA probes, for linkage to chromosome 17 and X.

3. Method:

3.1. The patients' names were selected from the records of the neurophysiology laboratory of the Neurology unit and the Department of Human genetics.

3.2. Patients were notified of the proposed study and invited to participate after informed consent had been obtained.

3.3. Index cases were included in the study when;

a) there was a chronic history of weakness in the distal legs and arms;
b) with or without a positive family history;
c) electrophysiological evidence of motor or sensori-motor involvement.

3.4. The index cases, with as many symptomatic and asymptomatic family members as possible, were examined neurologically and electrophysiologically. All clinically affected members were questioned to exclude other possible causes for their neuropathies and the index cases underwent a routine laboratory screen to exclude known causes of neuropathy.

3.5. The functional impairment in affected individuals were evaluated by determining a total neurologic disability score (NDS-T) for each case. This is a predetermined set of evaluations scoring motor weakness (NDS-W), deep tendon reflexes (NDS-R) and certain sensory (NDS-S) parameters as follows (21):

Muscle weakness
- 0 = normal strength
- 1 = 25 % decrease
- 2 = 50 % decrease
- 3 = 75 % decrease
- 4 = 100 % decrease

Reflexes
- 0 = normal
- 1 = unequivocally decreased
- 2 = absent

Sensation for the index finger and great toe were graded as for the reflexes.

A score for muscle weakness (NDS-W) was determined in the following muscle groups; in the arm for shoulder abduction, elbow flexion and extension, wrist flexion and extension, and finger abduction and flexion. In the legs a muscle weakness score was determined for hip flexion and extension, knee flexion and extension, ankle dorsiflexion and plantar flexion and toe flexion and extension. If toe extension and ankle dorsiflexion was evaluated to be 50% weak in both legs, the score would be NDS-W: 2x2 + 2x2 =8. The grading depended on the examiners concept of what was normal considering the age, sex and physical fitness of the individual. When a unilateral focal nerve injury or surgical procedure interfered with the grading of the deficit due to HSMN, the values from the uninjured side were used for the injured side.

Sensation was evaluated with respect to pain, touch and position sense. If both great toes showed an unequivocal reduction in touch sensation (2 x 1) with normal proprioception (0) and absent pain sensation (2 x 2), the total NDS-S score would be 6, assuming the sensation in the fingers were normal.

A NDS-T score was determined for each subject by adding the respective scores for NDS-W, NDS-R and NDS-S for that particular individual.

Gait was assessed and scored objectively as;

0- normal;
1- footdrop;
2- complete footdrop requiring ankle-foot orthoses;
3- requiring crutches;
4- requiring wheelchair intermittently;
5- wheelchair bound.

All the neurological examinations were performed by the author and were done prior to nerve conduction studies.

3.6. Nerve conduction studies were performed on symptomatic and asymptomatic individuals under standard conditions according to our laboratory protocol on a Medelec Mystro GR 20. Limb temperatures were measured and kept constant with a bath and/or warming lamp. Arm temperatures were maintained above 31.5 °C and leg temperatures above 30.5 °C as measured at the wrist and ankle. Electrophysiological nerve conduction responses were measured with suprathreshold stimuli.

Motor nerves were examined electrophysiologically with the active surface electrodes (G1) over the mid-position of the muscle belly and the reference electrode (G2) over the tendon of the same muscle. The nerve was stimulated 8 cm proximal to the G1 electrode. In children less than 5 years the distance was 5 cm but these distal latency values were not included in calculations. Motor amplitudes were measured from the baseline to the negative peak.

Median and ulnar digital sensory conductions were performed via orthodromic stimulation and the sural sensory nerve via antidromic stimulation. The distance between the stimulating electrode and the G1 surface pick up electrode was 14 cm in all cases. The distance between the active and reference electrode was 2.5 cm and both were placed directly over the nerve. The sensory amplitudes were measured from peak to peak after eight responses were averaged, and the sensory latency was measured form onset to peak.

Nerves examined electrophysiologically included (where possible);

- Right Common Peroneal nerve (CPer) (motor)
- Right Post Tibial nerve (PTib) (motor)
- Right Sural nerve (sensory)
- Right Ulnar motor and digital (sensory) nerves
- Right Median motor (Med) and digital (sensory) nerves

The electrophysiologic study in all index cases included electromyography (EMG) with a standard concentric needle electrode. All family members, affected or unaffected, were clinically and electrophysiologically examined but needle examinations were only performed in these individuals when consent was given.

3.7. Blood was drawn for Duffy blood group typing by the Provincial laboratory for Tissue Immunology. LOD scores were determined to assess linkage to chromosome I using the LIPED programme (22). DNA was also freeze-stored by the Department of Genetics (UCT) for DNA probe evaluation at a later date (separate study).

Results:

This prospective series comprises all the patients with electrophysiological evidence of motor with or without sensory dysfunction, examined at Groote Schuur Hospital between May 1990 and January 1993 that satisfied the clinical inclusion criteria. A total of 75 affected patients from 38 pedigrees were examined. The patients have been classified into 3 groups according to electrophysiological and clinical features (Table 4.1);

1)hereditary sensory-motor neuropathy (**HSMN**) group (n=58: *25 families*);

2)hereditary motor neuropathy (**HMN**) group (n=12: *11 families*);

3)hereditary sensory and autonomic neuropathy (**HSAN**) group (n=5: *2 families*).

The results will be presented separately for each group. Statistical analyses were done using the SSPS computer programme under the supervision of Mr S Isaacs from the Department Biostatistics at Groote Schuur Hospital. Statistical analysis of the data was performed using the Student-T test.

TABLE 4.1: Demographic data.

	cases	mAge(years)	race
Sensori-motor(HSMN)			
Type I: Inheritance		31.1	
Dominant	38	29.8	19 M/A 19 W
Recessive/Sporadic	2	22.5	1 M/A 1 B
X-linked? male	3	21.0	3 W
X-linked? female	5	47.6	5 W
Type II Inheritance		41.8	
Dominant	1	72	1 W
Recessive/Sporadic	9	38.4	4 B 4 M/A 1 W
Motor (HMN)	12	35.3	6 W 3 M/A 2 I 1 B
Sensory-autonomic (HSAN)	5	40	5 W

mAge - mean Age at assessment

SA racial groups:
M/A : mixed-ancestry
W : white
B : black
I : indian

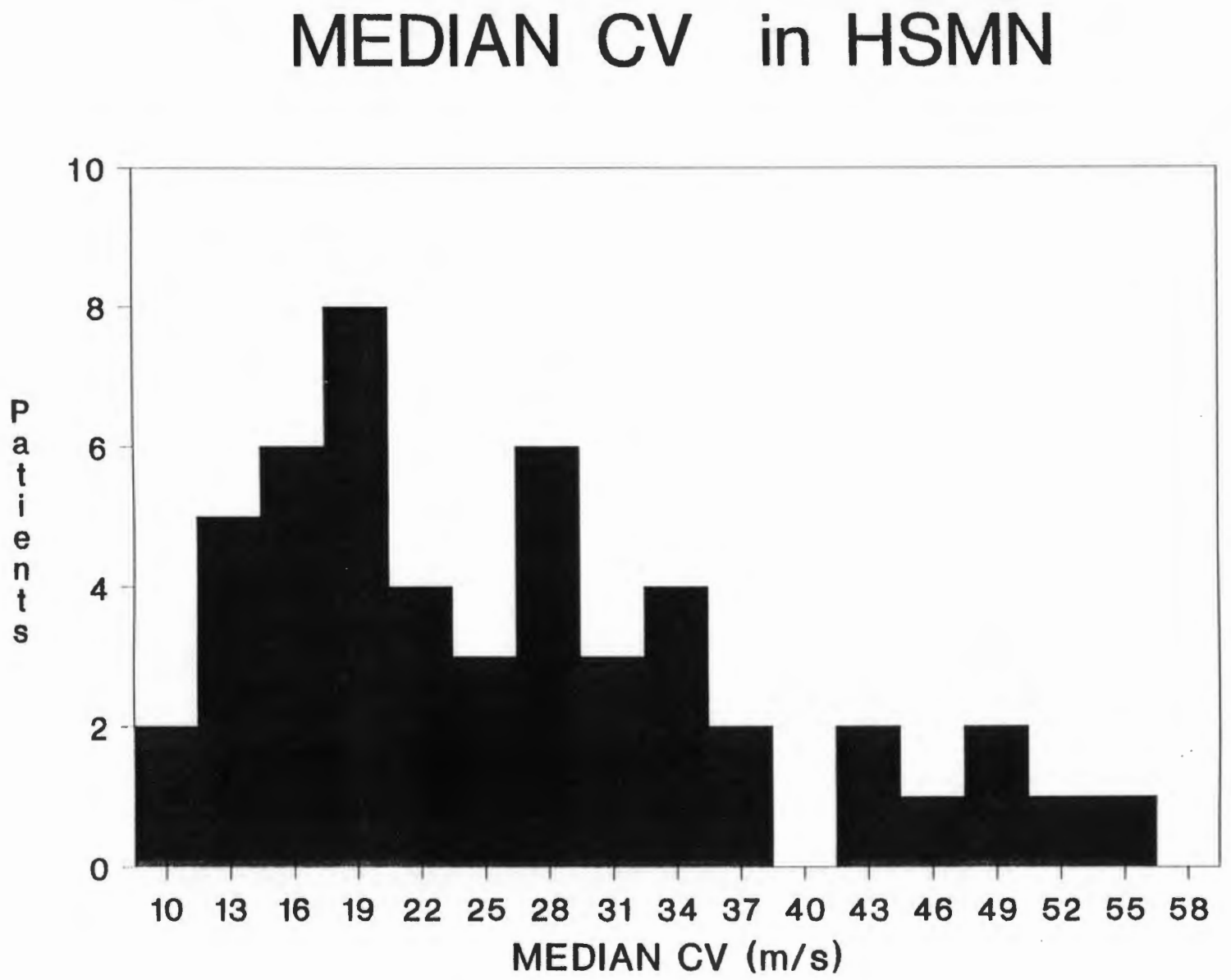

MEDIAN CV in HSMN
Patients
0
2
4
6
8
10
10 13 16 19 22 25 28 31 34 37 40 43 46 49 52 55 58
MEDIAN CV (m/s)

figure 1

4. HEREDITARY SENSORY-MOTOR NEUROPATHY GROUP (HSMN):

There were 58 affected cases in this group with a mean age of 32 years, comprising 23 index cases, each from a different pedigree, and 35 affected relatives. All the patients in this group had clinical and electrophysiological evidence of sensory and motor dysfunction. The predominant racial subgroup was of mixed ancestry ethnic origin (Table 4.1).

A value for motor conduction velocity for the median nerve was obtained in 50 cases and for the peroneal nerve in 29. In 26 cases a value could not be obtained for the peroneal nerve as the extensor digitorum brevis muscle was totally denervated. In only 1 case could a proximal median nerve response at the elbow not be obtained, due to markedly reduced distal motor unit potentials in the abductor pollicis brevis muscle. Figure 1 shows the distribution of motor conduction velocities for the median nerves.

4.1 Classification:

The HSMN group could be divided into 2 groups based on electrophysiological criteria, as previously described (fig. I):

-**HSMN I** or demyelinating variety of Charcot Marie Tooth
(N=48);

-**HSMN II** or axonal variety of Charcot Marie Tooth
(N=10).

These two groups were divided according to their mean distal latencies (DL). (Table 4.2) This method was used in an attempt to increase the objectivity of the division in conduction speeds, by using an additional parameter of distal nerve conduction velocity.

The HSMN I cases all had median (Med) nerve DL's slower than 130% of the upper limit of normal with a mean Med DL of 229 % of the upper limit of normal (Range 6.3- 17.1 msec; Normal < 4.5 msec) The mean median conduction velocity (Med CV) was 22.2 meters per second (m/s) (SD 7.9; n=35) with a range of 12.8 - 33.1 m/s (Normal > 48 m/s). Median nerve DL values were not included in children where it was not possible to use the adult distances. There were individuals that refused an upper limb examination after the leg examination.

Group II (N =10) all had normal distal latencies with a mean Med DL of 88 % of the upper limit of normal (Range 3.3- 4.9 msec.). The mean Med CV was 43.7 m/s (SD 7.81; range 34.8 - 54.4 m/s). A statistically significant difference (p=0.000) was found between the mean Med CV of HSMN I and HSMN II. A mean Med CV of less than 33.1 m/s therefore corresponded to the HSMN I group and a value over 34.8 m/s to the HSMN II group.

The unaffected relatives of both groups I and II had a mean Med DL of 3.66 msec (SD= 0.37) and a mean Med CV of 55.63 m/s (SD= 5.48). The former did not differ significantly from the HSMN II (p= 0.037) but the mean Med CV of the unaffected relatives did differ from HSMN II (p= 0.000).

Table 4.2: HSMN Classification

	mMedL(ms)	(SD)	mMed CV(m/s)	(SD)
HSMN I	10.17	(3.19)	22.17	(7.90)
HSMN II	4.00	(0.52)	43.72	(7.80)
P=	0.000		0.000	

mMed DL - mean Median nerve distal latency
mMed CV - mean Median nerve conduction velocity

4.2 Inheritance patterns:

Autosomal dominant (AD) inheritance was observed in the majority of type I individuals (12 families) with the exception of only 2 families with possible Autosomal recessive or sporadic (AR/S) inheritance. Nine HSMN II cases showed predominant AR/S as a possible inheritance pattern with 1 family having AD inheritance according to the family history (see Table 4.1).

