MILLER FISHER SYNDROME

THE LOCALISATION OF PATHOLOGY

by

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A thesis submitted for the degree of

Doctor of Medicine (MD)

of the University of Glasgow

Department of Neurology
Faculty of Medicine

JUNE 1987

dedictaed to

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whose enduring encouragement, patience and unselfish assistance have brought this to fruition

and to my parents

who are a continuing source of inspiration to me

DECLARATION

The work reported in this thesis was carried out by myself. Advice was sought from Professor J.A. Simpson.

ACKNOWLEDGEMENTS

I am immensely grateful to my adviser Professor J.A. Simpson for his help, advice, support and guidance. I wish to express my sincere gratitude to my colleague Dr. J. P. Ballantyne for his collaboration and constant encouragement. I am indebted to Dr. Stig Hansen for his technical assistance and to Dr. A. I. Weir for his support. I owe thanks to Dr. David Ramsay for instructions on the pupillometric methods.

I would also like to thank all my colleagues in the Department of Neurology at the Institute of Neurological Sciences, Glasgow for permission to see patients under their care and for their encouragement. The help and support received from colleagues in the Department of Neurological Sciences, St. Bartholomew's Hospital, London is greatly appreciated.

My very special thanks go to Kathleen and John Phillipson who, through their combined expertise in computing and word processing, drafted and typed the thesis with admirable speed and accuracy.

Finally, my deep hearted thanks go to my wife and family who have not only put up with me during this period but also helped me in completing it. Most of the time that I gave to this task was really their time.

SUMMARY

The syndrome described by Miller Fisher (1956) comprises an acute ophthalmoplegia (or ophthalmoparesis) associated with severe ataxia, predominantly of gait and trunk, and a mild to moderate increase in the cerebrospinal fluid protein level unassociated with pleocytosis. As in the Guillain-Barré syndrome, there is usually an antecedent infection commonly of the upper respiratory tract. The illness has a benign course with rapid and usually complete recovery.

The precise nature, aetiology and main site of pathological changes in the Miller Fisher syndrome are not well understood and have been the subject of some controversy. Since neuropathological evidence from typical cases of the syndrome is lacking, due to the benign nature of the illness, hypotheses have been based on clinical observations. Opinions have suggested either that the syndrome is related to acute inflammatory demyelinating polyradiculoneuropathy, or, that it is due to a brainstem inflammatory lesion, or, that both such types of component are present.

This thesis is an attempt to address the question of identification of the main site of action of the pathological process in the Miller Fisher syndrome. Comprehensive multimodal and serial neurophysiological investigations, testing both the peripheral and central nervous system, have been applied to a group of seven typical patients with the syndrome at standardised intervals from onset of the illness up to and after full recovery. The results are compared with those from 20 patients with classical Guillain-Barré syndrome systematically investigated in a

similar way, and with those previously reported in the literature. The findings are then discussed in the context of peripheral versus central nervous system dysfunction.

In the first chapter, a review is presented of a small number of reports of similar cases described incompletely prior to Fisher's original 1956 account, followed by an analysis of 84 patients with the syndrome reported in the literature and by an outline of some of the controversies concerning the underlying pathology. Chapter 2 describes the clinical findings together with the course, laboratory investigations and case analysis of 7 patients with typical Miller Fisher syndrome.

In chapter 3, the neurophysiological methods and the timing of their application are detailed, together with a critical appraisal of their reliability. The investigations used included:

1. electromyography.
2. nerve conduction studies.
3. late response (H-reflex and F-wave) studies.
4. estimation of motor unit numbers and motor unit potentials analysis.
5. peripheral facial nerve and blink reflex studies.
6. computerised quantitative sensory (thermal and vibration) threshold measurements.
7. muscle silent period studies.
8. multimodal evoked potentials (somatosensory, brainstem auditory and visual) studies.
9. electroencephalography.
10. Quantitative pupillometric and pharmacological observations on the pupils.

The results of the neurophysiological investigations and their evolution with time are presented in chapter 4. The findings indicated the presence of a significant dysfunction in the peripheral nerves of the limbs, the facial nerves and in the postganglionic parasympathetic fibres subserving the pupils. They also provided support for a peripheral disturbance as the underlying mechanism for the ataxia observed in patients with the Miller Fisher syndrome.

The results of comparably timed, similar comprehensive neurophysiological investigation in 20 patients with the Guillain-Barré syndrome for a total period of 18 months are described in chapter 5. The results are compared with those of other studies from the literature.

In chapter 6, the lack of any significant neurophysiological or brain imaging evidence for central nervous system involvement in the group of patients with the Miller Fisher syndrome is outlined.

In the main discussion in chapter 7, the neurophysiological findings in the patients with the Miller Fisher syndrome are critically assessed and compared with those from the patients with the Guillain-Barré syndrome in the present study and in reports from the literature. This discussion is set in the context of concepts of peripheral and of central nervous system involvement. Clinical similarities between the Miller Fisher and the Guillain-Barré syndromes are outlined and 20 patients who appear to have overlapping features which suggest a link or continuum between the two syndromes, are reviewed from the literature. The ocular and other signs alleged to represent a brainstem disorder

are discussed and alternative explanations on the basis of peripheral dysfunction are given. Pathological and immunological observations on cases of the Miller Fisher and the Guillain-Barré syndromes providing additional support for peripheral dysfunction are also reviewed and correlated with the neurophysiological results. Lastly, in this chapter, there is an outline of some of the possible differential diagnoses of this syndrome.

In chapter 8 the conclusions are drawn together. The findings of this study and other observations in the literature support the concept that the Miller Fisher syndrome is a variant of acute inflammatory demyelinating polyradiculoneuropathy in which the main manifestations occur in the ocular motor system with overt or subclinical involvement of other parts of the peripheral nervous system. Neither the present study, nor previous ones reported in the literature, provide evidence for a central lesion significant enough to explain the findings of this syndrome. Indeed such a notion is hard to sustain until firm evidence for it is provided in typical cases of the Miller Fisher syndrome.

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ABBREVIATIONS

MFS	Miller Fisher Syndrome
GBS	Guillain-Barré Syndrome
AIDP	acute inflammatory demyelinating polyradiculoneuropathy
INO	internuclear ophthalmoplegia
PDR	pupillary darkness reflex
EMG	electromyography
NC	nerve conduction
EEG	electroencephalography
SDML	shortest distal motor latency
FMNCV	fastest motor nerve conduction velocity
MUAP	motor unit action potential
SNAP	sensory nerve action potential
D-R	direct response (facial nerve,motor)
SP	silent period
SEP	somatosensory evoked potential
BAEP	brainstem auditory evoked potential
PRVEP	pattern reversal visual evoked potential
VPT	vibration perception threshold
HT	heat threshold
CT	cold threshold

INTRODUCTION

In 1956, Miller Fisher reported three cases of an acute neurological illness characterised by total external ophthalmoplegia, severe ataxia and loss of tendon reflexes with a benign outcome without any specific treatment. In all three cases a mild respiratory infection preceded the onset of the neurological illness by a period of 4 - 14 days and in each patient the neurological disease reached its maximum over a period of 3 - 4 days.

The external ophthalmoplegia was complete in two of the cases but in one of them downward gaze was relatively less affected. An almost complete internal ophthalmoplegia with markedly reduced or absent pupillary light and accommodation reflexes accompanied the external ophthalmoplegia in all three patients. Ptosis was present in only two of them. The ataxia was strikingly severe, incapacitating and "*seemed clearly to be of a cerebellar type*". Walking or even self feeding was impossible and yet there was little or no evidence of sensory changes or limb weakness to account for the ataxia and the latter "*was not influenced by eye closure*". The author explained that "*If the cerebellar system is not to be incriminated, one must postulate that in the syndrome herein discussed, a unique, widespread and selective attack on the sensory neurons underlying postural adjustments must have occurred*". However, "*a cerebellar speech was noted*" in none of the cases.

Complete recovery was the rule. This started 7 - 10 days after onset of the illness and shortly after it reached its peak and in all three patients this improvement took 12 - 17 weeks to

complete. The author noted *"the perfect alignment of the eyes during the period of complete immobility"*, the symmetry with which ocular movements occurred during recovery, the restoration of conjugate downward gaze and convergence when conjugate lateral and upward gazes were still severely limited and the less severe involvement of the levator palpebrae muscle and the pupils compared to the external ophthalmoplegia in one patient, observations *"not to be anticipated in lesions of peripheral nerves"* and *"point to a more centrally placed interruption"*. Mild peripheral sensory changes and motor weakness in the same patient, the later development of a complete lower motor neuron type facial weakness with involvement of taste in the anterior part of the tongue, loss of tendon reflexes and above all, the occurrence of a high CSF protein unassociated with pleocytosis have led Miller Fisher (1956) to postulate that these *"provided good evidence that the syndrome was related to the Guillain-Barré type of neuropathy"* and that *"the pathologic process was located in the peripheral part of the oculomotor nerves and merely displayed an unusual symmetry"*. Absence of mental changes and long tract signs were further arguments against a brainstem lesion. Fisher (1956), however, added that *"further observations are necessary to establish this point"*.

Following the description of these cases by Fisher (1956), more than 80 cases have been reported (see chapter 1) involving identical but also some additional features. The precise nature and aetiology of the syndrome is, however, still not well understood. In particular, the localisation of the pathological changes has since then been a subject of a continuing controversy.

Clinicopathological correlation in exemplary cases of the syndrome is lacking due to the benign nature of the disorder. Speculations are, therefore, mainly based on clinical observations. Some authors consider the syndrome to be a part of the spectrum of the acute inflammatory demyelinating polyradiculoneuropathies of which the Guillain-Barre´ syndrome is the most familiar example and believe that the pathological changes are localised to the peripheral nerves or nerve roots (Fisher 1956; Munsat and Barnes 1965; Elizan et al 1971; Guiloff 1977; Ropper 1983). Others implicate a brainstem inflammatory lesion or encephalitis (Bickerstaff 1957, 1978; Al-Din et al 1982, 1985; Meienberg and Ryffel 1983; Meienberg 1984) or a combination of central brainstem and peripheral lesion (Van Allen and MacQueen 1964; Green 1976; Becker et al 1981).

The often profound degree of ataxia without appreciable sensory deficit or motor weakness has raised the question of cerebellar or brainstem cerebellar pathway involvement (Fisher 1956; Bickerstaff 1957; Al-Din et al 1982; Meienberg and Ryffel 1983, Meienberg 1984). Many of the oculo-motor signs have been proposed to represent examples of a central nervous sytem (CNS) disorder (Jampel and Haidt 1972; Keane 1977; Al-Din et al 1982; Meienberg and Ryffel 1983; Meienberg 1984). Arguments in this respect centre mainly around the conjugate nature of occurrence and recovery of ophthalmoplegia, the recovery of upward gaze before horizontal versions, preservation of Bell´s phenomenon despite impairment of voluntary upward gaze, the presence of horizontal dissociated nystagmus (i.e., a syndrome resembling internuclear ophthalmoplegia) and rebound nystagmus and the

observation of mild ptosis in the presence of severe ophthalmoplegia, all alleged to be of a brainstem origin.