The HSMN I AR/S cases had a mean Med CV of 15.3 m/s (SD= 0.4) which did not differ significantly from the HSMN I AD cases with a mean Med CV of 22.2 m/s (SD= 5.7: p= 0.10) These results are in contrast with those of other investigators (7, 15) in which a significantly slower median conduction velocity was found in the autosomal recessive cases. Although the Type I AR/S sample size consists of only 2 cases, statistical analysis was performed due to the negligible variance.

Two families had a distinctive phenotype suggesting X-linked ('XL') inheritance which

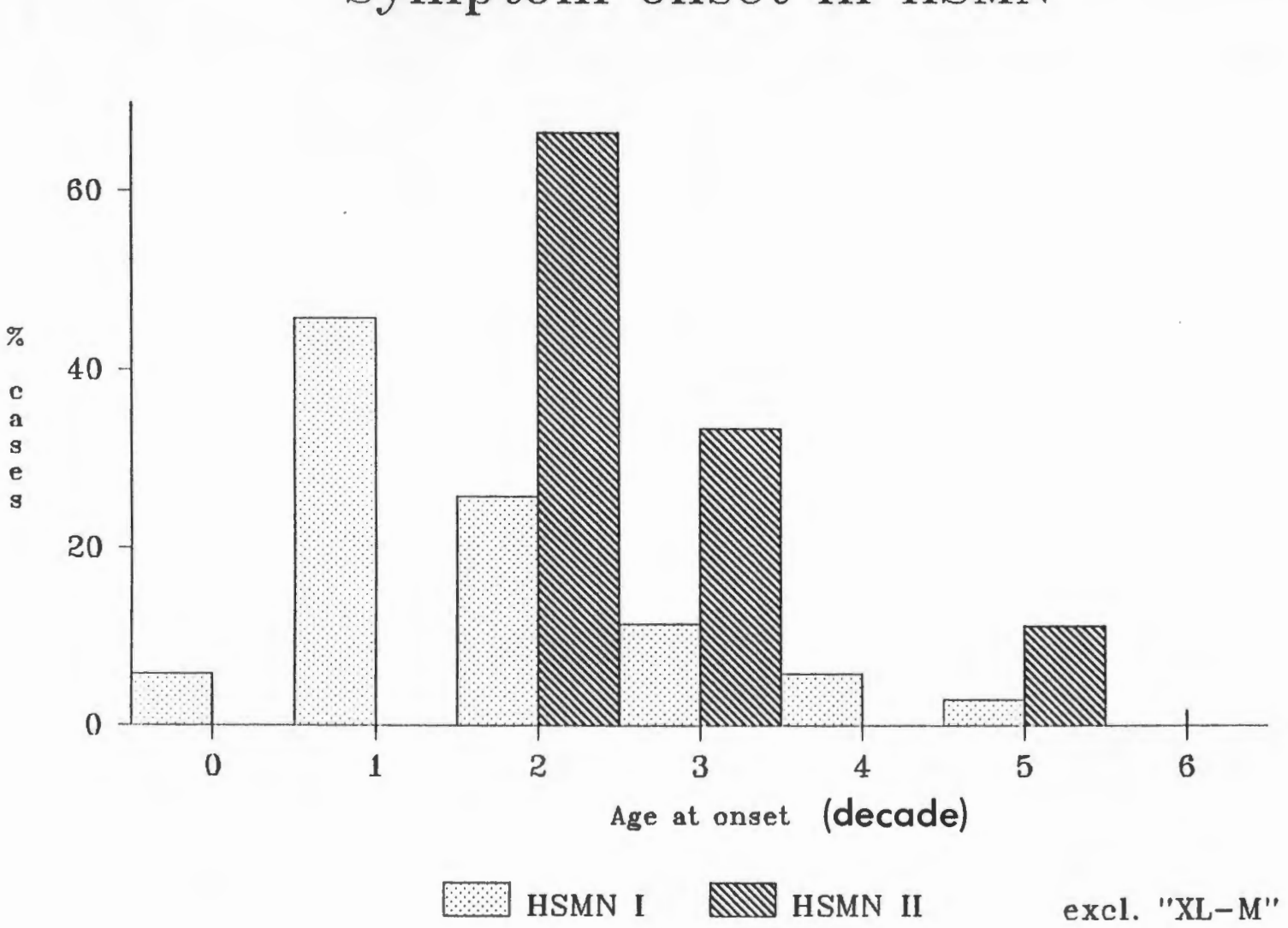

Symptom onset in HSMN
60
40
20
0
% cases
0
1
2
3
4
5
6
Age at onset (decade)
HSMN I
HSMN II
excl. "XL-M"

Figure II

distinguished them from the rest of the HSMN I group;

I) In family Q (see Fig VII) case II1 was moderately affected (NDS-T=40). (see section 3). The rest of the family, apart from the mother(I1), was unaffected. She was asymptomatic but had minimal objective clinical involvement (NDS-T=8) and absent sensory responses in the upper and lower limbs on electrophysiological examination. The motor conductions were normal and EMG was refused. This unusual pattern could be consistent with X-linked recessive inheritance pattern (personal communication AE Harding).

II) Family B (see Fig VIII) was characterised by no male to male transmission of the trait in 4 generations, as well as a significant number of asymptomatic female cases that were subsequently found on testing to be affected . Furthermore, a significant difference in motor conduction velocities between affected males ('XL-M') and "carrier" females ('XL-F') was also found. (Table 4.9) These clinical results have to be confirmed with DNA studies.

4.3 Symptoms:

Symptom onset in HSMN I, AD and AR/S, occurred predominantly in the first decade. (Fig. II) HSMN 'X-L M' (n=3) experienced, symptoms initially in the first (n=1) and second decade (n=1), but one individual was still asymptomatic at age 23 years. Other asymptomatic individuals, who were subsequently found on clinical and electrophysiological examinations to be affected, included four subjects from type I AD families with mean Med CV 18.9 m/s and a mean NDS-T score of 15.5, and three 'XL-F' in the probable X-linked family (cases B IV8; B V2; B III6; See Fig VIII) who had a mean Med CV of 46.5 m/s and a mean NDS-T score of 6.5 points.

HSMN type II presented with symptoms predominantly in the second decade (n=8), with one HSMN type II AD index case experiencing his first symptoms in the 5th decade. (Fig. II) There was no difference in the presentation of symptoms or their frequency between HSMN I and II (see later).

There were 4 type I families in which a number of individuals from 3 generations were examined. It appeared as if each subsequent generation experienced earlier onset of symptoms than the preceding one. (Table 4.3) Generation numericals were assigned in most instances, according to when the symptoms of the disease first appeared in the family .

Table 4.3 Age of onset in successive type I generations (yrs):

Generation:	I	II	III	IV	V
Family A *	63	8	2		
	50	25	3		
	35	4			
		27			
Family O•	23	15	5		
	15	15			
		5			
Family R•			10	15	5
				5	5
Family H#		15	8	4	
		15			
mean	37.2	13.2	5.6	8.0	5.0
SD	19.54	8.34	3.36	6.08	0

* Fig IX
• Fig X
Fig XI

The earliest and commonest symptoms experienced in HSMN were ankle instability and clumsiness (68%). The other common symptoms were difficulty with walking (49%), cramps (39%), weakness of the legs and cold feet (28%), persistent toe walking during childhood (16%), and patella dislocation (7%). (Table 4.4) Cramps were only considered significant if they occurred more than once per month for at least six months, and they were usually experienced in the fingers or toes after exercise. A number of patients also experienced frequent nocturnal calf cramping. The only symptoms in unaffected family members (n=37) were cramps in 2 individuals and an episode of patella dislocation in 1. Weakness of the hands were experienced by 28% of the subjects with the onset occurring predominantly in the 4th

were experienced by 28% of the subjects with the onset occurring predominantly in the 4th decade. Sixteen percent of the affected individuals complained of numbness in the feet and occasionally in the hands. None of the patients had experienced paresthesiae.

Recumbent positional dyspnoea was a complaint in one HSMN I individual (age=62 yrs). Examination revealed paradoxical diapraghmatic respiratory movement and his Forced Vital Capacity in a standing and lying position were 1100ml and 600ml respectively. Phrenic nerve conduction studies showed a consistent CMAP response with a delayed latency on the left (DL= 24.9 msec; normal= 6.9-9.2 msec), and no response could be obtained on the right. This patient had a Med-CV of 19.2 m/s in 1983, but I was only able to obtain a delayed distal motor response (Med DL = 9.9 msec.) without a proximal response during the most recent examination (1991). The disability score (NDS-T) at the time of examination was 98 and he was able to walk with ankle-foot orthoses and a walking stick.

TABLE 4.4: SYMPTOMS IN HSMN.

SYMPTOMS	n=57*
Ankle instability	39
Clumsiness	39
Gait difficulty	28
Cramps	22
Cold feet	16
Weakness/feet	16
Hand weakness	16
Numbness	9
Toe walking	9
No symptoms	8
Patella dislocation	4
Dyspnoea(positional)	1

* 1 case from Type II family had severe complicated Tuberculous meningitis.

4.4 Dysmorphic features

Pes cavus, wasting of distal legs and clawing/hammering of the toes were the commonest dysmorphic features in type I and II HSMN. Wasting of the muscles of the hands and forearms were more frequent in type II (80%) than type I (46.8%), whereas hand clawing due to presumed disproportionate distal weakness and finger flexor contractures, was found in 2 HSMN I subjects and 1 HSMN II.

Three HSMN I and 1 HSMN II individuals had no evidence of the abovementioned dysmorphic features, whereas 84,6% unaffected family members had no such features. Dysmorphic features in the latter group included hyperextensibilty of the joints (n=1), narrow forehead, stubby fingers and small hands & feet in one child with profound mental retardation (n=1) and pes cavus (n=4). The latter included adult and child (older than 5 years) relatives who exhibited arching of the lateral and medial aspect of the feet, off a flat surface. These individuals however had normal neurological and electrophysiological examinations.

Table 4.5 DYSMORPHIC FEATURES in HSMN:

	n=58
Distal leg wasting	35
Pes cavus	44
Toe clawing & hammering	23
Wasting of the hands/forearms	22
Webbed fingers	5
Hand clawing	3
Hyperextensibilty of joints	3
Scoliosis	2
Toe syndactely(2nd & 3rd)	1
Webbed neck	1
Blepharophimosis	1
Genu valgus	1

4.5 Signs:

Postural tremor did not entirely co-segregate with HSMN I in any of the kinships. (Table 4.6) Tremor in the upper limbs were found in 64.9% of HSMN I, 2 unaffected relatives and in 2 HSMN II patients. Tremor was not observed in the presumed X-linked families.

Table: 4.6 Tremor in HSMN I families:

Family	CASES	TREMOR	NO TREMOR
• A	10	3	7
• C	1	1	-
• E	1	-	1
• F	4	1	3
• H	4	4	-
• J	1	-	1
• K	1	-	1
• L	1	1	-
• O	3	1	2
• P	1	-	1
• R	6	3	3
• S	5	-	5

Mental retardation was evident in 1 HSMN I (n=37) case, 2 affected sisters with HSMN II (n=10) and 3 of the unaffected family members (perinatal trauma in 1 case; n=39).

Clinical evidence of nerve thickening at the fibula head and ulnar groove was found in only 54.1% of HSMN I cases who were classified as such on subsequent electrophysiological testing. I found the presence of nerve thickening therefore a reliable clinical sign of a demyelinating neuropathy. One HSMN type II subject also had evidence of clinically thickened nerves.

Complete areflexia was present in 38% (n=14) of HSMN I and 60% (n=6) of HSMN II individuals. Normal deep tendon reflexes were found in 6/37 of HSMN I cases and 2/5 of 'XL-F'. All the HSMN II cases had abnormal reflexes. Hyperreflexia and extensor plantar responses were not found in any of the patients.

Motor examination revealed lower limb distal weakness in HSMN I and II predominately in the anterior tibial and peroneal muscle groups. Ankle dorsiflexors were at least 50% weaker than the plantar flexors in 40% of the HSMN cases that had not undergone any surgical procedures to their feet. The reverse was found in only 2 cases where plantar flexors were 50% weaker than ankle dorsiflexors. The leg weakness usually did not progress more proximally than the distal thighs. Weakness in the arms usually involved the fingers with resultant hand clawing, and mild wrist weakness. Upper limb involvement proximal to the elbows was not found in any of the affected subjects.

Sensory involvement was usually mild, although the HSMN II subgroup showed the greatest clinical sensory dysfunction (Table 4.8). As with motor involvement, few patients experienced subjective sensory impairment. None of the patients complained of paresthesiae or lancinating pains which is not part of this syndrome (1). Severe sensory loss with perforating ulcers were not encountered in any of the HSMN cases.

Scoliosis was found in 2 HSMN I patients; the 1 case (16 yrs) came from an autosomal recessive/sporadic pedigree and had experienced symptoms for 1 decade; the other case (26 yrs) also suffered from mental retardation, had experienced symptoms for at least 2 decades and came from a definite autosomal dominant family.

Objective gait assessment in HSMN I showed that 40.5% of cases walked normally; 43.2% had mild foot drop; 13.5% needed ankle -foot orthoses and a further 5.4% required additional crutches for ambulating. The 'XL-M' cases all had mild footdrop, whereas the 'XL-F' (n=5) walked normally. None of the 10 HSMN II subjects walked normally; 3 had mild footdrop; 3 needed ankle-foot orthoses; 1 required crutches to walk; 1 used a wheelchair intermittently and 1 patient was wheelchair bound (4th decade).

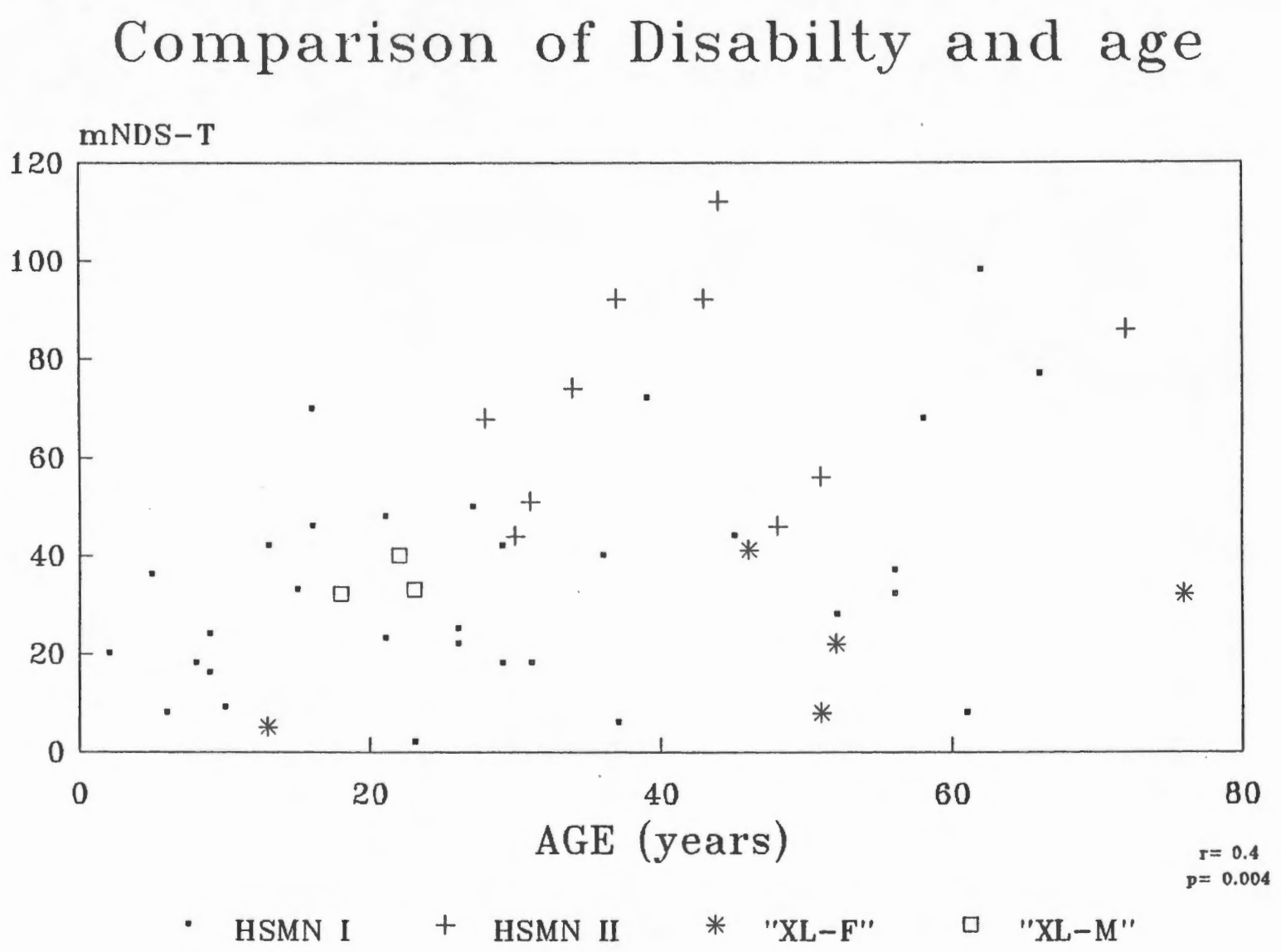

Comparison of Disabilty and age
mNDS-T
120
100
80
60
40
20
0
0
20
40
60
80
AGE (years)
r= 0.4
p= 0.004
HSMN I
HSMN II
"XL-F"
"XL-M"

Figure III

HSMN Type I (Autosomal Dominant) : Comparison of NDS and Gender

NDS - T	n	mean	SD	p value
	M 16 F 22	42.36 38.50	23.16 29.23	0.66
NDS - W	M 16 F 22	20.63 22.55	14.18 19.32	0.74
NDS - R	M 16 F 23	14.13 10.30	6.83 8.30	0.14
NDS - S	M 16 F 22	7.63 6.09	6.03 5.36	0.41

Table 4.7

4.6 Neurologic disability score (NDS)

Functional disability as determined by the neurologic disability score was most severe in the type II families (NDS-T= 72.1; SD=23.0) compared to type I (NDS-T= 35.3; SD=22.8). Unaffected family members (n=39) had disability scores of zero apart from 4 individuals who each had a total disability score of 2 due to reduced ankle jerks (mAge= 43 years).

In the HSMN I group with autosomal dominant inheritance, there was no objective difference in neurological disability between the sexes in each of the different categories. (Table 4.7) Disability scores in the 'X-linked' families also showed no significant difference between 'XL-M' (NDS-T= 35; SD 4.4) and 'XL-F' (NDS-T= 21.6; SD 15.4) despite the fact that most of the latter had no symptoms (p=0.3). The small sample size, greater mean age and much variance about the mean of the 'XL-F group could produce an erroneous conclusion. (Table 4.6)

The mean disability score for HSMN I AR/S (mean NDS-T= 56) was greater than that for HSMN I with autosomal dominant inheritance (NDS-T= 33.4). Statistical comparisons were not performed due to the small sample size (n=2) in the former.

Total neurologic disability showed a linear relationship with increasing age (fig. III; p=0.004, r=0.40) in HSMN I and II. However a bar graph (Fig. IV) depicting the duration since subjective onset and objective disability (NDS-T) does not show an unequivocal increase in disability with increasing disease duration. It is noteworthy however that in some of the columns there was only one patient which precluded the calculation of a mean value.

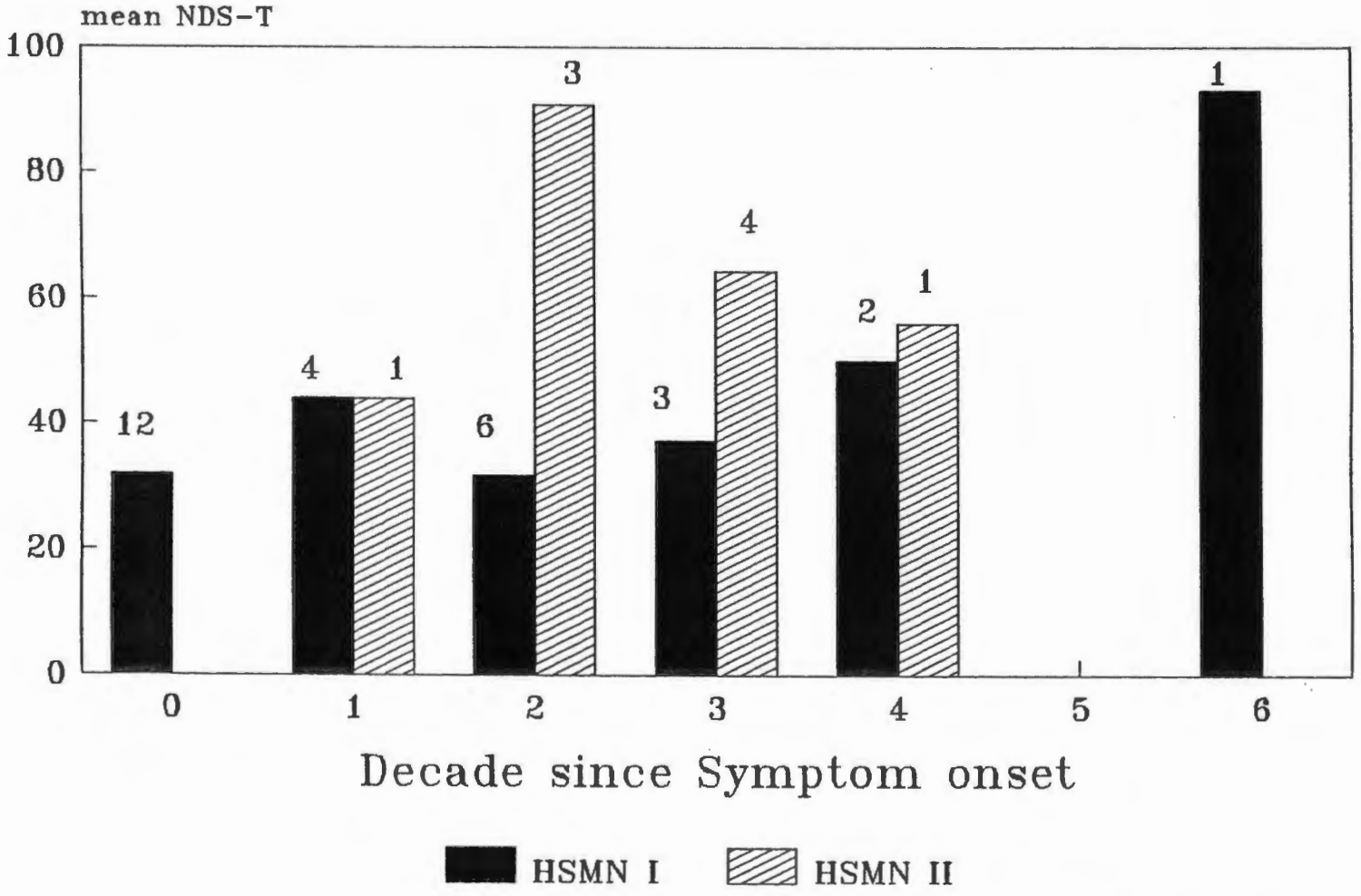


Figure IV

(numbers indicate no. of cases)

Table 4.8 :Comparison of age, median conduction velocity and functional disability (NDS) in HSMN I and II and HMN.

	HSMN I	XL-M	XL-F	HSMN II	HMN
Cases(n)	37	3	5	10	9
mAge yrs	29.8	21	47.6	41.8	35.3
mMed CV m/s	21.7	31.4	46.9	43.7	52.0
mNDS-W	22.3	15.7	10.0	45.0	22.8
mNDS-S	6.9	5.3	8.4	12	3.8
mNDS-R	11.9	12.6	7.2	15.1	4.5
mNDS-T	35.3	21.0	35.0	21.6	72.2

m = mean
mAge- at assessment

4.7 Electrophysiological characteristics

The patients were classified into the HSMN I or HSMN II groups according to the distal conduction velocities of the median nerves (see section 4.2). No electrophysiological abnormalities were found in any individuals with normal clinical examinations.

The Med CV range for HSMN I was 12.8- 33.1 m/s and for type II, 34.8- 54.4 m/s. The clear separation of these 2 groups supports our method of classification.

There was no significant gender difference in the mean Med CV's between males (17.0 m/s) and females (20.5 m/s) in HSMN type I or II. (Table 4.9) Families with possible X-linked inheritance were not included in these calculations. The latter group however showed a significant gender difference between 'XL-M' with a mean Med CV= 31.4 m/s (SD= 1.1), and asymptomatic affected females('XL-F') who had a mean Med CV= 46.9 m/s (SD= 8.1)(p= 0.019). (Table 4.9) .

TABLE 4.9 MEDIAN NERVE CONDUCTION VELOCITY vs GENDER:

	HSMN(excl. X-L)		
SEX	n	**mMED CV**	SD
MALE	14	16.97	10.51*
FEMALE	17	20.53	8.58*

* p=0.31

mMED CV- mean Med CV

HSMN I individuals from families with an autosomal dominant inheritance pattern, had a significantly slower median nerve conduction speed to males in the proposed X-linked families whom exhibited only moderate slowing of nerve speed (p=0.005)

In an attempt to evaluate the uniformity of the disease process I compared the conduction

velocities of 2 upper limb motor nerves. No significant difference was detected in the Median and Ulnar nerve conduction velocities in HSMN I ($p > 0.1$) Table 4.10. Statistical analyses were not performed for the other subgroups in Table 4.10 due to their small sample size. HSMN II however, appears to follow the same trend as HSMN I. The proposed 'XL-M' and 'XL-F' how an apparent difference between the aforementioned nerve speeds, and this may be a useful electrophysiological clue for the identification of this subgroup from HSMN I.