Despite the potential value of demonstrating peripheral versus central nervous system disturbance, detailed neurophysiological documentation is strinkingly inadequate in the literature on this syndrome and is confined to a few undetailed reports of conventional nerve conduction and EMG findings with conflicting results (Bell et al 1970; Elizan et al 1971; Guiloff 1977; Becker et al 1981; Al-Din et al 1982). In a single report, however, serial nerve conduction studies in a classical case of this syndrome produced evidence of a mild peripheral nerve disorder in the limbs in the absence of a clinical dysfunction (Jamal and MacLeod 1984). Application of serial comprehensive multimodal neurophysiological tests investigating both the peripheral and central nervous system, from onset up to and after recovery in patients with classical presentation of this syndrome is a good alternative to clinico-pathological correlation in elucidating the patho-physiological changes and the localisation of the lesion (Jamal and MacLeod 1984). This study presents the results of such application in several typical patients with this syndrome and compares the results with those of 20 patients with classical Guillain-Barre' syndrome and with those of the literature. The results are discussed in the context of peripheral versus central nervous system dysfunction. An attempt will be made to characterise this syndrome in terms of the pattern of abnormalities encountered from these serial studies and to differentiate it from more serious pathologies with similar clinical manifestations.

CHAPTER 1

SYNDROME OF ACUTE OPHTHALMOPLEGIA, ATAXIA AND AREFLEXIA: REVIEW OF THE PREVIOUS LITERATURE

The essential features of the Miller Fisher syndrome (MFS) can be summarised as follows. It is an acute bilateral, usually symmetrical external ophthalmoplegia (or ophthalmoparesis) with variable degrees of iridoplegia and ptosis associated with severe ataxia, which mainly involves the gait but sometimes also the trunk and to a lesser degree the limbs, and a generalised areflexia (Fisher 1956; Elizan et al 1971). No mental changes are present and there is commonly no appreciable or only slight motor weakness or sensory deficit. Other cranial nerves may be involved including the 7th, 10th, 9th and 5th in order of frequency (Fisher 1956; Elizan et al 1971; Behan and Geschwind 1973). The illness has a benign course with rapid and usually complete recovery within weeks to months after onset. A slight to moderate increase in the CSF protein unassociated with pleocytosis is usually present and the syndrome is commonly preceded by an antecedent event usually in the form of an upper respiratory infection.

Acute bilateral ophthalmoplegia of the degree exhibited in Miller Fisher syndrome (MFS) is an uncommon event and has long been known to occur in acute inflammatory demyelinating polyradiculoneuropathies (AIDP) but usually in association with severe widespread paralysis of the extremities (Pinckney 1936; Garvey and Slavin 1938; Baker 1943; Dempsey et al 1947; Haymaker and Kernohan 1949). Besides the classical description of Guillain-Barre´ syndrome (GBS) with facial diplegia, Collier (1932)

recognised a four limb peripheral AIDP associated with an external ophthalmoplegia in some of which the eye muscles were severely affected and the limbs only mildly involved. His description was as follows *"a four limbed neuritis associated with external ophthalmoplegia. The malady is apyrexial, painless and rapidly oncoming. In some of the cases ophthalmoplegia is severe and it may be absolute, in so far as the external muscles are concerned, but the internal muscles usually escape, while limb paralysis might be slight, and may be nothing more than slight weakness in the extensors of the periphery, with jerklessness throughout. In other cases, limb paralysis is severe and ophthalmoplegia slight. The cerebrospinal fluid has shown no definite change in all my cases"*. The author also mentioned that recovery was *"rapid and complete"*. Although the description was brief and ataxia was not described, most authors, including Fisher (1956) feel that this is the first clinical description of the syndrome.

In 1937, Guillain described a form of Guillain-Barre´ syndrome in which the cranial nerves were the only site of involvement under the title *"la forme mesocephalique pure"*. Van Bogaert and Maere (1938) reported three cases of *"acute bilateral polyradiculoneuritis cranialis"* as a variant of the same disease. Their cases presented with combinations of ataxia, ophthalmoplegia and areflexia. The authors stated that *"since polyneuritis of the limbs can occur without clinical involvement of the cranial nerves, it seems reasonable to ask whether there might also exist a syndrome of bilateral cranial neuropathy without clinical involvement of the limbs"*. Both of these reports noted the presence of albuminocytological dissociation in the cerebro-spinal

fluid (CSF) and they proposed inclusion of these cases into the GBS (Guillain and Kreis 1937; Van Bogaert and Maere 1938). Several other reports of similar *"ophthalmoplegic forms"* of the GBS have been published in the European literature (Mastrangelo 1939; Massion-Verniary 1940; Maestro 1942; Darcourt and Cossa 1959; Arnould et al 1960). All these cases probably represent cases of the same syndrome, albeit less well documented.

The first detailed report of the syndrome, at least in the English literature, was provided by Miller Fisher in 1956. He reported three cases and referred to another two cases. He described three characteristic features of the clinical picture, namely total external and usually symmetrical ophthalmoplegia, severe ataxia and loss of the tendon reflexes. He established the existence of this condition as a distinct clinical entity and discussed its possible relation with the GBS. This triad of clinical signs has subsequently been known as the Miller Fisher syndrome (MFS). Since Fisher's account at least 84 cases have been reported. In this chapter they are reviewed and analysed (table 1) and the clinical features of the syndrome and state of present knowledge about it are outlined.

The aetiology and underlying mechanism for both MFS and GBS are unknown. Infections particularly viral (Petch 1949; Eiben and Gersony 1963; Gibberd and Kelly 1964), vaccinations (McIntyre and Krouse 1949; Kisch 1958), serum sickness, collagen disease, dysproteinaemia, leukaemia and visceral carcinomatosis precede about 75% of cases of GBS (Kennedy et al 1978; Ropper and Shahani 1984). A number of cases of GBS follow mononucleosis (Creaturo 1950; Garvin 1953; Gautier-Smith 1965; Jordan et al 1973),

TABLE 1

SUMMARY OF CLINICAL FEATURES OF 84 PATIENTS WITH FISHER'S SYNDROME

Case No	Author (s) & year	Author's case No.	age & sex	M x D (days)	OPHTHALMOPLEGIA						Cranial nerves	ATAXIA	REFLEXES	SENS.		WEAKNESS	CSF		RECOVERY		
					diplopia	extern.	intern.	Ptosis	Bell's Phen.	O C R				Smp	Sn		Ptn	Cells	Onset (days)	dur (wks)	degree
1	Fisher (1956)	1	45 M	3	+	C	+	+	−	−	7	+	−	+	+	+	↑	5	8	12	0
2		2	63 M	7	+	C	+	+	−		−	+	−*	−	−	−			7	7	0
3		3	63 M	6	+	C	+	+	+	−	−	+	−*	+	−	−	N	2	10	13	1
4	Smith & Walsh (1957)	1	38 M	4	+	C	−	+			−	+	↓	+	−	−	↑	4	11	8	0
5		2	63 M	4	+	C	+	+			5 , 7	+	−	+	−	−	↑	0	16	22·5	0
6	Neubert (1958)		19 F	3	−	C	+	−			7 , 9 , 10	+	−	+	+	+	↑	5			0
7	Hynes (1961)		46 F	7	+	C	+	+			5,7,9,10,11,12	+	−	−	−	−	↑	5	16	20	0
8	Goodwin & Poser (1963)		54 M	4	+	C	+	+			5,7,10,11,12	+	−	+	+	+	↑	1	14	31	0
9	Gibberd & Kelly (1964)	1	52 F	10	−	C	+	−			7 , 5	+	−	−	+	+	↑	5	30	38	0
10		2	58 F	3	−	C	+	+			7	+	−	+	−	+	↑	N	30	16	0
11		3	70 F	2	−	C	+	+			−	−	−	−	−	+	↑	N	30	10	0
12	Van Allen & MacQueen (1964)	1	7 F		−	C	+	+			7	+	−	−	+	−	N				0
13		2	62 M		−	C	−	+			7	+	↓	−	−	−	↑				0
14		3	11 F		+	C	+	+	−	−	7	+	−	−	−	+	↑				0
15		4	36 M		+	C	−	+			7	+	−	+	+	−	↑				0
16	Munsat & Barnes (1965)	1	5 M	6	+	C	−	+	−	−	7	+	−			−	↑	5	30	6	0
17		2	20 M		−	I	−	−		−	7	+	+	−	−	−	↑	0	6	20	0

18	Patel et al (1966)	1	80	M		–	C	–	–			–	+	–	–	–	–	↑	N		24	0
19		2	6	F		–	C	–	–			–	+	–			+	↑	N		8	0
20	Gibberd (1970)	5	30	M	7	+	I	+	–			7,10	+	–	+	–	–	↑	0	10	36	0
21	Bell et al (1970)	1	5	M	6	+	I	+	+			7,11	+	–	+	–	+	↑		14	52	1
22		2	12	F	4	+	C	+	+	–		7	+	–	–	–	+	N		16	12	1
23		3	7	F	4	+	I	+	+			–	+	–	–	–	–	N		18	6	1
24	Qugundah&Taylor (1970)		1·8	F	4		C	+	+			7,10	+	–			+	↑	6	14	24	0
25	Elizan et al (1971)	1	27	M	6	+	I	–	+		–	–	+	↓	–	–	–	↑	8	14	13	0
26		2	68	M	8	+	C	+	–			–	–	↓	+	+	–	N	0	17	9	0
27		3	49	M	10	+	C	–	+		–	7,10,11	+	–*	–	+	+	↑	0	42	9	0
28		4	19	M	3	+	C	+	+			7	+	–	+	–	–	↑	0	12	16	0
29		5	39	M	3	–	C	+	+			–	+	–	+	–	–	N	0	42		⊕
30		6	54	M	4	+	I	–	–			–	+	–	+	–	–	↑	3	21		⊕
31		7	57	F	6	+	C	+	+	–	–	–	+	–	+	+	–	↑		16	44	0
32		8	30	M	1	+	C	–	+			–	+	–	–	–	–	N	0	11	28	0
33		9	60	F	2	–	C	+	–			–	+	–	–	+	–	N	32	24	5·5	1
34		10	22	M	2	+	I	–	–	+		5,7,10,12	+	↓	+	+	+	N	1	14		⊕
35		11	56	F	7	–	I	+	–			10	+	–	+	+	+	↑	1	10	4·5	0
36	Adams (1971)		49	M	5	–	C	+	+	–	–	7	+	–	–	+	+	↑	N	21	14	1
37	Yalaz & Selekler (1971)		8	M		+	C	+	+			7,10	+	–	–	–	–	↑	0			0
38	Ashworth (1973)	1	61	F	2	–	C	+	+			7,9,10	+	–	+	+	+	↑	N	7	13	0

TABLE 1 (Cont.)