Table 4.10 COMPARISON of MEDIAN and ULNAR NERVE CONDUCTION in HSMN groups (m/s)

	HSMN I (n=30)			**HSMN II (n=10)**	**'XL-M' (n=2)**	**'XL-F' (n=4)**
	mCV	m#	SD	mCV	mCV	mCV
MED	20.39	9.58	9.36*	43.7	31.4	46.9
ULN	22.57	8.58	10.45*	46.83	42.1	55.1

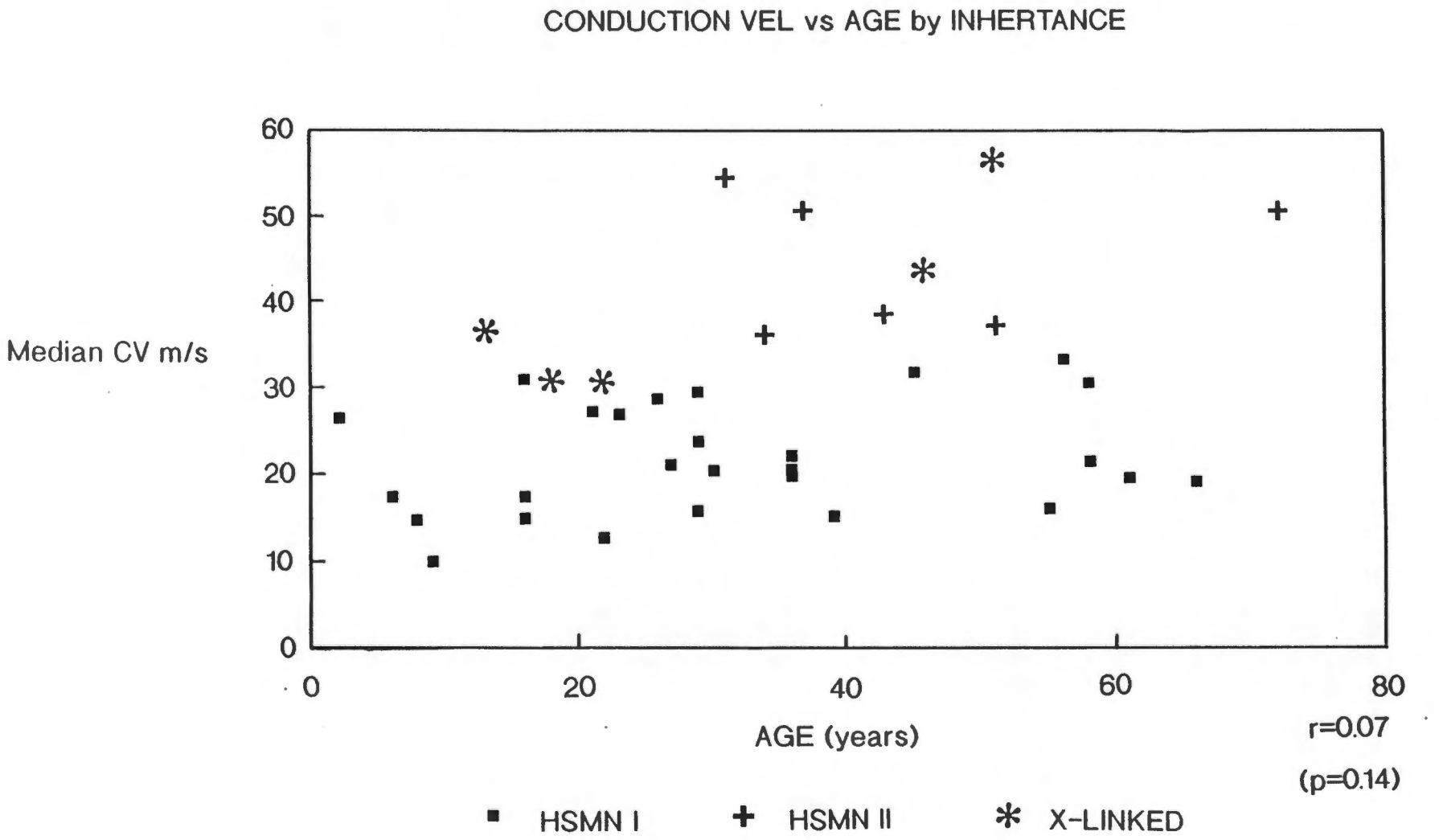
Normal:- MED (Median) CV= 48-66 m/s
ULN (Ulnar) CV= 51-71 m/s

m# = mean (mean normal CV - patient CV)

* $p > 0.1$

There was no significant difference in nerve conduction velocities between the HSMN I propositi and affected members of the same kindred, excluding the 'X-L' cases. (Table 4.11)

Fig V


CONDUCTION VEL vs AGE by INHERTANCE
Median CV m/s
60
50
40
30
20
10
0
0
20
40
60
80
AGE (years)
r=0.07
(p=0.14)
HSMN I
HSMN II
X-LINKED

Indirectly this serves as further evidence against a relationship between nerve conduction speed and disability if the propositus, whom is the individual presenting with the symptoms in the family, is considered the most functionally disabled. In the proposed X-linked family the mean Med CV of the 'XL-M' (propositi) differed from the 'XL-F' cases.

Table 4.11 Median conduction velocity (m/s) in Propositi and Affected relatives

HSMN I	n	mean	SD
Propositi	6	28.20	6,72*
Relatives	19	22.53	9.16*
X-LINKED			
Propositi (male)	2	30.75	0.07
Relatives (female)	3	46.86	8.12

* p= 0.06

No significant correlation between median motor conduction velocity and the age of the affected individual could be shown. (fig. V) (r=0 07; p= 0.14)

The sensory nerve action potentials (SNAP's) were entirely absent in the sensory nerves tested (see section 3) in 24/27 HSMN I cases and 2/9 HSMN II cases. Reduced SNAP's in the upper limbs associated with absent sural nerve SNAP's were found in only 2/27 type I and 4/9 type II cases. In the upper limbs both median and ulnar SNAP's were unrecordable in 25/26 type I and 3/9 type II individuals. An absent SNAP in one of the two aforementioned upper limbs motor nerves, together with a reduced response in the other, was found in 1/27 Type I and 3/9 Type II cases.

In most patients the electromyographic examination consisted of sampling four quadrants in three muscles although some cases could only tolerate needling of 1 or 2 muscles. Needle examination in both HSMN I and II showed fibrillation potentials and positive sharp waves in more than 60% of cases examined, but fasciculations and chronic repetitive discharges(CRD's) were not frequently seen. The motor units are characteristically large, polyphasic and with voluntary activation showed a pattern of reduced recruitment.

Longitudinal studies of nerve conduction speed was only available in a few individuals that had been studied by our department in previous years. Progression of nerve conduction slowing was not observed in any of these patients (Table 4.12) which included an affected male and female from our proposed 'X-L' HSMN I family. In 2 individuals the distal leg CMAP's became unrecordable within a 2-4 year period due to progressive denervation of the distal foot muscles.

Table 4.12 Longitudinal data of nerve conduction velocity (m/s)

Patient		CPER CV	MED CV	Ulnar CV
R V_2	1976	19	nd	18
	1979	22	nd	19
	1988	17.4	26.4	nd
	1991	nd	27.3	18.6
R IV_2	1976	nd	nd	24
	1991			38.5
I II_2	1983	NR	34.5	44.5
	1991		37.2	50.0
U II_1	1979		36.0	38.0
	1992		35.1	21.6#
B IV_{6*}	1988	29.7	45.3	
	1992	NR	43.4	
B $IV_{1\xi}$	1986	33.3	35	
	1988	NR	30.8	

* X-L F
ξ X-L M
conduction block at elbow
nd- not done
NR- no response

4.8 Genetic Linkage Studies

Duffy linkage analyses were performed in 6 families where more than three affected members from at least two generations, were examined. Family T (Table 4.13) however, had only 2 affected sisters and the family was thus analysed as having an autosomal recessive inheritance pattern. Linkage to chromosome 1 was excluded in family O (LOD scores = -2). The remainder of the families apart from Family L, all showed negative LOD scores. In family L the LOD score showed a tendency toward 0.1 with decreasing recombination fractions.(Table 4.1) Unfortunately the remainder of the family refused to be examined and we could therefore not increase the sample size and thereby get a more definitive result with respect to linkage to chromosome 1 in this family.

Table 4.13 LOD scores for Duffy Linkage Analysis program LIPED (5)

	RECOMBINATION FRACTION(θ)					
Family	0.4	0.3	0.2	0.1	0.05	0
A	-0.01	-0.0	-.14	-0.19	-0.26	-0.34
T*	-∞	-∞	-0.01	-0.01	-0.01	-0.01
R	-∞	-.02	-0.05	-0.09	-0.13	-0.18
H	-0.02	-0.07	-0.19	-0.44	-0.7	-1.9
O	0.03	-0.01	-0.16	-0.49	-0.84	-2.62
S	-∞	-∞	-∞	-0.01	-0.01	-0.01
L	0.02	0.03	0.05	0.06	0.07	0.08

* AR/S family - program applied to AR linkage program. The other families analysed as AD inheritance patterns.

4.9 Discussion:

The HSMN type I and II (Charcot-Marie-Tooth Syndrome) are known to be the commonest encountered familial neuropathies with an occurrence of approximately 36 per 100,000 in studied populations (19). Although the local prevalence is not known, it was interesting to note that a "neuromuscular research program" at a Dutch university hospital only diagnosed 109 patients with HSMN (68 cases with HSMN I) over a 20 year period, compared to our 57 cases in 3 years (23). It is therefore reasonable to presume that the previously defined subgroups of HSMN type I and II are also commonly encountered in the South African white and mixed ancestry ethnic groups. The data interpretation for black patients in this series is extremely difficult as various socio-political factors could be contributing very significantly to the low number of diagnosed cases. HSMN III was not encountered in this series.

Although there is clinical phenotypic heterogeneity in both HSMN I and II, the electrophysiologic evaluation is abnormal in the distal limbs of all affected individuals. All the patients that were found to be affected clinically were found to be electrophysiologically affected even though some of them were asymptomatic. Motor nerve conduction slowing in type I individuals may however not be fully developed until 3-5 years of age (24). Patients of this age generally tolerate the examination of at least 1 nerve. I, as well as others have shown that the conduction slowing was uniform in all the electrophysiologically examined nerves and a reasonably confident diagnosis of autosomally inherited type I disease could therefore be made at this age, provided that age appropriate normal conduction speeds are used for comparison. (Table 4.10).

The Median nerve conduction velocity was used for the electrophysiological classification of patients, as the peroneal nerve conduction was often unrecordable due to denervation of the Extensor Digitorum Brevis muscles. The conduction speed segregation point for division of HSMN into Type I and II in this study, differed from previous studies. Evaluating conduction speeds in their populations, Harding et al. (25) and Dyck et al. (9) found segregation occurring at 38 m/s and 40 m/s respectively. This series however shows a segregation point at approximately 33-34 m/s with complete concordance of median conduction speeds in families, excluding the probable X-linked families. (Table 4.2)

I have shown that Med DL measurements in conjunction with Med CV scores improves classification accuracy, particularly when Med CV in a warmed limb falls between 34 to 38 m/s.

Harding (26) found autosomal dominant inheritance to be the commonest mode of inheritance in type I and II, but locally the AR/S pattern was found to predominate in type II families. As I was unable to examine most of the family members in the latter group, I have assumed inheritance patterns on the basis of the history in the majority of the type II cases with the exception of a Xhosa family. In this family 2 out of 4 siblings were affected with unaffected non-consanguineous parents (1 examined; 1 by history; Fig. XI-family T). (Table 4.1)

The HSMN I phenotype has been shown to be associated with at least three chromosomal locations of which the X chromosome and chromosome 1 linkage are the least frequently

encountered. The commonest genotype in type Ia is a gene duplication at band p11.2 on chromosome 17 which is thought results in overexpression of the candidate gene, peripheral myelin protein-22 (PMP-22) (13, 14, 15, 16, 27). PMP-22 is a myelin molecule produced by the Schwann cells in the peripheral nervous system (28).

Sporadic cases may occur if the repeat sequences at 17p11.2 misalign during meiosis resulting in unequal cross-over and submicroscopic gene duplication (29, 30). If the 17p11.2 locus undergoes an interstitial deletion however, the phenotype of hereditary neuropathy with liability to pressure palsy (HNPP) results (31). This suggests that underexpression of the PMP-22 gene results in the predisposition of peripheral nerves to demyelination in response to minor trauma as occurs in HNPP (31). Nerve histology shows unravelling of myelin lamellae in HNPP and the PMP-22 gene may code for a cell adhesion molecule important in maintaining myelin adherence (31). Partial deletion of band p11.2 on chromosome 17 has also been found in patients with an axonal neuropathy, developmental delay, abnormal sleep function and specific behavioural abnormalities (32).

HSMN Ib, an uncommon genotype in previously reported populations, are those families where linkage has been demonstrated to the Duffy blood group marker located on chromosome 1q (17). The LOD score is the logarithm of the odds ratio for linkage of a marker locus with a disease locus, and the conventional LOD score for accepting the linkage hypothesis is a value of 3 at a given recombination distance (θ) (22). We have not demonstrated linkage to the Duffy antigen in any of these South African families although linkage could not be excluded in 1 family (Table 4.12; family N).

A third subgroup of the HSMN I phenotype (X-L) has been shown to be linked to the long arm of the X-chromosome (Xq11-q13) (18, 19). Although this genotype is uncommon with an estimated frequency of 3.6 per 100,000 and our clinical data have not yet been substantiated with DNA analyses, we base our assumptions of a probable X-linked dominant pedigree (fig. VIII) in our series on the following features;

a) no male-to-male transmission in 4 generations;

b) 90% of the females that were found to be affected clinically and electrophysiologically, were asymptomatic;

c) males had slower mean Med CV than the "affected" females and would therefore be classified as type I, yet the females could be classified as type II. This gender difference is apparent in reported X-linked families (33) and was not found in HSMN I or II. It is well documented that despite clinical and symptomatic heterogeneity in HSMN type Ia and Ib, the kinships always display an uniform electrophysiological picture (6, Table 4.11);

d) there was however no significant gender difference in the calculated functional disability between 'XL-M' and 'XL-F individuals. Despite the aforementioned comparable disability scores, the majority of the 'XL-F' subjects were asymptomatic. Although this could suggest a more insidious pathological process in the females with greater functional adaptation and less symptoms, I feel the small sample size and the significantly older age of the females precludes further interpretation.

No distinguishing clinical or electrophysiological features could be determined between males

of HSMN I AD and HSMN I 'X-L' which supports the pathological similarities. Both are characterised pathologically by segmental demyelination and onion bulb formation (33, 34) Prediction of this phenotype can therefore presumably only be made by clinical or electrophysiological examination of the female subjects in the pedigree .

A X-linked recessive form of type I inheritance has also been described and we possibly have such a family in our series as well (19). (see fig. VII)

Autosomal recessive inheritance has been described in HSMN I where scoliosis and teenage wheelchair dependency is said to be common (23, 35). Other features mentioned by the authors such as abnormal motor development from the first year of life with persistent toe walking, clumsiness and poor running, I also found in certain HSMN I AD family members. Such cases were often the product of third or subsequent affected generations. It is unclear without genetic studies, whether this is the result of *anticipation* in these families, or just increasing awareness of "tell-tale" signs amongst family members in subsequent generations. The conduction velocities of these reported HSMN I AR cases are also comparable to this series' HSMN I AD cases, and I suspect that at least some of these presumed AR cases are type I "new" mutations.

It is well recognised that HSMN II also occurs in an autosomal dominant and recessive form as is seen in this series, but the exact chromosomal location is unknown. Some authors have reported a subgroup of HSMN II with recessive inheritance that presented in childhood (usually 18 months to 4 years) and is more disabling (36). Nine of the 22 cases were wheelchair bound in their 2nd or 3rd decade. Some of these children were also found to have optic atrophy, deafness and mental retardation. Even though sporadic or autosomal recessive inheritance is highly represented in this local type II group, I have not encountered cases with the aforementioned phenotype.

The appearance of first symptoms in the 2 subgroups of HSMN was similar to previous series' with HSMN II patients presenting in the second decade and type I in the first. One individual with HSMN type II, however developed his first symptom as late as the seventh decade. Eight percent of the affected HSMN individuals were asymptomatic (age range 9- 31 years) and if the 'X-L' families are included, the figure increases to 17%. Harding (26) also found a substantial number of asymptomatic (>10%) affected individuals. This also highlights the importance of accurate clinical **and** electrophysiological examination in families for genetic counselling and research purposes.

The presence of dysmorphic features particularly distal leg wasting and pes cavus, was a good clinical indicator of affected members, although by no means pathognomonic. These features were also often mild and needed a trained eye to observe them. I did however try and obtain the highest level of objectivity with my interpretations by only accepting "distal leg wasting" if accompanied by unequivocal EDB atrophy, and "pes cavus" if there was arching of the entire plantar surface of the foot off a flat surface. A small number of patients however had normal arches and some even had flat feet.

I did not find any evidence for a separate Roussy-Levy phenotype as tremor was found in 65% of HSMN I cases and was not necessarily present in all the affected members of a particular pedigree.

Mental retardation was found to co-segregate with the HSMN II phenotype in 2 Xhosa sisters with probable autosomal recessive inheritance (fig. XI). Mental retardation was encountered with equal frequency (5%) in affected HSMN I individuals and the examined unaffected family members.

Total absence of deep tendon reflexes was found more frequently in HSMN II whereas Harding (21) found this occurrence more commonly in type I. Scoliosis was found in 2 HSMN I individuals and was not only associated with the AR/S pattern as one case came from an AD family.

Motor examination invariably revealed greater evidence of motor involvement than the patient complained about. The distribution of distal weakness in HSMN I and II was predominantly in the anterior tibial and peroneal compartments. The leg weakness usually did not progress more proximally than the distal thighs. Weakness in fingers usually resulted in clawing. Upper limb involvement proximal to the elbows was not found and have only rarely been reported (37).

Diaphragmatic weakness resulting in positional dyspnoea was found in 1 case of HSMN I. This is an uncommon occurrence in HSMN. Six cases were described from Queens Square Hospital, London, of which 4 were HSMN I and the remaining HSMN II (38). These patients like our case, had advanced disease with severe neurologic disability. It is however important to recognise this complication as measures reducing nocturnal hypoventilation such as a rocking bed or nocturnal positive pressure ventilation, must be instituted if necessary.

Spasticity was not found in any of the HSMN I or II cases. A condition similar to HSMN II but associated with spastic paraplegia, has been previously described (39) but our cases with spasticity satisfied the electrophysiological criteria of HMN (see HMN-MND) and were therefore classified accordingly.

Total functional disability scores and upper limb involvement were both greater in HSMN type II. These findings contrasts with conclusions reached by other groups who found HSMN II to be milder and exhibit less arm involvement (26, 34). One possible explanation for this finding could be our high proportion of presumed autosomal recessive inheritance together with the fact that this pattern of inheritance, at least in HSMN I, is known to be associated with a more disabling phenotype than autosomal dominant inheritance.

Longitudinal electrophysiological data was available in 6 subjects with no apparent change in the conduction velocities of the nerves tested over 2 to 17 years in individual cases. Although the small number of patients precludes statistical analysis, the data supports the previous findings of Gutmann et al. in type I patients (40). Dyck found a small increase of a few meters per second (2-4 m/s) in certain nerves but unfortunately the sample numbers were also small and there were no controls to assess comparative test variation in normal individuals (21).

Most patients had adapted to their disability extremely well including those with upper limb involvement, and some were gainfully employed. A few patients participated in sport or dancing activities up until their 2nd to 3rd decades and disability with respect to ambulation was generally not severe.

Curative therapy is unknown at present. Symptomatic therapy for weakness and ankle

instability is available as orthotic devices. Most patients had to resort to ankle-foot support in their 40's, but only a few required crutches later in life. Only 1 HSMN II patient was not ambulatory and 1 needed a wheelchair intermittently. When weakness in the anterior tibial and peroneal muscle compartments is significantly greater than the plantar flexors, tendon transfers may be considered. Prior to surgery the patient and family should be counselled regarding the progressive, albeit slow, nature of the disease as well as the palliative nature of the procedure. In certain circumstances when foot drop is severe, stabilization of the ankles by arthrodesis may be indicated.

Despite the fact that this group of diseases only produced relatively "moderate" disability with a normal life-span, I encountered a number of individuals that did not want their children to know that they had an inherited disease. Most affected cases indicated that they would make use of antenatal diagnostic tests for genetic analysis if this were available, and furthermore, would be prepared to act on the result. HSMN I is the commonest inherited neuropathy and I feel that we should explore genetic analysis for diagnostic purposes so that counselling may be offered to affected individuals. Currently , prior to the availability of definitive DNA analysis, we have to rely on accurate clinical classification for families requiring genetic counselling, as for example, HSMN II in our population is associated with greater functional disability.

HMN
decade of onset

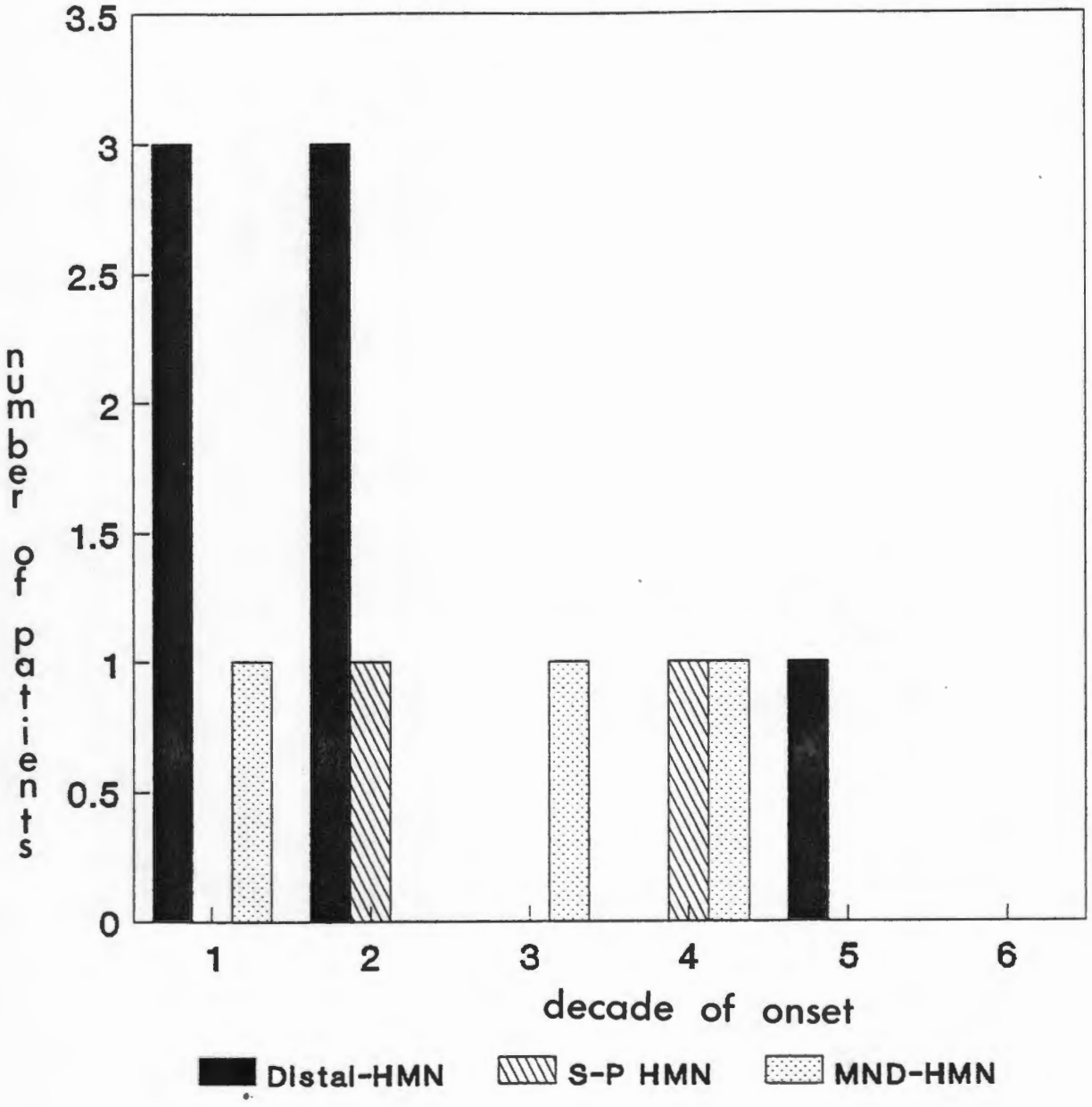


figure VI

5. HEREDITARY MOTOR NEUROPATHIES:

5.1 Results:

There were 12 patients that fulfilled the criteria for Hereditary motor neuropathies (HMN); chronic history of weakness in the legs and electrophysiological evidence of motor nerve involvement with entirely normal sensory potentials in all limbs. This group had a mean age of 35.9 years (SD= 10.61). The hereditary motor neuropathies are a heterogeneous group of disorders. Three distinct phenotypes were identified;

- Distal HMN (n=7);
- Scapuloperoneal (n=2);
- Familial Amyotrophic Lateral Sclerosis (FALS) (Motor neurone disease variant (n=3).

Table 5.1 HMN-subgroups: Racial and sexual distribution:

HMN-subgroup	Race	(n)	Sex	(n)
Distal	W	4	F	5
	M/A	2	M	2
	B	1		
Scapuloperoneal	M/A	1	M	2
	I	1		
FALS	I	2	M	2
	W	1	F	1

5.1 Symptoms:

Symptom onset in the HMN group was generally in the first and second decade (see fig VI) although 1 case presented with symptoms as late as in the 5th decade. Symptoms included ankle instability and clumsiness (50%), weak legs (42%), subjective difficulty with gait and cramps (25%), and patella disclocation (17%). Weak hands was a subjective symptom in 50% of patients, of which 2 experienced the onset from the 3rd decade, 1 in the 4th decade and 3 in the 5th decade respectively. One patient only complained of fatiguability (see below).

Sensory symptoms were present in only 2 individuals; 1 patient with distal-HMN complained of numbness in the toes (less than 10 yrs since symptom onset); and 1 patient in the Scapuloperoneal (S-P) HMN group complained of paresthesiae in the legs immediately after crossing his legs (2 decades since symptom onset).

Table 5.2 : Symptoms in HMN

Symptoms	%	(n=12)
Ankle instability/Clumsiness	50	(6)
Weak legs	42	(5)
Gait difficulty	25	(3)
Cramps	25	(3)
Weak hands	25	(3)
Patella disclocation	17	(2)
Numbness	17	(2)
Fatiguability	8	(1)
Paresthesiae	8	(1)

5.2 Signs:

Examination revealed wasting of the distal legs and pes cavus (58%), scoliosis (25%) and clawing of the toes in 33% of HMN cases. Wasted intrinsic hand muscles were noted in 17% of the HMN group and 1 case had a predominance of upper limb motor involvement compared to the lower limbs.

Clinical evaluation of the motor system in the HMN group showed a mean NDS-W score of 26.55 (SD= 21.05) which did not differ from HSMN I (p= 0.44). Compared to HSMN II, HMN however exhibits less motor weakness (p= 0.05).

The pattern of weakness was similar to the HSMN group with ankle dorsiflexors being at least 25% weaker than the plantarflexors in 75% of cases. In half of these subjects with weaker ankle dorsiflexors, the difference in power between dorsiflexors and plantarflexors amounted to more than 50%. Three individuals whom had no detectable power in the dorsiflexors had at least 50% (MRC grade 3) plantar flexion power. None of the HMN cases showed a reverse pattern of weakness. A curious distribution of hand muscle weakness was seen in 1 S-P case. The thumbs were both flaccid with no detectable power in the thenar extensors. The rest of the hand musculature had at least 50% power including the remaining thenar eminence muscles.

Table 5.3 Signs in HMN

Signs	%	(n=12)
Wasting distal legs	58	(7)
Pes cavus	58	(7)
Wasting forearms	42	(5)
Hammer toes	33	(4)
Scoliosis	25	(3)
Wasting proximal legs	25	(3)
Wasted hands	17	(2)
Short stature	17	(2)
Pes planus	17	(2)
Hand clawing	8	(1)

Clinical sensory examination in the HMN group showed a mean NDS-S of 3.6 (SD= 4.40) which did not differ significantly from the HSMN I mean NDS-S (p= 0.11) but the HSMN II cases were found to have significantly greater sensory dysfunction (p= 0.001; Table 4.8). Five individuals had entirely normal sensory examinations. One of the distal-HMN subjects whom had neither sensory symptoms nor signs on clinical examination however had a large chronic ulcer on the lateral aspect of his 1 foot of several years duration.