Case No	Author (s) & year	Author's case No.	age & sex	M x D (days)	OPHTHALMOPLEGIA						Cranial nerves	ATAXIA	REFLEXES	SENS.		WEAKNESS	CSF		RECOVERY		
					diplopia	extern.	intern.	Ptosis	Bell's Phen.	O C R				Smp	Sn		Ptn	Cells	Onset (days)	dur (wks)	degree
39	Ashworth (1973)	2	65 M	3	+	C	–	+			9, 10	+	–	–	+	–	N	N		25	0
40		3	21 F	7	+	I	–	+			–	+	–	+	+	–	↑	N		8	0
41		4	55 F	10	+	C	+	+			7, 9, 10	+	–	+	+	–	↑	N		few wks	0
42		5	59 M	7	+	C	+	–			7, 9, 10		–	+	+	–	↑	N			0
43	Behan & Geschwind (1973)		85 F	1	+	C	+	+	–	–	–	+	–	–	–	+	↑	N	12	12	0
44	Swick (1974)		60 M	6	+	C	+	–			9, 10	+	–	–	–	–	↑	7	8	20	0
45	Rao & Urmila (1974)		5 M		–	C	–	–			7, 10	+	–			–	↑	30			1
46	Davis (1975)		31 M		+	C	+	+	–		7	+	–*	–	–	–	↑	0		8	0
47	Trip & Brett (1975)		6 M		+	C	–	+	–	–	–	+	–	–	–	–	↑	N		20	1
48	Guiloff (1977)	1	70 M	6	+	C	–	+		–	7, 8	+	–	+	+	+	↑	2	14		1
49		2	57 M	2	+	–	+	+			7, 8	+	–	+	+	+	↑	0	10	12	1
50	Marks et al 1977		8 M	3	+	C	–	+	–	–	5, 7	+	–	–	–	–	↑	0	9	23	1
51	Okajima et al (1977)		78 F	5	+	C	+	+			7	+	–	–	–	–	↑	6	10	16	0
52	Keane (1977)	1	20 F	5	+	I	+	+	+		7, 9, 10	+	–	+	–	+	↑	N	10	16	1
53		2	27 M	2	+	C	+	+	–	–	7	+	+	–	–	–	N	2	15	15	0
54	Weintraub (1977)		13 F	2	+	I	+	+			7	+	–	–	–	–	↑	11	14	12	0
55	Storey et al (1977)	1	19 M	4	+	C	–	+			7	+	–	+	–	+	↑	3	9	16	0
56		2	58 M	15	+	C	–	+			–	+	–	–	–	–	↑	N	18	2	1

57		3	70	M	5	+	C	–	+			–	+	–	+	–	+	↑	N	28	16	0
58		4	14	M	5	+	I	–	+			7	+	–	+	–	+	↑	N	14	16	0
59	Price et al (1978)		3	M	3	–	C	–	+	–		7	+	–			–	↑	N	14	20	1
60	Derakhshan et al (1979)		7	F	1	–	C	+	+	–	–	7	+	↓	–	–	–	N	0	14		1
61	Blau et al (1980)	1	37	F	3	+	C	–	–			7,9,10	+	–	–	–	+	N	0	15	12	0
62		2	44	M	8	+	C	+	+			7,9,10	+	–	+	+	+	N	0	12	42	0
63	Becker et al (1981)	1	7	F	12	+	C	+	+			–	+	–			–	↑	1	15	8	0
64		2	12	M	6	+	C	+	+	–		–	+	–	–	–	–	↑	125	10	72	1
65		3	2	F	5	+	C	–	+			–	+	–				↑	2	11	5	0
66	Barontini et al (1981)	1	56	F		+	I	–	+	–	–	7,9,10	+	–	–	–	–	↑	2		3	0
67		2	26	F	1	+	I	+	+	–	–	–	+	↓	+	–	–	↑	3			
68		3	25	F		+	I	–	+			9,10	+	–	+	–	+	N	1			⊕
69	Al-Din et al (1982)	3	2	M		–	I	–	–			7	+	–			–	N	N		12	0
70		5	62	M	9	+	C	+	–			5,7,9	+	–	–	+	–	N	N	14	10	0
71		6	18	F	10	+	I	+	–			5,7,8,9,10,11,12	+	–	–	–	+	↑	40	17	13	0
72		11	12	M		–	I	+	+			–	+	–	–	+	–	N	N	12	5	1
73		13	20	M	14	+	I	+	–			9,10	+	–	–	+	+	↑	0	21	12	1
74		15	8	M		–	C	+	–			10	+	–	+	–	–	N	N	14	8	0
75		16	40	F		+	I	–	–			–	+	–	–	–	–	N	N		24	0
76		18	69	F	7	–	C	+	–			10	+	–	+	–	+	↑	0	10	12	1
77	Keane & Finstead (1982)		15	M	3	+	I	–	+	+		7,10	+	–	–	+	–	↑	10	8	8	0

TABLE 1 (Cont.)

Case No	Author (s) & year	Author's case No.	age & sex	MxD (days)	OPHTHALMOPLEGIA						Cranial nerves	ATAXIA	REFLEXES	SENS.		WEAKNESS	CSF		RECOVERY		
					diplopia	extern.	intern.	Ptosis	Bell's Phen.	OCR				Smp	Sn		Ptn	Cells	Onset (days)	dur (wks)	degree
78	Ropper & Shahani	(1983)	43 M	4	–	C	+	+			7	+	–	+	+	+	N	2			
79	Meienberg & Ryffel	(1983)	59 M	4	–	I	+	+	–	–	–	+	–	–	+	–	↑	2	14	29	1
80	Jamal & McLeod	(1984)	57 M	4	+	I	+	+	–	–	–	+	–	–	–	–	↑	0	7	30	0
81	Phillips et al	(1984)	67 F	4	+	C	+	+			7, 10	+	–	+	+	+	↑	3	Died at 27 days		
82	Al-Din et al	(1985)	33 M	5	+	C	+	+			–	+	–	+	+	–	↑	0		12	0
83	Schapira & Thomas	(1986)	33 M	7	+	I	+	–			7	+	–	+	–	+	↑	0	21	12	1
84	Vincent & Vincent	(1986)	58 F	2	+	C	+	–	–	–	–	+	–	–	+	–	↑	4	9	8	0

Blank spaces indicate unavailable information.
For grading of degree of recovery see table 9.

C	:	Complete	+	:	Present
I	:	Incomplete	–	:	Absent
N	:	Normal	↑	:	Increased
MxD	:	Maximum neurological deficit	↓	:	Decreased
OCR	:	Oculo-cephalic reflex	*	:	Asymmetrical

atypical pneumonia (Berlacher and Abington 1958) or acute exanthemas (Taylor and McDonald 1932; Bourne and Scott 1952; Jackson 1961; Marshall 1963; Ropper and Shahani 1984). Table 2 presents a summary of the antecedents described in the patients with MFS. About 80% of the patients reviewed had an antecedent 2-30 (mean = 10.4 ; SD = 7.3) days before the onset of the MFS. This was in the form of an upper respiratory tract infection (24%), sore throat (15.5%) or a flu-like illness (15.5%). A case of MFS following infectious mononucleosis has been reported by Price et al (1978). An insect bite occurred two days before the onset of the syndrome in one patient (Becker et al 1981) and MFS had also developed in another 8 year old boy two days after multiple bee stings (Marks et al 1977). In the latter patient, serum antibodies to myelin were found by immuno-fluorescent staining techniques. Light et al (1977) reported a man with GBS ten days after multiple bee stings and the neurological findings included external ophthalmoplegia, absent deep tendon reflexes, involvement of the peripheral nerves in the extremities and elevated CSF protein level but not ataxia. Antimyelin antibodies were not, however, demonstrated in this case. Delayed hypersensitivity could not be induced in animals by injection of bee venom extract in a study by Saida et al (1977). Peripheral neuritis has been reported following bee stings but these cases usually occur after an interval suggestive of serum sickness (Becker et al 1981). One case of MFS has been reported to occur two days after uncomplicated childbirth (Neubert 1958).

Waksman and Adams in 1955 pointed out the similarity, in clinical and pathological pictures, between the GBS and

TABLE 2

Incidence, type and latent period of the antecedent illness in 84 cases of the Miller Fisher Syndrome reviewed from the literature

Type	Number	Percentage
Any illness	67	79.8%
Upper respiratory tract infection	20	23.8%
Sore throat	13	15.5%
Flu-like illness	13	15.5%
Pneumonitis	3	3.6%
Common cold	2	2.4%
Influenza vaccination	2	2.4%
Diarrhoea & GIT upset	3	3.6%
Mumps virus infection	3	3.6%
Sinusitis	1	1.2%
Infectious mononucleosis	1	1.2%
Child delivery	1	1.2%
"Malaise"	1	1.2%
Bee sting	1	1.2%
Insect bite	1	1.2%
"Viral syndrome"	1	1.2%
"Systemic infection"	1	1.2%

Latent period (days) between the prodrome and the Miller Fisher Syndrome (n = 57)

mean = 10.44

SD = 7.26

range = 2-30

experimental allergic neuritis in rabbits and this led to the concept of auto-immune mechanisms being involved in the GBS. Subsequent studies suggested that the GBS is produced immunologically, either by a circulating myelinotoxic IgM antibody (Cook et al 1969, 1971; Dubois-Dalcq et al 1971) or by a cell mediated process of delayed hypersensitivity in which peripheral nerve tissue, in particular myelin, is attacked by specifically sensitised lymphocytes (Behan et al 1969, 1972; Currie and Knowles 1971; Rocklin et al 1971; Caspary et al 1971). With a similar temporal relationship to upper respiratory and other infections in 80% of cases of MFS, it is tempting to postulate a similar mechanism. In a single case of MFS, a cell mediated immunity to peripheral nerve but not to central myelin antigens has been demonstrated (Behan and Geschwind 1973).

MFS has been recognised in patients as young as 22 months (Ququndah and Taylor 1970) and as old as 85 years (Behan and Geschwind 1973) but the mean age of the 84 cases described is 36.8 $\mp$ 24 years. Fifty one (60.7%) were male and 33 (39.3%) were female. Maximum neurological deficit in 67 cases with MFS evolved over 1 - 14 (mean = 5.12; SD = 3.0) days.