Objective gait assessment in HMN showed that 4 patients walked normally; 1 patient had a mild footdrop; 2 needed local support and 1 needed crutches (FALS).

Thickened nerves, tremor or mental retardation were not found in any of the HMN patients.

Normal deep tendon reflexes were found in 4 of the distal-HMN group and none of the patients with HMN had complete absence of deep tendon reflexes.

Total disability appeared to be more severe in the 2 S-P HMN cases (mean NDS-T= 55; SD= 9.99) compared to Distal-HMN (mean NDS-T= 25.14; SD= 19.56) and FALS cases (mean NDS-T= 29.0). A comparison of total disability between HMN and HSMN was not feasible as HMN would be expected to have less sensory disability which is incorporated in the total disability score.

5.3 Electrophysiology:

Med CV was determined in 9 patients with a mean Med CV of 57.6 m/s (SD= 4.38). Common peroneal conduction speed could only be determined in 8 patients (mean CPer 48.8 m/s; SD= 8.2) as 4 cases had either denervated EDB muscles or the CMAP was so small that a proximal response could not be obtained.

Electromyography (EMG) showed typical active chronic neurogenic changes in the examined muscles of 67% of cases with fibrillation potentials and positive sharp waves. CRD'S were more frequently observed than in HSMN. In the majority of cases the motor unit potentials consisted of large polyphasic units with a reduced recruitment pattern. In four of the cases, including both S-P HMN cases, certain localized regions showed an excess of small motor units. Inadequate examination of the muscle may therefore give a false impression of a "myopathic" appearance. However, if at least 4 quadrants of a muscle is sampled, the overall impression will be that of a neurogenic picture with the presence of large (greater than 2mV) polyphasic motor units. These features were confirmed histologically in 1 of the cases. The electromyographic examination of more than 1 trajectory in a muscle is therefore imperative.

Table 5.4 Longitudinal data on conduction velocity (m/s) and CMAP (mV) in HMN:

	CPer CV	*(CMAP)*	*Med CV*	*(CMAP)*	*Ulnar CV*	*(CMAP)*
Case MA:						
1983	NR		65	(12)	60.0	(15)
1992	NR		60.3	(5.3)	53.9	(4.5)
Case MC:						
1984*	51	(0.2)	60.0	(4.0)	nd	
1992	42.7	(0.3)	62.7	(6.5)		

* Performed by MS Schwartz, Dept Neurol., Atkinson Morley's Hospital, UK.

Longitudinal data on nerve conduction velocity was available in 2 cases. (Table 5.4) Both individuals showed a mild reduction in nerve speeds although the actual conduction velocity was still in the normal range at the follow-up evaluation. As expected with a progressive axonopathy, the CMAP amplitude may decrease over several years.

5.4. Distal -HMN:

This was the commonest phenotype in the HMN group and was characterised by distal weakness and wasting in the legs. Associated distal upper limb involvement was found in 30% of cases. One individual with a symptom duration of less than 5 years exhibited predominant weakness and wasting in the distal arms.

Distal weakness was evident in the lower limbs in all but 1 case. This patient was a 30 year old gentleman that had been complaining of increasing exercise intolerance since his second decade. The patient claimed that his exercise tolerance improved dramatically with alcohol ingestion, but this could not be consistently documented in the laboratory using controlled methods such as administering non-alcoholic beer via a nasogastric feeding tube (Dept. Sports Medicine, UCT) He had been serially examined by numerous neurologists who documented progressive ascending areflexia over 2 decades. No objective evidence of weakness could be found on clinical testing, but an EMG and a muscle biopsy showed chronic neurogenic changes. His asymptomatic mother was also areflexic, with no other clinical evidence of motor or sensory dysfunction. His older brother with similar albeit milder symptoms, was also found to be areflexic in the legs.

The majority of the patients presented with symptoms in the first two decades and 1 case experienced his first symptoms in the fifth decade. (Fig. VI)

Fifty-seven percent of the cases had normal deep tendon reflexes in the upper and lower limbs.

Two cases in the distal-HMN group had family histories suggestive of definite AD inheritance. The family histories of two other subjects suggested AR/S patterns but this could not be confirmed. Three of the index cases however had parents with only a history of excessive muscle cramps. The latter were found to be normal on neurological examination and electromyography was refused. Their cramps all responded dramatically to Quinine Sulphate therapy.

5.5 Scapuloperoneal HMN (S-P HMN)

These two cases had weakness and wasting of the distal arms and legs associated with high-riding scapulae and shoulder girdle weakness. The symptoms started in the patients' 2nd and 3rd decade respectively (fig. VI). They exhibited varying degrees of areflexia in the legs and both experienced difficulty with walking. One patient (34 yrs) had bilateral foot drop requiring ankle-foot orthoses, and the other (52 yrs) required the additional assistance of a walking aid for ambulation.

The families of the two S-P HMN cases could not be examined but AD inheritance (3 generations) and AR inheritance (2 affected siblings with unaffected parents and offspring) patterns were highly suggestive on history taking in the 2 respective families.

5.6 Familial Amyotrophic Lateral sclerosis (FALS):

The first case I felt was consistent with a familial form of MND was a 44 year old white male (MP) with a 20 year history of slowly progressive peroneal muscular atrophy and weakness. He has been followed up by this neurology unit for the last 14 years, and I have personally

been unable to document any objective change over the last 2 years. Examination reveals marked peroneal muscle atrophy and weakness associated with proximal hip girdle weakness (predominantly L4,5). He also had unequivocal spasticity in the legs with absent ankle jerks but very brisk knee jerks with clonus. The sphincters, upper limb and bulbar muscles were normal. Sensory examination revealed mild, but unequivocal pain and temperature disturbance in the distal feet with vasomotor changes in the lower aspects of the legs.

Presently he has a waddling gait with bilateral foot drop, and is only able to walk with the aid of crutches and ankle foot orthoses. There is no family history of a similar illness and I have examined one of his two siblings, who is clinically and neurophysiologically normal.

I also encountered 2 siblings from a family of Indian origin where a brother (37 yrs) and sister (34 yrs) both had deafness, short stature, pes planus, scoliosis and peroneal atrophy with unequivocally exaggerated lower limb deep tendon reflexes. There was no history of consanguinity in family.

The reasons for classifying these patients as familial MND are;

a) Chronic history of progressive wasting, weakness and spasticity with electrophysiological evidence of motor involvement only,
b) Clinical evidence of distal lower limb sensory (predominantly small fibre) involvement in 2 cases which excludes idiopathic or sporadic MND,
c) Normal SNAP's electrophysiologically which excludes HSMN.

All 3 cases had the typical pattern of weakness consistent with the "peroneal muscular atrophy" phenotype where ankle dorsiflexors and evertors are disproportionately affected. Case MP also had selective proximal weakness and fasciculations in the myotomes that were affected distally suggesting discrete bilaterally symmetrical spinal cord motor system degeneration. The 2 siblings of Indian origin however exhibited only peroneal and anterior tibial weakness but the normal sensory responses on electrophysiological testing excludes them from the HSMN type V category.

Only one of these 3 patients had mild involvement of the upper limbs with finger flexion weakness (4th decade since symptoms).

5.7 HMN Discussion:

HMN may be clinically difficult to distinguish from HSMN I and II as they are all characterized by predominant motor weakness, but electrophysiologically HMN have normal sensory conductions (10, 41). Motor nerve conductions are usually in the normal range but electromyography shows a chronic neurogenic picture with little or no evidence of active denervation (10).

Consensus has not been reached in the literature regarding the clinical sensory examination

findings in HMN. Authors reporting on distal-HMN ("distal SMA") have only included cases with normal sensation on clinical as well as electrophysiological testing (41). The phenotype of scapuloperoneal HMN is so characteristic that sensory examination is seldom mentioned and in a series of 52 cases of "familial motor neurone disease", 3 cases had clinical evidence of distal small fibre sensory loss similar to our patient (MPI), and a further 5 cases complained of paresthesiae (42).

I have however included patients with mild subjective and/or objective clinical sensory disturbance provided the sensory electrophysiological evaluation was normal, for the following reasons:

a) a significant number of my cases who would have satisfied any other HMN protocol, had either *symptoms* of sensory disturbance which is well recognised in HMN, or minimal, occasionally equivocal reduction of sensation on examination,

b) certain forms of familial motor neuropathy such as the X-linked bulbospinal form ("bulbospinal muscular atrophy"), is now known to pathologically involve primary sensory neurones (43).

The clinical sensory deficit in HSMN I may be very mild and I could not demonstrate a significant difference on clinical sensory testing between HSMN I and HMN (Table 4.8; p= 0.44). The differentiation between these 2 phenotypes could therefore only be made electrophysiologically in most instances. HSMN II and HMN both exhibit the typical electrophysiological features of a motor axonopathy but differ with respect to the latter's normal sensory electrophysiology.

HMN is also phenotypically heterogeneous even within the same family. The prognosis in HMN as in HSMN I is good with the disease showing only slow progression over many decades. Individuals with HMN and HSMN often claim that their disease had not 'progressed' for years to be followed by a subacute deterioration. Certain authors have suggested that the disease process may arrest in some individuals although often only temporarily although I feel this is most likely due to adaptation by the patient to the slow progressive nature of the disease. The patient copes for months to years without noticing any change symptomatically. Relatively *sudden* decompensation is then interpreted as disease progression although it is perhaps only the patient's compensation threshold that is exceeded and a new status quo has to be reached.

5.7.1. Distal-HMN:

Seven cases of distal-HMN was found amongst the 69 cases of familial "peroneal muscular atrophies" (10%). Harding and Thomas (44) found 34 "Distal SMA" cases in a series of 262 (13%) familial neuropathies collected over a decade. Autosomal dominant and recessive inheritance patterns have been observed in distal-HMN families (10).

Individuals usually presents in the 1st and 2nd decade with progressive symmetrical weakness of the distal aspects of either or both upper and lower limbs (41, 44) We had 1 patient where

the wasting and weakness was most prominent in the arms although less than 10 years had lapsed since disease onset. It has been suggested that families with this presentation may represent a distinct subgroup of distal-HMN (45).

Areflexia was much less prominent in distal-HMN than in HSMN I and II.

5.7.2. S-P HMN:

S-P HMN have a pathologically heterogeneous origin which includes myopathy (46, 47); neuropathy (48); and motor neuronopathy (10, 49). Brossard (1886) first described cases with a scapuloperoneal distribution of weakness and Hanel (1890) added this description to the inherited neuropathies (50, 51).

The neuropathic varieties of S-P HMN represents an axonal neuropathy with conduction velocities in the normal range. There has been one report however of HSMN type I presenting with a scapuloperoneal distribution of weakness (37). Autosomal recessive inheritance is common and have an earlier onset and greater functional disability than the less frequently encountered autosomal dominant type S-P HMN (10).

The weakness usually starts in the shoulder girdle and progresses slowly to the anterior tibial muscles and later may involve the pelvic girdle musculature (52). The anterior tibial compartment weakness may be so slow and insidious that the patient may have adapted to their 'clumsiness and ankle instability' and do not complain of these symptoms spontaneously. The patients then presents, as one of ours did, with chronic proximal arm weakness, high riding scapulae and more recent onset of proximal lower limb weakness. Another diagnostic pitfall may be the occurrence of chronic fasciculations in limb muscles. EMG have also not shown concordant results in published series (52) Unwary clinicians, together with a confusing EMG picture (see section 5.3), can therefore lead to a misdiagnosis of muscular dystrophy or motor neurone disease.

Mild facial weakness may be seen in S-P HMN I (10) although facial involvement is more frequently observed in Scapulo-peroneal myopathy (53). I have subsequent to the closure of my database for analysis, encountered such a patient. She had experienced mild progressive symptoms of facial involvement for 4 decades starting initially in the second decade with difficulty in whistling and drinking from a straw. Presently in her 6th decade, she has mild dribbling of food out of the sides of her mouth when eating.

Muscle biopsy is often necessary to contribute to the diagnosis but this will also need an experienced myologist to distinguish primary from secondary muscle changes in this group (52). One of our patients had a confirmatory muscle biopsy (Pathologist: Dr. R Hewlett).

Davidenkow reported a number of patients with scapuloperoneal distribution of weakness, pes cavus and distal sensory loss, accompanied by reduced motor and sensory conduction velocities possibly suggesting a HSMN variant (54, 55). Both our cases (including subsequent case) had normal sensory conductions.

5.7.3. FALS:

The term *Familial Amyotrophic Lateral sclerosis* was coined by the World congress of Neurology in September 1990 for the group of inherited motor system disorders with clinical evidence of lower and upper motor neuron involvement. Others have however also referred to *familial motor neuron disease* (59). The incidence of FALS is generally accepted at between 5% and 10 % of all cases (56). Although most families show an AD inheritance pattern (42, 57, 58) Williams et al (59) found variable penetrance in their Australian AD families with some individuals inheriting the gene without developing the disease.

We are following a woman in her 6th decade who has had signs and symptoms of Amyotrophic Lateral Sclerosis (without bulbar involvement) for at least 5 years and still is leading an active, independant life. Even though her paternal grandfather died of MND we have not included her as an unequivocal familial MND as her father had not displayed the phenotype by the age of 76 years when he died of 'cancer', and we have only been able to follow her disease clinically for the past 4 years. The short disease duration however does not exclude familial MND as the majority of patients in the literature have a disease duration of less than 5 years (42, 58, 60). There is thus marked heterogeneity clinically and prognostically in this group (42, 58, 60).