The typical ocular finding in MFS is a marked external ophthalmoplegia with a variable degree of internal ophthalmoplegia and ptosis. Diplopia was the presenting symptom in 71% of the patients and the diplopia was present in the central position and/or attempted lateral gaze in 64%. In 5% it was present also on attempted vertical gaze. The ophthalmoplegia was complete on examination at one stage during the first few days after onset in 70% of the cases. It was marked in 9.5% and incomplete in 19.3%.

One patient (1.2%) did not develop external ophthalmoplegia throughout the course of his illness but had a degree of internal ophthalmoplegia (Guiloff 1977, Case 2). Ptosis of some degree was present in 71% of patients. Among the cases with ptosis, eyelid drooping was complete in 28% (bilaterally in 24.6% and unilaterally in 3.4%), moderate in 41% (bilaterally so in 39.3% and unilaterally in 1.7%) and mild in 31% (bilaterally in 18% and unilaterally in 13%). Internal ophthalmoplegia, manifested as pupillary involvement, was present in 64% of MFS patients. In these patients with pupillary involvement, 58.5% had complete internal ophthalmoplegia presented as dilated pupils with no reaction to light or near vision while in the remaining 41.5%, internal ophthalmoplegia was incomplete; being marked in half of these cases and mild in the other half. Internal ophthalmoplegia manifested itself most commonly as an increase in the pupillary diameter (96%) and/or a decrease in the light reflex (90.5%) and accommodation reflex (88.7%). In 26% of patients with internal ophthalmoplegia anisocoria was present.

Many of the ocular findings in MFS have been considered by some authors to suggest a supranuclear disorder (Keane 1977; Meienberg and Ryffel 1983; Meienberg 1984). Emphasis has been placed, amongst other features, on the conjugate abnormality of ocular movements and the pattern of ophthalmoplegia in these cases. In about one third of the patients with MFS the external ophthalmoplegia is symmetrical in nature with progressive impairment of conjugate lateral, upward and sometimes downward gaze and in the majority of these, improvement also occurs in a symmetrical manner so that the patient does not have diplopia

throughout the whole course of the illness. Other ocular features alleged to represent central nervous system disorder include preservation of Bell's phenomenon despite impairment of voluntary upward gaze, observed in 4 patients (Fisher 1956; Elizan et al 1971; Keane 1977; Keane and Finstead 1982), presence of horizontal dissociated nystagmus in the abducting eyes similar to the internuclear ophthalmoplegia observed in 14 (16.7%) patients with the MFS (Swick 1974; Weintraub 1977, Keane 1977; Derakhshan et al 1979; Becker et al 1981; Barontini et al 1981; Meienberg and Ryffel 1983), less involvement of downward gaze compared to upward and lateral gaze in 18 patients (Smith and Walsh 1957; Elizan et al 1971; Keane 1977; Derakhshan et al 1979; Barontini et al 1981; Meienberg and Ryffel 1983), rebound nystagmus (Meienberg and Ryffel 1983) and retention of convergence despite the adduction palsy on conjugate gaze (Fisher 1956; Swick 1974; Meienberg and Ryffel 1983). Presence of mild (19 cases) or moderate (25 cases) ptosis and of mild (10 cases) or no (30 cases) internal ophthalmoplegia in association with complete external ophthalmoplegia are other examples of features believed by these authors to reflect a supranuclear disorder (Keane 1977; Meienberg and Ryffel 1983; Meienberg 1984).

Ataxia was a prominent feature in 98% of the patients. In the patients in whom the details of ataxia were given (n=74), gait ataxia (93%) was more frequently observed than limb ataxia (78%) or truncal ataxia (20%). Severity of gait and truncal ataxia was always more and out of proportion to the limb ataxia causing a considerable disability for the vast majority of the patients. The ataxia was clinically indistinguishable from cerebellar ataxia

and was not merely a clumsiness of the limb associated with neuropathy in all the patients. These features of the ataxia and its degree of severity in the presence of slight or no sensory and/or motor deficit clinically, have seriously raised the question of involvement of the cerebellum or its connections in the brainstem as the underlying mechanism rather than a peripheral nerve dysfunction (Al-Din et al 1982; Meienberg 1984). A remarkable feature of this ataxia was, however, the absence of nystagmus or speech disturbance of the kind usually associated with a disorder of the cerebellum or its pathways in the brainstem. Nystagmus was observed in only two patients (2.7%) (Becker et al 1981; Meienberg and Ryffel 1983). None of the patients had a cerebellar type speech disorder. No ataxia was reported in two cases of MFS (Elizan et al 1971, case 2; Gibberd and Kelly 1964, case 3).

Complete loss of all the deep tendon reflexes was reported in 75 (89.3%) of the patients and in 7 (8.3%) patients the reflexes were abnormally diminished. In two patients only (2.4%) no abnormality of reflexes was reported (table 1). The abnormality of reflexes was generalised in all but two patients. In one of them, biceps reflex on both sides was present but lost elsewhere (Schapira and Thomas 1986) while in the other patient only both ankle reflexes were present (Storey et al 1977, case 2). Similar findings were reported in six more patients during the course of recovery following generalised reflex abnormality initially (Gibberd 1970, case 5; Elizan et al 1971, case 3; Storey et al 1977, case 1; Becker et al 1981, cases 1,3; Meienberg and Ryffel 1983). In four patients, asymmetry of reflexes was noted at one

stage in the course of recovery when they were closely observed (table 1).

It is believed that the areflexia in MFS probably indicates a peripheral afferent lesion, albeit insufficient to explain the ataxia alone (Fisher 1956; Elizan et al 1971; Ropper 1983; Ropper and Shahani 1983). Fisher (1956) argued that this reflex abnormality is a manifestation of radicular involvement. An alternative explanation of the hyporeflexia on a basis of involvement of the mesencephalic and upper pontine reticular formation was proposed by other authors (Al-Din et al 1982). This was based on the finding in animals that the rostral portion of the reticular formation has an excitatory and the medullary portion has an inhibitory action on muscle tone and reflexes (Magoun and Rhines 1946; Niemer and Magoun 1947) and that the latter effect is dominant following midbrain and pontine transection (Keller 1945).

Slight limb weakness was present in 32 (38%) patients. Distribution of the weakness was reported in 27 patients and this was proximal in 15 (55.6%) or proximal and distal in 12 (44.4%) patients. Both upper and lower limbs were involved in 21 (77.8%) patients, upper limbs alone in 4 (14.8%) and lower limbs alone in 2 (7.4%) patients. Mild sensory symptoms were reported in 36 (46%) of the patients usually in a distal distribution in the fingers, hand and/or the toes and feet. These sensory symptoms included tingling (76.5%), numbness (32.4%) and pain (5.9%). Sensory signs also in a distal distribution were present in 39% of the cases. Abnormality of vibration was most frequent (71.4%) followed by abnormality of proprioception (46.4%), pinprick

(35.7%), touch-pressure (25%) and temperature (10.7%) sensation. Twelve patients had sensory signs but no symptoms while 18 had sensory symptoms but no signs.

Facial weakness was present in 48 (57%) patients. Its type and distribution was reported in 35 patients. In these, the weakness was of a lower motor neuron type in 34 (97%) patients, being unilateral in 11 (31%) and bilateral in 23 (66%) cases. In a single case "*a mild supranuclear facial weakness was noted on the right when she tried to show her teeth*" (Derakhshan et al 1979). The authors, however, did not present their evidence for this. Other cranial nerves were involved. These included the 10th (31%), 9th (18%), 5th (10%), 11th (6%), 12th (5%) and the 8th (4%) nerves.

CSF abnormalities similar to those observed in the GBS have been found in patients with the MFS (Figure 1). The CSF protein was abnormally increased in 75% of cases, the highest value reported was 5g/l (Elizan et al 1971; figure 1). This was associated with no significant increase in CSF cells in all but four patients with cell counts ranging from 30 to 125 (table 1). In 41 patients with high CSF proteins, and in 10 patients with normal CSF proteins, the time from onset of the neurological illness at which the CSF examination was undertaken, was mentioned. In the 41 patients with abnormal CSF proteins, the examination was performed 2-49 (m=14; SD= 10.7) days after onset and in the 10 patients with normal CSF proteins the CSF examination was performed 3-34 (m=14.5; SD= 9.3) days after onset. Eighteen patients had one CSF value above 100g/l and in these, the CSF examination was performed 7-49 (m=18.5; SD= 12.3)

FIGURE 1

CSF protein values as function of time the test performed from onset of the neurological illness in the cases of the Miller Fisher syndrome reviewed in table 1. Patients in whom the time of examination has not been mentioned are excluded. Each symbol represents a CSF protein value and histograms represent mean values for each week from onset of the the neurological illness. The number of individual CSF protein values in each group is indicated at the top. Histograms with interrupted lines represent groups with a small number of patients or individual CSF protein values.

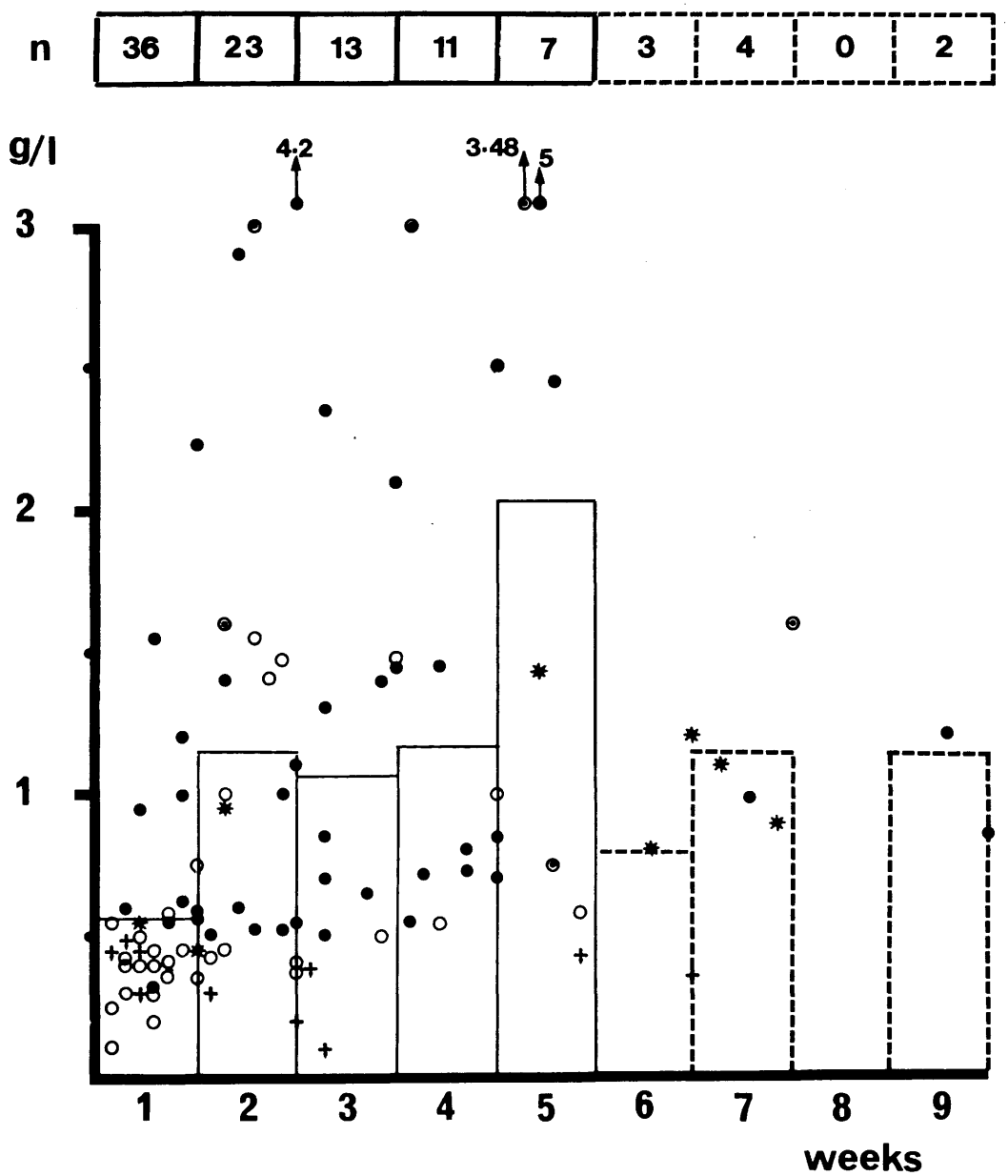
(◉) patients with abnormal values but who had a normal CSF protein earlier the amount of which was not mentioned.

(o) patients whose CSF protein values became abnormal or further elevated in a repeat examination later in the course.

(*) patients whose CSF protein values became normal or decreased in a repeat examination later in the course.

(+) patients with normal CSF protein values but who did not have their CSF examination repeated.

The figure clearly demonstrates that the CSF protein value in patients with the Miller Fisher syndrome is likely to be elevated from the second week onwards and highest values are usually encountered at the 5th week after onset. Most of the patients with normal CSF protein values in the first 2 weeks (and especially so in the first week) showed abnormal values when the test was repeated at a later date.


n
36
23
13
11
7
3
4
0
2
g/l
4·2
3·48
5
3
2
1
1
2
3
4
5
6
7
8
9
weeks

days after onset of the neurological illness. There is, therefore, some indication that higher values of CSF proteins were obtained in those patients in whom the examination of spinal fluid was performed later. Fourteen patients had normal CSF protein values initially but an abnormal rise was detected when sought for later on (figure 1). The occurrence of albuminocytological dissociation is, therefore, important in the diagnosis of the MFS but one should remember its variability and that it may be a very delayed finding. In the typical case there is no increase in cells in the CSF, but a slight pleocytosis may occur occasionally (table 1). These findings are rather similar to those observed in patients with the GBS. In Haymaker and Kernohan's series (1949) 20% of 50 autopsy-proven cases of GBS had CSF protein values within normal limits and in Baker's series (1943), the CSF protein was normal in 21% of 28 cases.

Complete recovery occurred in 98.7% of 78 patients whose follow up was reported. One patient (1.3%) , aged 67 years, died from bronchopneumonia after recovery had started (Phillips et al 1984). Four patients were reported to have a favourable recovery without any details and no information in this regard was available in two cases (table 1). The interval from onset of the MFS after which improvement started was mentioned in 61 cases. This ranged from 6 to 42 (m=15.6; SD=7.7) days. The recovery duration was variable and ranged from 3 weeks to 18 months but the mean duration was 17 + 12 weeks. In all patients improvement started in the ophthalmoplegia and/or ataxia while areflexia was the last to disappear. However, although most of the patients with the MFS follow a benign course some experience severe

weakness of the respiratory muscles leading to respiratory distress (Blau et al 1980). Sudden respiratory muscle paralysis occurred in 6 patients which necessitated tracheostomy and assisted ventilation (Hynes 1961; Gibberd and Kelly 1964, case 1; Elizan et al 1971, case 10; Ashworth 1973, case 1; Blau et al 1980, cases 1 and 2). Careful observation is, therefore, necessary as progression to respiratory paralysis could be rapid (Blau et al 1980).

At least three well documented cases of relapsing MFS have been reported (Van Allen and MacQueen 1964; Schapira and Thomas 1986; Vincent and Vincent 1986). Another two patients claimed that they each had had one attack similar to the one they presented with many years earlier but these were not witnessed (Elizan et al 1971; Barontini et al 1981). The interval between recurrences varied from one year (Schapira and Thomas 1986) to 29 years (Elizan et al 1971). Relapses occur in approximately 3% of patients with the GBS (Thomas et al 1969; Arnason 1984).

The pathogenesis of Fisher's syndrome is as yet not well understood and in particular the location of the pathological changes producing the clinical manifestations has been a subject of continuing controversy since Fisher's report in 1956. Many authors maintain that the relationship of the MFS to the GBS is debatable. Whereas Fisher (1956) and many others (Munsat and Barnes 1965; Elizan et al 1971; Ropper 1983) believe that the syndrome is related to the AIDP and that the pathological lesion is located in the peripheral nerves or nerve roots, other authors implicate a brainstem encephalitis (Bickerstaff 1957, 1978; Al-Din et al 1982; Meienberg and Ryffel 1983; Meienberg 1984). Some

authors claim that the MFS is best explained by a combination of both peripheral nerve and central brainstem involvement producing a mixture of central and peripheral lesions with features referrable to supranuclear pathways in the CNS, the cerebellum and the brainstem in addition to the peripheral nervous system (Smith and Walsh 1957; Van Allen and MacQueen 1964; Green 1976; Price et al 1978; Becker et al 1981).

Many of the clinical features are believed by proponents of the peripheral theory to indicate a disorder of the peripheral nerves. These include the presence of ptosis and diplopia in the majority of patients and of strabismus in some patients in association with the ophthalmoplegia, the identical involvement of reflex and voluntary eye movement on presentation and throughout recovery, the demonstration of asymmetry of reflexes in some cases, the presence of peripheral type of facial weakness, the demonstration of signs of peripheral nerve dysfunction in the limbs and the albuminocytological dissociation in the CSF.

The evidence for CNS involvement in the MFS has been based on other clinical observations; the pattern of ocular involvement, the type of ataxia and CT scan findings in some patients. Many of the oculomotor signs observed in patients with this syndrome have been considered to be due to a supranuclear CNS disorder (Jampel and Haidt 1972; Keane 1977; Meienberg and Ryffel 1983; Meienberg 1984). Much emphasis in this regard has been placed on the conjugate abnormalities of ocular movements at onset and during recovery, improvement of upward before horizontal gaze, preservation of Bell's phenomenon despite impairment of voluntary upward gaze, the presence of horizontal dissociated nystagmus

similar to internuclear ophthalmoplegia and the relative sparing of pupillary reflexes and levator palpebrae superioris muscle in the presence of marked or complete external ophthalmoplegia. All these are held to be of a brainstem origin (Jampel and Haidt 1972; Keane 1977; Meienberg and Ryffel 1983; Meienberg 1984). Moreover, the profound degree of ataxia in relation to the slight sensory and/or motor deficit has raised the question of involvement of the cerebellum or its connections in the brainstem (Al-Din et al 1982; Meienberg 1984). Proponents of the central theory claim additional evidence from CT scan abnormalities observed in three patients with the MFS (Derakhshan et al 1979; Barontini et al 1981; Al-Din et al 1982) (table 3). CT scan findings were mainly in the form of "*a low density abnormality in the medulla*" (Al-Din et al 1982, case 18) or an area of increased contrast in the midbrain extending into the thalamus (Derakhshan et al 1979; Barontini et al 1981) (table 3). Many other CT scan studies in other patients, however, showed no abnormality (Swick 1974; Keane 1977; Price et al 1978; Barontini et al 1981; Keane and Finstead 1982; Al-Din et al 1982, 1985; Meienberg and Ryffel 1983; Jamal and MacLeod 1984; Vincent and Vincent 1986) including special brainstem views (Jamal and MacLeod 1984; Vincent and Vincent 1986). Arguments for speculation on the site of the lesion in the MFS are, therefore, constructed mainly on theoretical bases and clinical observations. As no clinico-pathological correlation of exemplary cases of the MFS is available due to the benign nature of the syndrome, the precise location and nature of the pathological lesion remains undetermined.

TABLE 3

Head CT Scan Findings in patients with the Miller Fisher Syndrome

Author (s) & Year	Author's Case No	Time performed after onset (days)	Result	Site of Abnormality
Swick (1974)		5	Normal	
Keane (1977)	2	?	Normal	
Price et al (1978)		?	Normal	
Derakhshan et al (1979)		14	Abnormal	Midbrain
		28	Normal	
Barontini et al (1981)	1	?	Normal	
	2	8	Abnormal	Midbrain & thalamus
		53	Normal	
	3	?	Normal	
Al-Din et al (1982)	13	?	Normal	
	18	?	Abnormal	Medulla
Meienberg & Ryffel (1983)		8	Normal	
Jamal & McLeod (1984)		7	Normal	
		28	Normal	
Al-Din et al (1985)		?	Normal	
Vincent & Vincent (1986)		?	Normal	

Detailed multidisciplinary neurophysiological investigation of cases of the MFS is lacking in the literature. Only conventional nerve conduction studies have been applied to few patients and reported very briefly. Motor and sensory nerve conduction and EMG studies were reported to be normal in many patients (Gibberd 1970; Tripp and Brett 1975; Marks et al 1977; Storey et al 1977; Price et al 1978; Al-Din et al 1982, 1985; Meienberg and Ryffel 1983). These conventional studies, however, test the distal segments of nerves of the extremities and are especially insensitive to abnormalities in the proximal segments of these nerves (and to disorders of cranial nerves). Moreover they were performed once in each patient in the course of their illness. In a few patients, however, some abnormalities have been recorded by these methods. Elizan and his co-workers (1971) showed "*prolonged distal latencies*" in one patient and Guiloff (1977) demonstrated abnormality of sensory nerve action potentials (SNAPs) in 2 patients. However, it has been claimed that these abnormalities were demonstrated in atypical patients with the MFS who had clinical evidence of marked peripheral neuropathy whereas the majority of MFS patients do not have evidence of such changes clinically (Meienberg and Ryffel 1983; Meienberg 1984). Through serial application of these conduction studies, Jamal and MacLeod (1984) demonstrated, for the first time, convincing evidence of a significant peripheral nerve disorder in a case of the MFS with no clinical evidence of sensory changes or motor weakness. Improvement of the peripheral nerve parameters in our patient followed or accompanied clinical improvement. We emphasised the value of serial measurements in demonstrating evidence of mild but

significant dysfunction of the peripheral nerves in patients with the MFS (Jamal and MacLeod 1984).