Cases of "peroneal muscular atrophy with spasticity" have been classified as HSMN V, although some have been attributed to hypertrophic spinal roots impinging on the spinal cord in HSMN I cases (6). Harding published a series of 22 patients with peroneal muscular atrophy and spasticity, of whom only half had absent sensory responses and another third exhibited abnormal sensory responses. Five of the cases included in her series had entirely normal sensory responses as measured electrophysiologically and she justifies grouping these cases with HSMN as 2 cases from the same family each had 'normal', and 'abnormal' SNAP's (61).

6. Concluding remarks in HSMN and HMN:

Due to our ignorance regarding the pathophysiology and genetic basis of most of the familial neuropathies, various classifications have been proposed and used for decades. All the patients that I have described had peroneal muscular atrophy associated with or without other features. I have elected to classify the cases using objective electrophysiological measurements but I do realize that the ultimate classification will be based on the genetic and molecular aspects of these diseases.

I have attempted, particularly in the HMN subgroups, to describe unusual clincal features that I encountered in these patients. I hope this will assist other clinicians when confronted with similar cases. The question of peroneal muscular atrophy with spasticity is contentious and I think that this will ultimately only be settled by the molecular geneticist.

7. HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY (HSAN):

Five cases from 2 different consanguineous marriages were seen with evidence of sensori-motor neuropathy and marked autonomic dysfunction (Fig. XII). There were three affected individuals in family A-K aged 39 years (A-K II1), 44 years (A-K II2), and 49 years (A-K II3). Both siblings A-N II1 (33 years) and A-N II2 (39 years) from family A-N, were affected.

Table 7.1 Clinical features

cases	**A-N II1**	**A-N II2**	**A-K II1**	**A-K II3**	**A-K II2**
sex	M	F	M	M	F
cataracts	+	+	+	+	+
MR	+	+	+++	+++	+++
deafness	-	-	-	+	-
skin lesions	P	-	DP	DP	DP
neuropathy					
pain	+	+	+	+	+
proprioception	+	+	+	+	+
autonomic	++	+	++	++	++
motor	+	+	+	+	+
areflexia	-	-	-	-	-
acral ulcers	-	-	+	+	-

DP - depigmented
P - pigmented

Several clinical characteristics were noted in all 5 cases unless specified (Table 7.1):

a) Congenital cataracts - these were surgically removed in infancy. The patients had markedly reduced visual acuity with pendular nystagmus.

b) Mental retardation - the siblings from family A-K all had profound mental retardation with intelligence quotients (Old South African Individual Scale (OSAIS)(61)) measured as less than 34. The two affected cases in family A-N both had borderline to moderate mental retardation with intelligence quotients (OSAIS) of 84 (A-N II1) and 36-51 (A-N II2). Both individuals could transiently read some Braille in their second decade although they both lost this ability in their third decade due to the progressive small and large fibre sensory neuropathy in their fingers.

c) Freckled skin lesions - 4 cases had approximately 0.5- 1.5 cm freckled lesions predominantly on the dorsal aspects of the forearms. All 3 cases in family A-K had pigmented lesions whereas family A-N II2 had depigmented lesions, in a similar distribution.

d) All 5 cases had microcephaly (head circumference = 50.3- 53 cm), pes cavus, areflexic legs and wasting of the distal hands and feet. Case A-K II3 also had profound hearing loss.

e) A marked distal sensory neuropathy was found in all 5 subjects. The two members of family A-N had severe pain, touch and proprioceptive loss in the legs and fingers. Objective evidence of pain loss was found in family A-K, and although objective proprioception could not be tested due to oligophrenia, this was most certainly present as evidenced by the wide based, high steppage gait exhibited in all three cases. Acral foot ulcers were found in 2 cases.

f) A marked autonomic neuropathy was present in all 5 individuals. Three of the cases (A-K II3; A-K II2; A-N II2) had experienced diarrhoea since the second decade and A-K II1 since the age of 5 years. All 5 individuals showed marked postural hypotension with a systolic drop in blood pressure ranging from 40-60 mm Hg and a diastolic drop between 55-80 mm Hg. The ECG 30 : 15 'R-R' interval ratio was abnormal (1.0) on standing from a supine position (normal > 1.04).

The electrophysiological assessment showed a chronic active distal sensory motor axonopathy in the upper and lower limbs with the nerve speeds either in, or just below the normal range (mean Med CV= 52.2 m/s; SD= 11.9: normal Med CV $\geq$ 48 m/s). Sural, median and ulnar digital sensory nerve action potentials were unobtainable. EMG showed chronic neurogenic changes in the distal upper and lower limbs with large, polyphasic motor unit potentials. Active denervation was present, but less prominent in the hands.

Negative laboratory investigations included;

	cases tested
Blood count	5/5
Liver functions/electrolytes	5/5
Protein electrophoresis	3/5
Hexosaminidase	3/5
B-Galactosidase	3/5
Lipid profile	5/5
Organic acid screen	5/5
Amino acid screen	5/5
Phytanic acid	5/5
Nerve biopsy axonopathy/ no amyloid	1/5
MRI brain-normal	1/5
CT brain-normal	3/5

7.1 Discussion:

These five individuals clearly have the same syndrome characterized by a severe "pan-sensory-autonomic" neuropathy and peroneal muscular atrophy associated with congenital cataracts, mental retardation and skin lesions. One case also had deafness. This particular phenotype has not to my knowledge, been described.

The sensory neuropathy involved large and small fibres with all 5 sujects exhibiting a sensory ataxic gait and the loss of touch sensibility in at least 2 cases. Acral ulcers which are common in neuropathies involving the pain and temperature fibers, were seen in 2 subjects.

The Hereditary Sensory and Autonomic neuropathy (HSAN) group are characterized by an insensitivity to pain with normal power and reflexes and abnormal sweating over the acral regions. Even though peroneal muscular atrophy, mental retardation and hearing loss may be variably associated with HSAN type I and II, these individuals do not develop cardiovascular or gastrointestinal autonomic involvement (63). HSAN III (Familial Dysautonomia) exhibit severe postural hypotension and gastrointestinal motility abnormalities from *infancy* and these cases have normal intelligence without any other of our subjects' dysmorphic features (64).

The Familial Amyloid Polyneuropathies (FAP) characteristicly have autonomic involvement, but they do not show as severe cardiovascular autonomic instability as our patients (65). Furthermore the FAP's do not have the dysmorphic features or teenage onset of our cases. A

nerve biopsy in 1 case did not reveal any evidence of amyloid deposits (Dr. R Bowen, Neuropathology UCT.).

All the known metabolic causes of neuropathies including adult Refsum's disease have been excluded.

Two Dutch sisters were described in 1991 with mental retardation, cataracts, ataxia, deafness and sensory- motor polyneuropathy (66). Two other families with sensory-motor neuropathy including ataxia from proprioceptive loss, as well as associated mental retardation and deafness have also been reported (67, 68). Autonomic involvement, which is so marked in our patients, was however not mentioned in these reports. The Dutch sisters were both older than 50 years of age whereas our cases presented with the earliest signs of autonomic involvement early in their second decades. Furthermore the absence of skin lesions in any of the cases, as well as cataracts in the latter two reports distinguishes our two families from the literature. The authors of the abovementioned cases could also not demonstrate any known metabollic defects.

We thus describe a new autosomal recessive phenotype of severe sensory and autonomic neuropathy with peroneal muscular atrophy, in 2 South African families. These cases resemble the HSAN group although the particular constellation of phenotypic traits peculiar to our patients, have not been previously described.

Acknowledgement: The author wishes to thank Dr. R. Martell (Provincial laboratory for Tissue Immunology) for performing the Duffy blood group screening and LOD score estimation, Dr. J Carr for kindly referring family K for evaluation, Ms. C de Villiers for her assistance with the SSPS computer package and my husband for his constant support.

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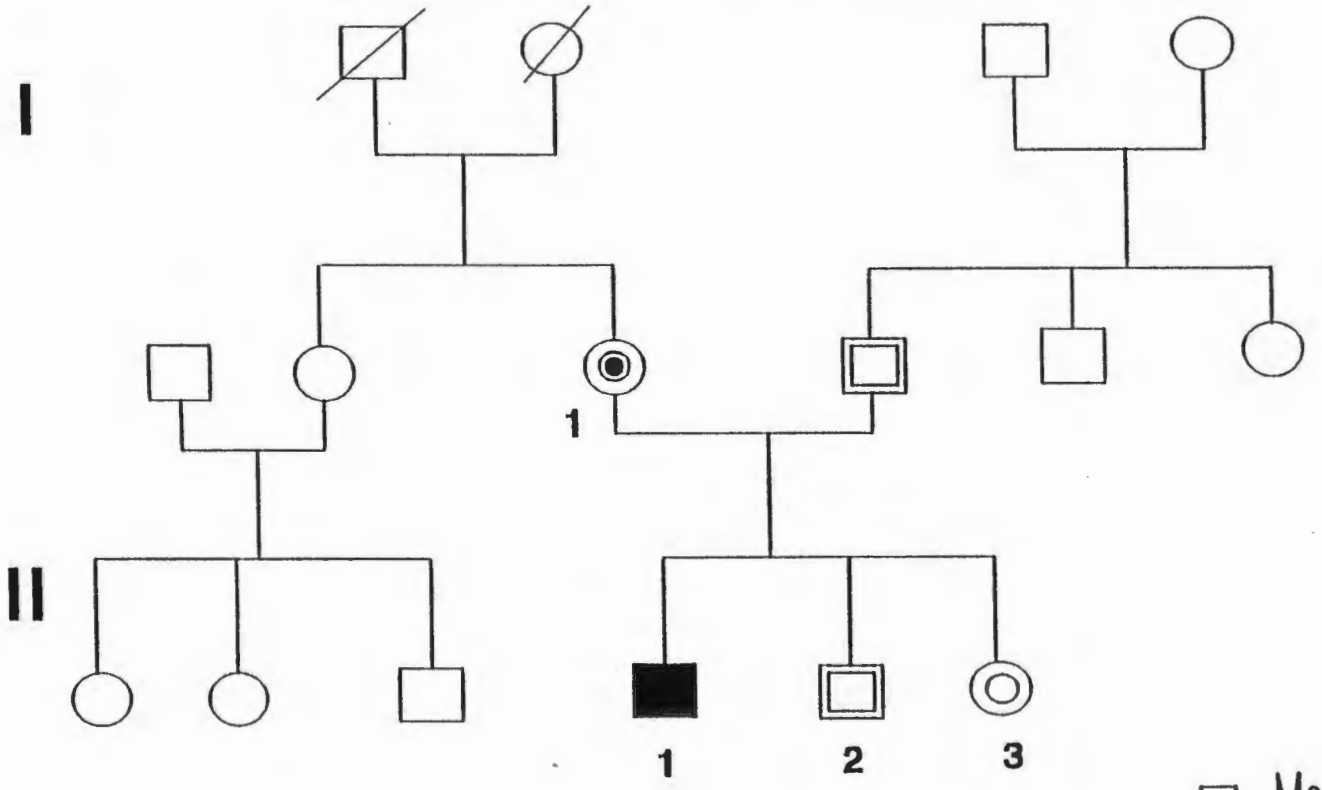
Fig. VII

Family Q : ? X - linked (Recessive)



- Male normal, by history
- Male normal, examined
- Male affected by history
- Male affected, examined
- Female,obligate carrier
- Female affected, examined

Fig.VIII

Family B : ?X-linked (Dominant)