Recently, many more sophisticated neurophysiological techniques have been introduced into clinical use. In combination with the conventional methods, these modern techniques have proved useful for the detection, localisation and quantification of various disturbances of function in the peripheral nervous system and neuromuscular apparatus, including those segments of the peripheral nerves inaccessible for examination using conventional methods, and in various pathways in the CNS including the brainstem. These neurophysiological methods represent the physiological counterparts to morphological techniques in neuropathology by autopsy or biopsy. Serial application of such multimodal neurophysiological techniques which test all segments of the neural axis of various systems is likely to contribute substantially towards understanding the pathophysiology and site of the lesion in typical cases of the MFS.

CHAPTER 2

THE MILLER FISHER SYNDROME PATIENTS INCLUDED IN THIS STUDY

During the period of five years since 1982 and following the reporting of one patient (Jamal and MacLeod 1984), seven patients with the MFS have been seen and are included in this study.

Patient 1: A previously healthy 21 year old man presented with sudden onset of double vision, unsteadiness of gait and difficulty of swallowing. Two weeks earlier he had developed a sore throat and abdominal, neck, shoulder and arm pain.

Two days after onset of the neurological symptoms, general medical examination was unremarkable. He had a partial left ptosis and the eyes were held in the primary position of gaze at rest. Eye movements were markedly restricted to all directions on both sides though abduction was relatively less affected. The same movement restrictions were present on attempting Bell's phenomenon and oculocephalic manoeuvres. Diplopia was present in the central position and on lateral and vertical positions of gaze. Both pupils were equally dilated (6 mm) and reacted sluggishly to light and accommodation. He had severe gait and truncal ataxia but minimal incoordination of the limbs and all tendon reflexes were absent but plantar responses were flexor. His speech had a nasal quality and palatal movements were absent but palatal sensation was intact. The remainder of the cranial nerves were normal. There was no abnormality in muscle power nor any sensory deficit of limbs or trunk.

The patient began a spontaneous recovery 12 days after presentation. His gait improved steadily and became completely

normal one month after onset of the illness. Eye movements started to improve at day 18. The improvement was disconjugate in pattern and diplopia remained till 30 days after onset of the illness when virtually no abnormality of eye movements was present on clinical examination with normal pupillary light and accommodation responses. At this stage, however, the patient still had double vision only at the extremes of lateral gaze to each side associated with few beats of nystagmus in the abducting eye on the right lateral gaze. The latter abnormalities disappeared when he was examined 60 days after the onset. Deep tendon reflexes remained absent until the examination 4 months after the onset when they reappeared and 2 months later no neurological abnormality was found.

Patient 2: A 56 year old man who enjoyed good health previously presented with a one day history of severe gait and slight limb ataxia, tingling sensation in the hands, diplopia and bilateral symmetrical drooping of eyelids. Ten days earlier he had a flu-like illness with sinusitis. His neurological symptoms progressed so that 2 days after onset he developed a nasal speech and regurgitation of fluid through his nose and this rapidly progressed to difficulty of swallowing of all kinds of food over the following 24 hours.

On admission, one day after the onset of his neurological illness, general medical examination was normal. He was found to have diplopia especially on lateral gaze to each side with severe limitation of eye movements in all directions on command or on pursuit of a target but no eye deviation was present. Eye movement limitation of the same degree was present on eliciting

Bell's phenomenon and on oculocephalic head manoeuvres. Pupil sizes were normal and equal and they reacted briskly to light and accommodation. His gait was grossly ataxic and he was incoordinate to performing finger-nose and heel-shin tests. Within 24 hours his unsteadiness had deteriorated to such a degree that he was unable to walk unaided and in addition developed severe truncal ataxia. Limb ataxia, however, continued to be slightly abnormal. All tendon reflexes were absent. There was a minimal right sided facial weakness of peripheral type. Sensory system examination revealed no abnormality and muscular power was normal. Two days after admission, he developed severe palatal weakness with intact palatal sensation.

Ataxia and ophthalmoplegia began to improve gradually 10 days after the onset of his neurological symptoms. When examined 10 days later, truncal and limb ataxia had disappeared and the patient could walk unaided though he had an ataxic gait. Ocular motility also improved and some movement in the vertical and lateral gaze positions were possible but he still had diplopia on lateral gaze to both sides. Limitations of voluntary and reflex eye movements were about equal. Ptosis was less severe. Difficulty of swallowing had eased and speech was better. The patient was still areflexic. When reviewed one month after the onset, his ataxia, facial weakness, swallowing difficulty and speech abnormality had all virtually disappeared and no eye paresis was evident on clinical examination but diplopia was still present on extreme lateral gazes and areflexia remained. Two months after the onset, no abnormality was present apart from absent reflexes and in a further two months his tendon reflexes

were normal.

Patient 3: A 15 year old boy developed a flu-like illness with cough and rhinorrhoea. One week later he had sudden onset of blurring of vision which over the ensuing 24 hours rapidly progressed to diplopia associated with bilateral eyelid drooping and unsteadiness of gait. Two days after this, difficulty of swallowing and a nasal quality of speech became evident. His equilibrium impairment increased over the following 24 hours so that unaided standing or walking became impossible and yet he felt no weakness in his limbs.

On admission, 5 days after onset of the neurological illness, general medical examination was unremarkable. Neurological examination revealed round and equally dilated pupils unresponsive to light or accommodation. there was a marked limitation of eye movements on both sides to all directions with complete paralysis of upward movement. Convergence and lateral gazes were absent but a minimum downward gaze was possible. He had diplopia in all directions. Bell's phenomenon and oculocephalic manoeuvres did not elicit further eye movements. Nystagmus was present in the abducting eye on lateral gazes (dissociated nystagmus). A lower motor neurone weakness of the left facial muscles was noted. Marked palatal weakness was present. None of the tendon reflexes could be elicited. There was severe gait and truncal ataxia with inability to walk or sit unaided but only minimal limb ataxia and no abnormality of other cerebellar functions was present. No limb weakness or sensory dysfunction was detected on clinical examination. the patient showed no mental confusion or memory deficit.

Ten days after onset of the neurological symptoms improvement started when ataxia, nasal speech and eye movement abnormality gradually began to recover. Downward gaze improved first and a few days later adduction and convergence began to improve while upward and lateral gazes began to improve only 10 days later. Improvement in reflex and voluntary eye movements was parallel. Examination one month after onset of the MFS revealed complete recovery of speech, minimal gait ataxia and slight left facial weakness. Eye movements were only mildly limited though double vision was present on lateral gazes. A dissociated nystagmus in the abducting eye on lateral gaze to both sides was present bilaterally. Pupils responded sluggishly to light and accommodation. All tendon reflexes were absent. At 2 month examination, only diplopia on extreme lateral gazes and areflexia were present. The former disappeared at 3 months. The reflexes were still absent at 6 month examination but were normal when the patient was re-examined one year later.

Patient 4: This 65 year old man had two attacks of the MFS. His hospital records show that three years before the attack investigated in this study (the second attack), he developed a sore throat followed three weeks later by sudden onset of horizontal diplopia and left sided ptosis of moderate severity. The following day he felt "pins and needles" like sensation in the palms and soles and became unsteady on his feet. On examination, one day after the onset of the neurological illness, he was found to have bilateral external ophthalmoplegia with severe restriction of eye movements in all directions with complete paralysis of abduction and elevation of the right eye. He had reduced palatal

movements with incoordination of swallowing but palatal sensation was normal. His speech was of a nasal character. A bilateral facial weakness was present and both sternomastoid muscles were weak. Upper and lower limbs were a little weak proximally. Vibration sense was reported to be absent at both ankles and reduced at the knees and wrists but other modalities of sensation were found to be intact. There was severe gait and truncal ataxia with incoordination of both upper and lower limbs. The ataxia was, however, believed to be disproportionate to both the sensory and motor changes and of a *"cerebellar type"*. Reflexes were lost in the upper limbs and present, though reduced, in the lower limbs but when re-examined two days later, none of the reflexes could be elicited.

A full battery of laboratory tests on the blood showed no abnormality (see under investigations in this chapter).

Spinal fluid examination, performed three days after onset, showed no abnormality and it remained normal when the CSF was examined one week later. Sensory and motor nerve conduction velocities of the right upper and lower limbs were reported to be *"within the normal limits"* and EMG of facial muscles *"showed no abnormality"*.

Complete recovery from this attack occurred in the following manner: Nine days after the onset of his MFS he started to improve both in terms of severity of ataxia and of ophthalmoplegia. One month later, he had no swallowing difficulty and no facial weakness was present but external ophthalmoplegia, particularly on vertical gazes, was still present and all reflexes were still undemonstrable. He was, however,

found to be fully recovered with no abnormal neurological signs when examined at three months after onset.

In the attack presently investigated, his neurological symptoms developed seven days after a sore throat. Diplopia in central position and bilateral horizontal gazes was followed the next day by nasal speech and regurgitation of fluid through his nose. A day later he developed paraesthesiae in the fingers and toes and unsteadiness of gait.

General medical examination, one day after onset of his neurological symptoms, was unremarkable and his mental status was entirely normal. Neurological examination revealed a little bilateral weakness of both medial and lateral recti and of both vertical gaze movements with unsustained nystagmus of the abducting eye on lateral gazes. There was no ptosis. Pupils were equal in size and normally reactive to both light and accommodation. He had reduced palatal movements but normal palatal sensation. A slight bilateral facial weakness of peripheral type was present. There was a moderate proximal and distal upper limb muscle weakness but normal muscle power in the lower limbs. A patchy diminution of pin prick sensation in both hands and feet in a glove and stocking distribution was present but other modalities of sensation were normal on clinical examination. He had severe gait ataxia but little limb incoordination. Upper limb reflexes were lost while lower limb reflexes were normal.

When examined two days later, there was a marked increase in his palatal weakness and further deterioration in his speech. He was found to have a marked weakness of the left lateral rectus

oculi and all his reflexes, except ankle jerks, were lost. A repeat examination three days later (i.e., the sixth day of neurological illness) showed a marked deterioration in his ophthalmoplegia with severe restriction of eye movements in all directions and complete loss of upward eye movement. Bell's phenomenon was absent and no eye movement was evident to passive head movements. Six days later (twelve days after onset of the neurological illness) the ophthalmoplegia became complete and reflex eye movements were still absent. At this stage a distinct glove and stocking loss of pin prick sensation became evident and vibration sense was lost at the fingers, wrists and ankles and reduced at the knees. All reflexes except the right ankle jerk, were absent.

Improvement started eighteen days after onset. Both eye movement and ataxia started to improve. At this stage the right biceps jerk returned but reduced, leg reflexes were normal on both sides but other reflexes were still lost. Vibration sense was absent to mid arm level bilaterally whereas abnormality of pin prick sensation was unchanged. When he was examined one month after onset of his MFS, the external ophthalmoplegia was nearly resolved but he still had diplopia and dissociated nystagmus in the abducting eye on both lateral gazes no abnormality of swallowing, gait, sensation or reflexes was found. Examination at two months showed no abnormality apart from mild diplopia on extreme lateral and upward gazes which was still present when examined at four months. No abnormality was found when he was reviewed six months after onset of his neurological symptoms.

Patient 5: This 29 year old man developed a dry cough and an upper respiratory tract infection followed after seven days by a progressive unsteadiness of gait and diplopia in all directions of gaze. Three days later he became unable to walk unaided, though he felt that his power was normal, and he noticed a "strange sensation" in his gum and finger tips. He was a non-smoker and only drank alcohol socially.

A general medical examination two days after onset was normal. Neurological examination revealed complete right and partial left palsy of the 6th nerves and one day later he also developed a mild weakness of gaze in all directions, moderate bilateral ptosis (right more than left) and anisocoria with dilatation of the right pupil and normal left pupil but normal light and accommodation reflexes. He had severe gait and truncal ataxia but only slight limb incoordination. All tendon reflexes were lost. Four days after the onset of his neurological illness, he developed mild dysphagia, bilateral facial weakness, an increase in the severity of ptosis and the external ophthalmoplegia became complete although downward gaze was less affected. Bell's phenomenon and oculocephalic responses were absent. No sensory or motor abnormality was found elsewhere. The rest of the cranial nerve examination was unremarkable and mentation and memory remained unaffected throughout his illness.

Thirteen days after onset of the neurological syndrome the ataxia started to improve and gait became less steady and eight days later some improvement in eye movement occurred mainly in ocular adduction (left more than right) and some movement of vertical gaze was retained but the lateral recti were still

paralysed and diplopia in all directions was present. Some improvement in the facial weakness occurred. When examined at one month following his neurological illness, he was found to have bilateral 6th nerve palsy; complete in the right but incomplete in the left eye while all muscles supplied by the 3rd cranial nerves were normal. The patient, however, still had bilateral ptosis and diplopia in all directions of gaze. The right side of the face was completely normal and only slight weakness of the left facial muscles was present. Minimal ataxia was present at this stage but he was still areflexic. Little change was noted a month later but when examined at the end of the following month (three months after onset), no ocular paresis was noted and diplopia was only present in the extreme lateral positions of gaze (probably due to residual lateral recti weakness) and ptosis completely disappeared. He had minimal ataxia and areflexia. A month later complete areflexia was the only abnormality and when re-examined at six months no abnormality was found.

Patient 6: Eleven days following an upper respiratory tract infection, this 57 year old man developed upper abdominal discomfort, shooting pain in the thighs and tingling sensation in the fingers and toes. Four days after this, the patient became unsteady on his feet and this repidly progressed to severe gait ataxia and inability to walk. Two days later (i.e., six days after the onset of first neurological symptoms) he developed bilateral dropping of eyelids, double vision for distance and on lateral gazes, increased tingling sensations which also involved his forehead and lips and a feeling of "dizziness" which he found difficult to describe.

Examination, six days after the onset, revealed normal general medical status. Neurological examination, however, revealed the presence of diplopia on both lateral gazes (suggesting mild bilateral 6th nerve paresis), bilateral ptosis of moderate severity, normal pupils, severe gait and truncal ataxia accompanied by incoordination of the limbs and fine tremor in the distal part of the extremities. Ankle and supinator jerks were lost bilaterally but other reflexes were normal and both plantar responses were flexor. Vibration sense was lost below the ankle, joint position sense was diminished in the toes and pin prick sensation was reduced below the wrist and ankle on both sides. Slight weakness of neck flexion was present but muscle power was normal in the extremities. When examined four days later, he was found to have incomplete bilateral lateral rectus paralysis and all the tendon jerks were lost.

On the 13th day of his neurological illness ophthalmoplegia and neck weakness started to improve and four days later the ataxia began to decrease so that he could stand unaided and walk a few steps. One month after onset, no ptosis was found and his ataxia was much better so that he could walk without help and had only mild unsteadiness. He still had diplopia on extreme lateral gazes although no clinically obvious extra ocular paresis was found. Paraesthesiae disappeared in the toes but remained in the fingers. Reduced pin prick sensation was now confined to the terminal phalanges of the fingers and toes while vibration and joint position senses remained unchanged on testing. At this stage he was still areflexic. No significant further improvement was noted when examined at the two month stage but examination

three months after the onset revealed complete resolution of ocular paresis and disappearance of diplopia and the presence of only minimal ataxia of gait but otherwise no change in his status. Six months after onset examination did not show significant difference. He remained with minimal ataxia, paraesthesiae of the finger tips associated with diminution of pin prick sensation in the toes and fingers, vibration sense below ankle and of joint position sense in the toes. He was completely areflexic.

Patient 7: This 35 year old woman was admitted to another hospital because of diplopia, unsteadiness on her feet, change of voice, weakness of the right leg and numbness and paraesthesiae of her hands and arms, all of sudden onset. Four weeks earlier, she had had a flu-like illness. Examination by the attending physician revealed a *"right sided 6th nerve lesion, gait and limb ataxia, bilateral loss of supinator, knee and ankle jerks and impairment of fine touch sensation in the hands"*. An expanding lesion in the brainstem was *"strongly suspected"* and the patient was referred for further investigation.

General medical examination was unremarkable. Neurological examination (three days after onset) showed complete external ophthalmoplegia, bilateral ptosis of moderate severity, equal and normal sized pupils with normal reaction to light and accommodation and slight bilateral facial weakness. Bell's phenomenon and oculocephalic manoeuvres did not evoke ocular movement. An edrophonium test was negative for myasthenia gravis. Slight proximal right lower limb weakness was present. Sensory deficit included diminished pin prick sensation in the tips of the fingers and toes, reduced temperature (heat and cold)

sensation in the right middle finger and all the toes on both sides, reduced touch pressure sensation in the toes bilaterally, lost vibration sense at and below ankle on both sides and impaired joint position sensation in all the fingers including the interphalangeal and metacarpophalangeal joints bilaterally. Lower limb and triceps reflexes on both sides and biceps and supinator reflexes on the left side were lost whereas biceps and supinator reflexes on the right side were present but reduced. There was severe gait and truncal but mild limb ataxia. Palate movement was reduced but palatal sensation was normal. On the fifth day of her neurological illness she lost all her reflexes and developed difficulty of breathing. She was transferred to the Intensive Care Unit where following an "impending respiratory arrest" she was ventilated and tracheostomy was performed.

Improvement started during the third week of her illness in both opthalmoplegia and ataxia and she was taken off the ventilator on the 15th day. One month after onset, examination revealed normal swallowing and speech, reappearance of some ocular movements, diplopia in all directions and mild ataxia. However, she developed a staph.aureus infection resistant to many antibiotics and this necessitated her isolation for several weeks. When examined two months after onset, she was found to have diplopia but no obvious extraocular paresis, no ataxia and no sensory symptoms but mild impairment of joint position sense in the distal interphalangeal finger joints with normal pin prick, vibration and temperature sensation. The reflexes were still lost. The patient did not attend for further follow up.

INVESTIGATIONS:

Table 4 summarises the CSF findings in the MFS patients of this series, the examination of which was performed 3 - 18 days after onset of the neurological illness. An abnormal rise of CSF proteins ranging from 0.61 to 1.62 g/l was seen in all but case 4. This rise of protein was unassociated with a rise in the cell count and gamma globulin content, abnormal CSF: blood glucose ratio or abnormal CSF pressure. No oligoclonal IgG bands were noted on CSF protein electrophoresis. A significant rise in the CSF proteins was noted when lumbar puncture was repeated a week later in cases 5 and 6.

Normal investigations included blood glucose and glucose tolerance test, full blood count and ESR, serum electrolytes, urea, creatinine, gamma glutamyl transferase, B12 and folate, red cell folate, serum and urine protein electrophoresis, thyroid and liver function test, blood lead and porphyrin screen. VDRL and TPHA tests for syphilis, the indirect FA test for Legionella and Dye test for toxoplasma were negative. No abnormal titres of autoantibodies (nuclear, mitochonrial, thyroid epithelium, thyroid colloid, thyroid microsomal antigens, gastric parietal cell, skeletal and smooth muscles and rheumatoid factors) were found and serum complement levels were normal

A positive IgM antibody to Eptein-Barr virus was found in case 1. Otherwise, paired serum and CSF antibody studies for a range of viruses and virus-like organisms revealed normal titres for cytomegalo virus, herpes simplex, varicella zoster, measles, mumps S, mumps V, influenza A, influenza B, adenovirus, respiratory syncitial virus, Coxsackie, mycoplasma pneumoniae, psittacosis,

TABLE 4

Summary of CSF findings in seven patients with the Miller Fisher Syndrome

Case No	Days After onset	Protein g/l	Gamma Globulin	CSF : Blood Glucose Ratio	Cells per c.mm.	CSF Pressure
1	7	0.8	N	N	0	N
2	3	1.28	N	N	0	N
3	9	0.99	N	N	0	N
4	11	0.36	N	N	0	N
	16	0.43	N	N	2	N
5	4	0.61	N	N	0	N
	11	1.62	N	N	0	N
6	10	0.33	N	N	0	N
	18	1.33	N	N	0	N
7	10	1.35	N	N	0	N

N : Normal

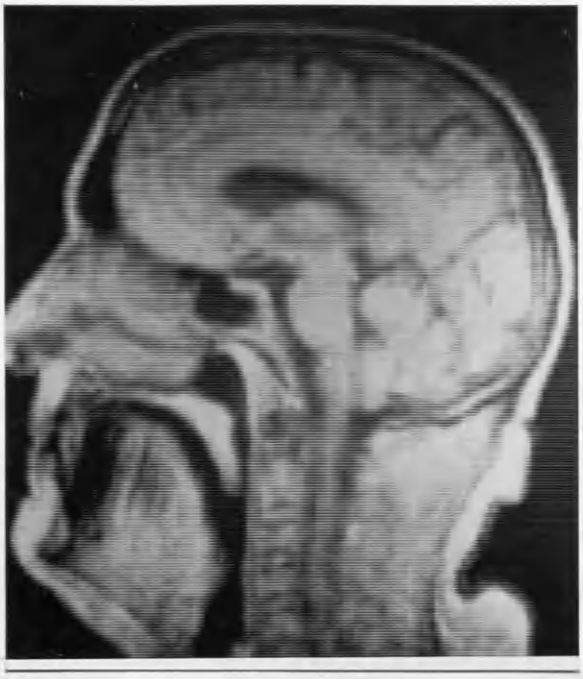
Q-Fever, C.Burnetii and lymphogranuloma venerium.