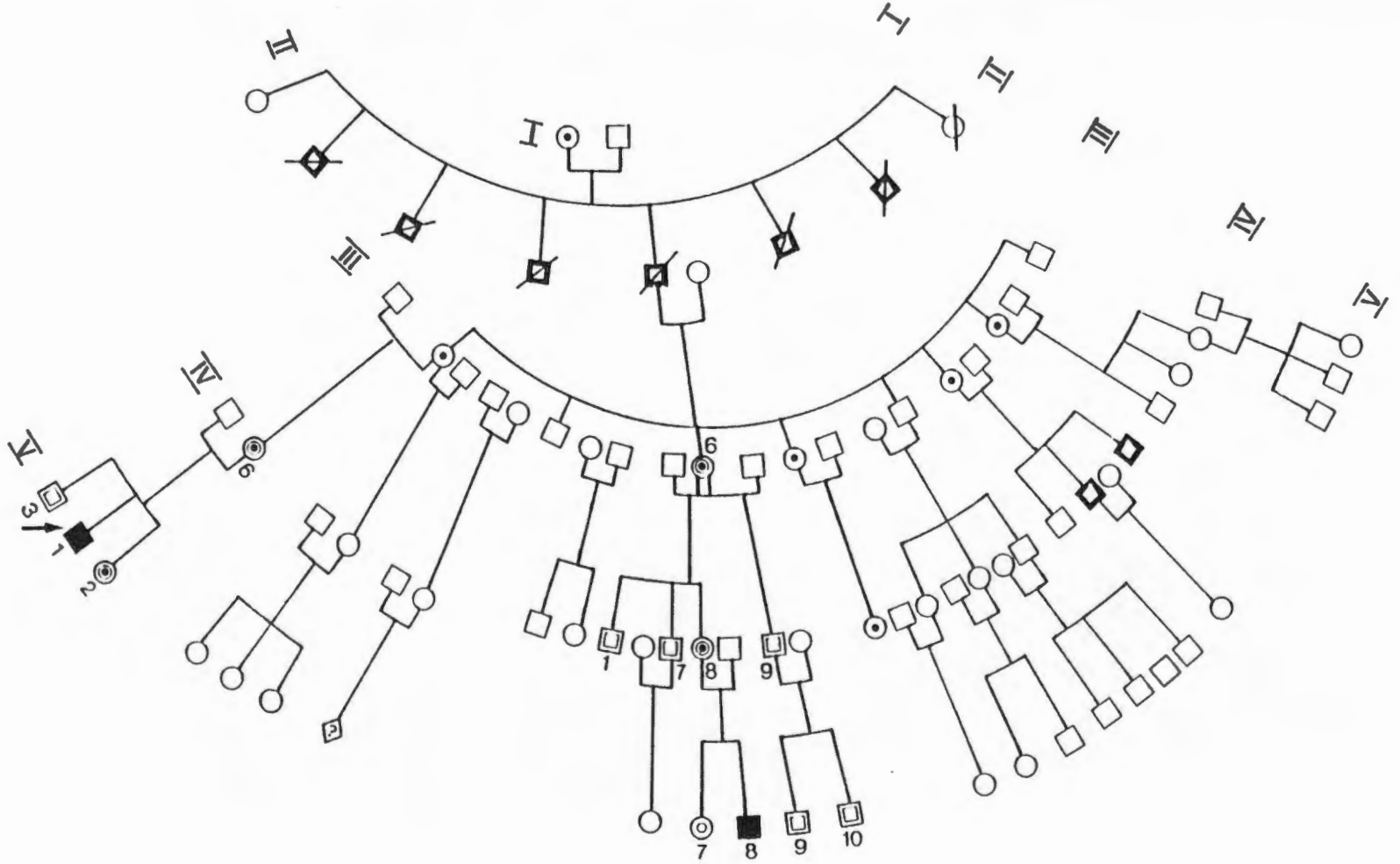


Fig.IX

Family A : Autosomal Dominant

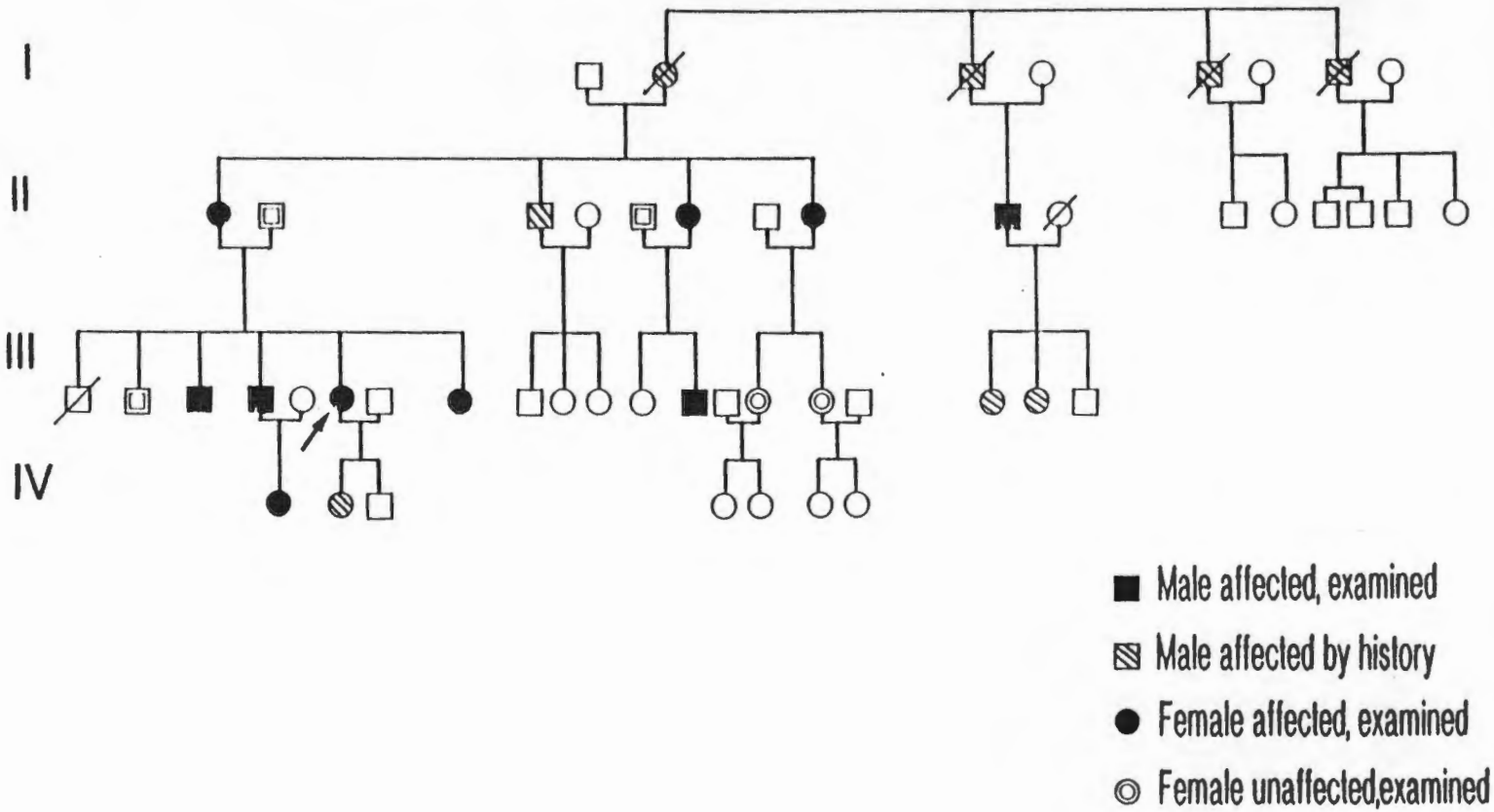
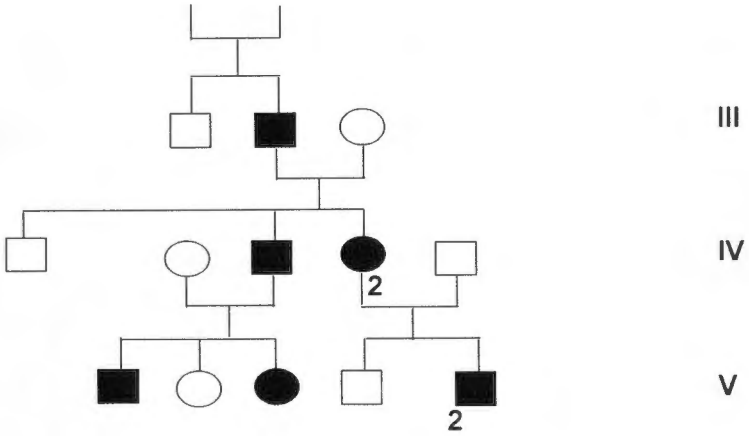
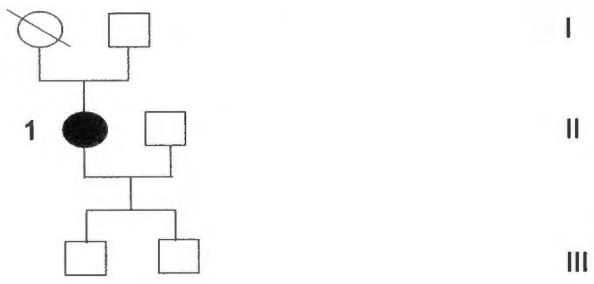


Fig. X

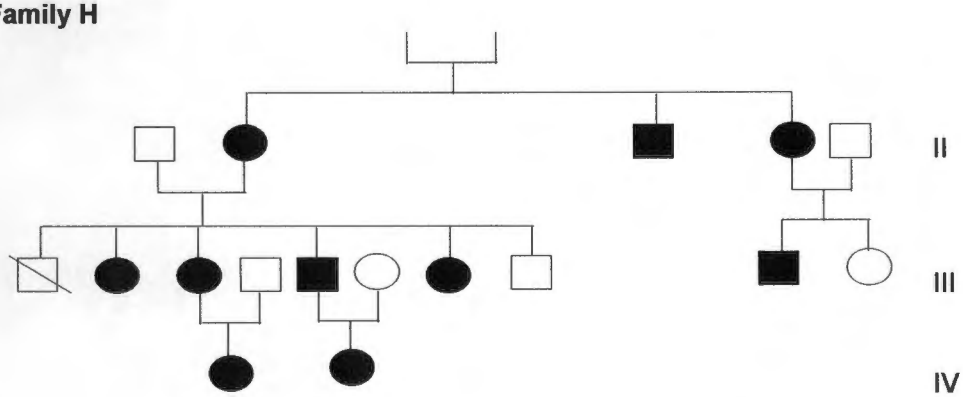
Family R



Family U



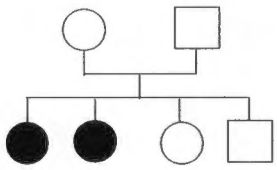
Family H



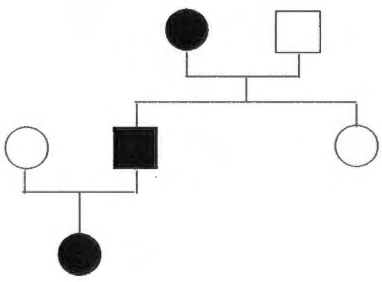
Family I

Figure XI:

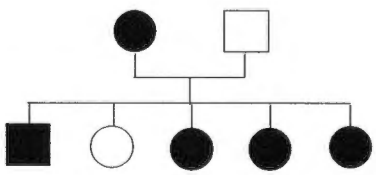
Family T



Family L



Family S



Family O

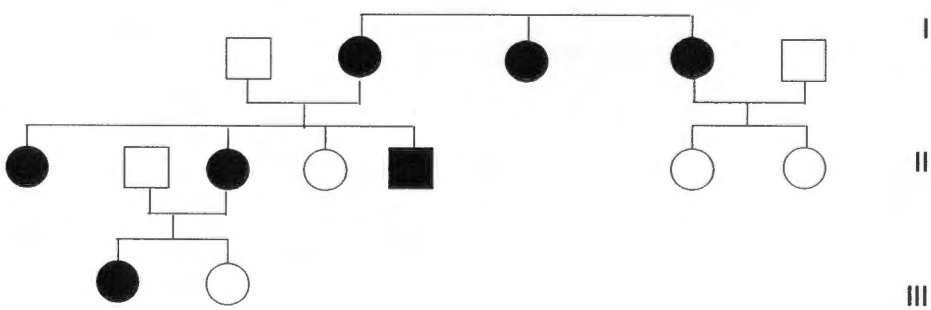
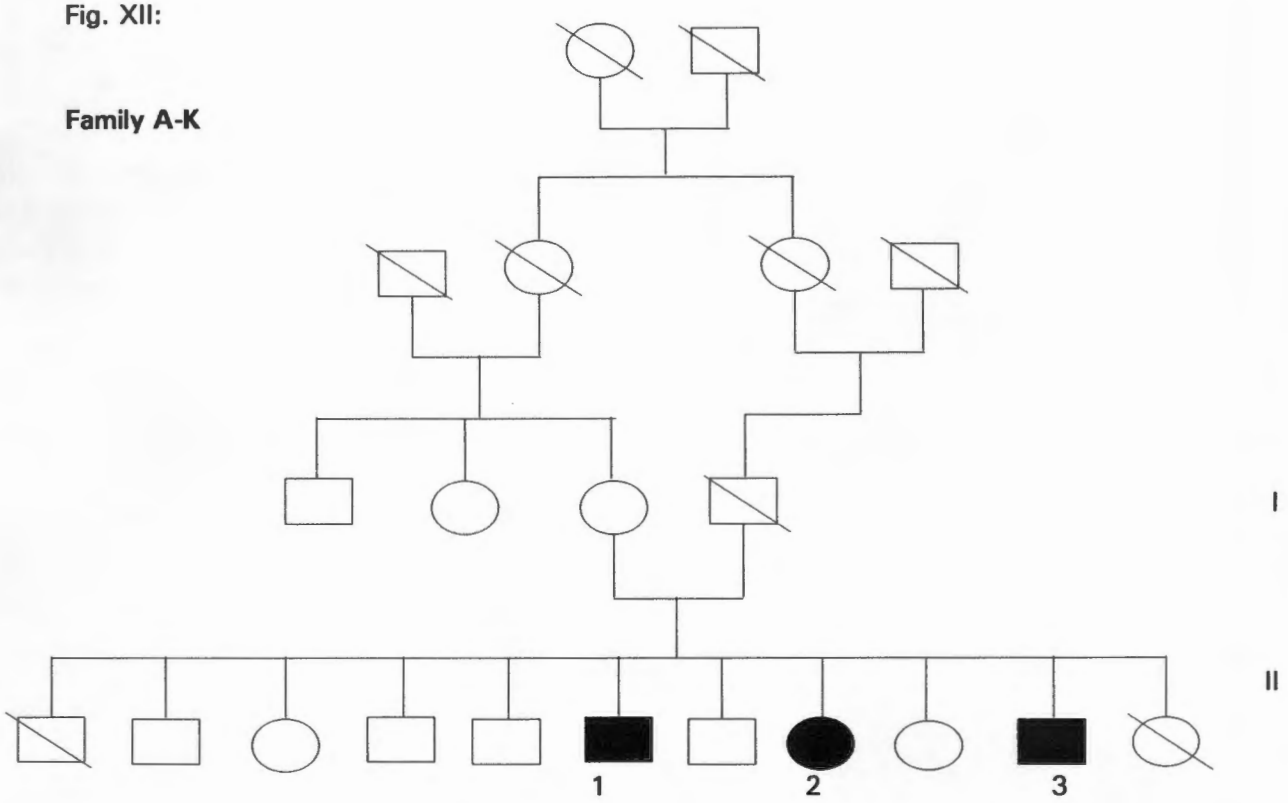


Fig. XII:

Family A-K



Family A-N