Plain skull and chest x-rays were normal in all the 7 patients. High definition CT scans of the head with and without contrast enhancement and with special brainstem views were performed at days 10, 6, 9, 14, 14, 10 and 8 for cases 1, 2, 3, 4, 5, 6 and 7 respectively and showed no abnormality. The CT scan studies were repeated for case 7 about 12 days later with normal results. Nuclear magnetic resonance brain scan studies were performed for the cases 4, 5 and 6 at days 20, 21 and 17 of the illness with longitudinal sagittal views of the brainstem and these revealed no abnormality (figures 2,3).

ANALYSIS OF CASES

The constellation of features displayed by these patients and summarised in table 5 makes them typical cases of the MFS. There were 6 men and one woman whose ages ranged from 15 to 65 years. In all 7 cases an antecedent illness preceded the onset of neurological complaints with a latent period of one to four weeks. This was in the form of an upper respiratory tract infection (cases 1, 3, 5, 6), a flu-like illness (cases 2, 7) or a sore throat (case 4). Viral and virus-like agent antibody titre studies on the serum and CSF did not show significant change on paired testing in 6 cases. In case 1, a positive Epstein-Barr virus IgM test suggested a recent infection with that virus.

The neurological syndrome developed to its height over a period of 2 to 6 days. Presenting symptoms in decreasing order of frequency were diplopia (all patients), ataxia (6 patients), ptosis (3 patients), difficulty of swallowing (2 patients) and dysphonia (1 patient). Cases 1 - 7 had external ophthalmoplegia;



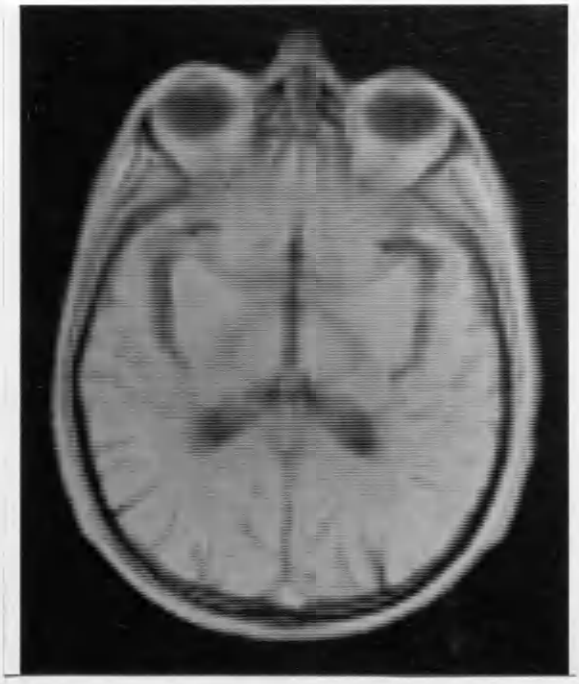
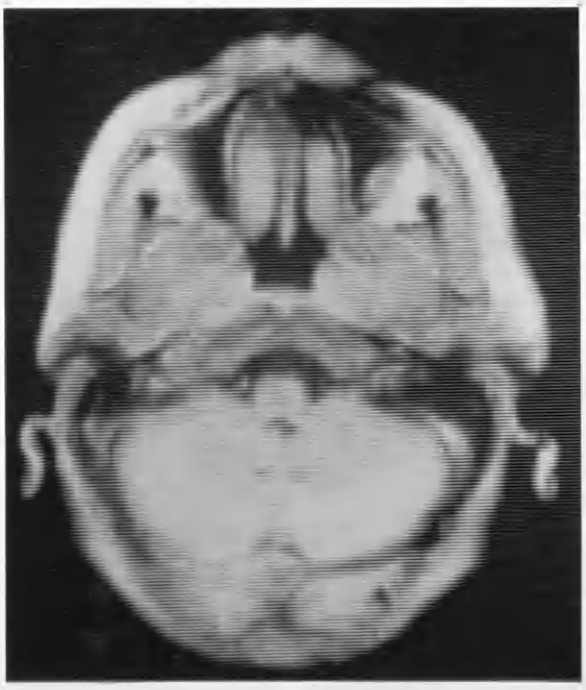
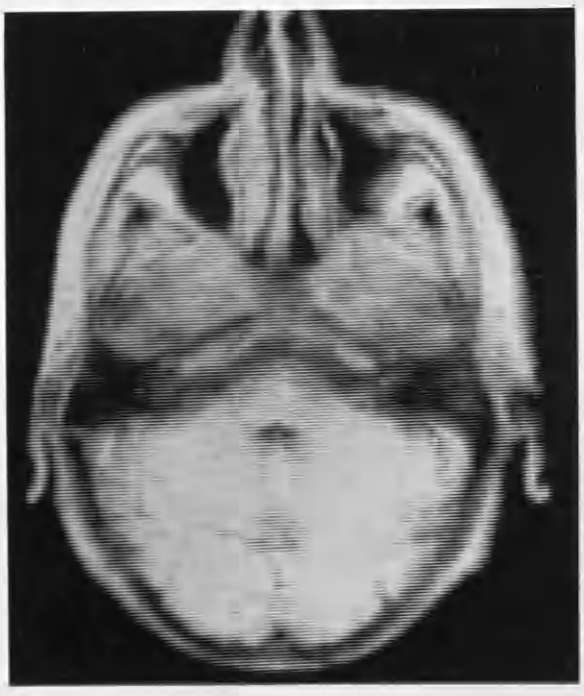
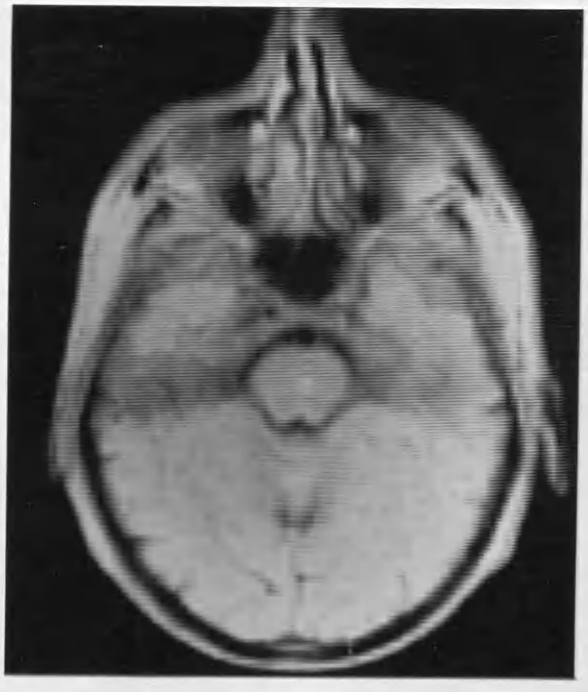


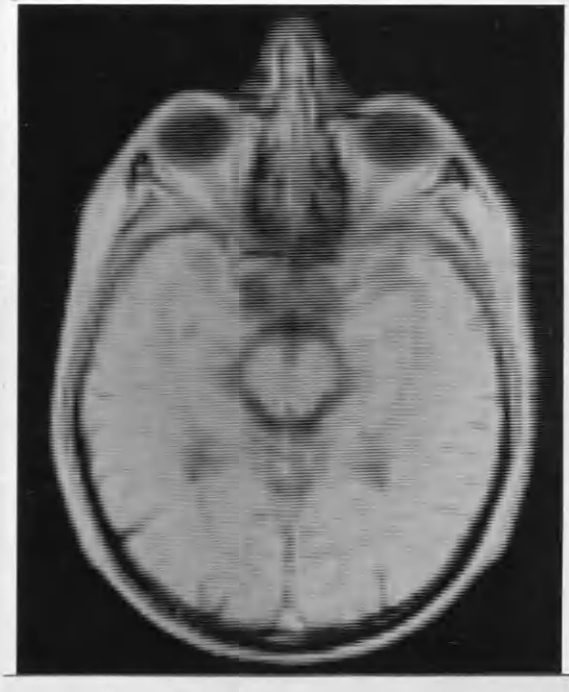
FIGURE 2

Nuclear magnetic resonance (NMR) head scans in case 4 with the Miller Fisher Syndrome performed 20 days after onset of the neurological illness. No abnormality is noted.









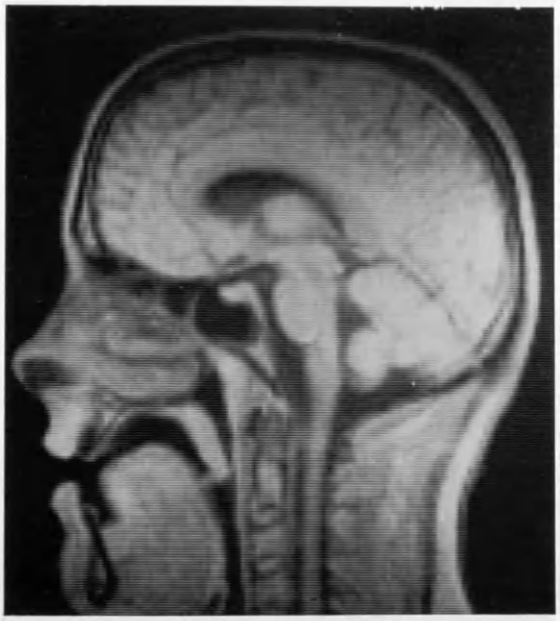
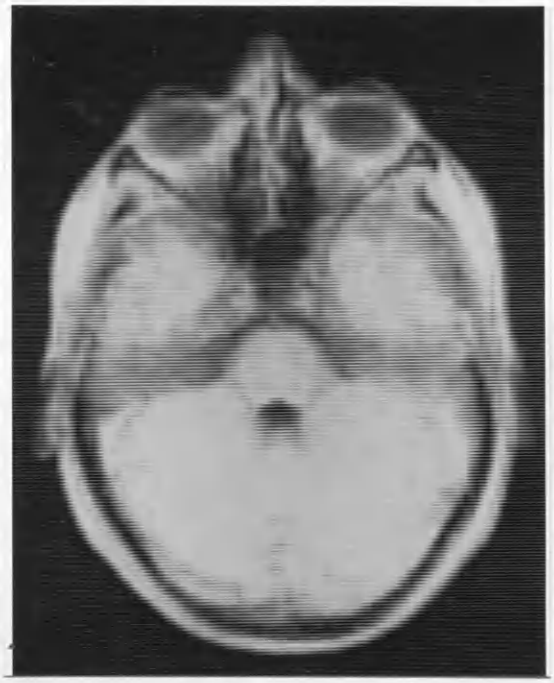
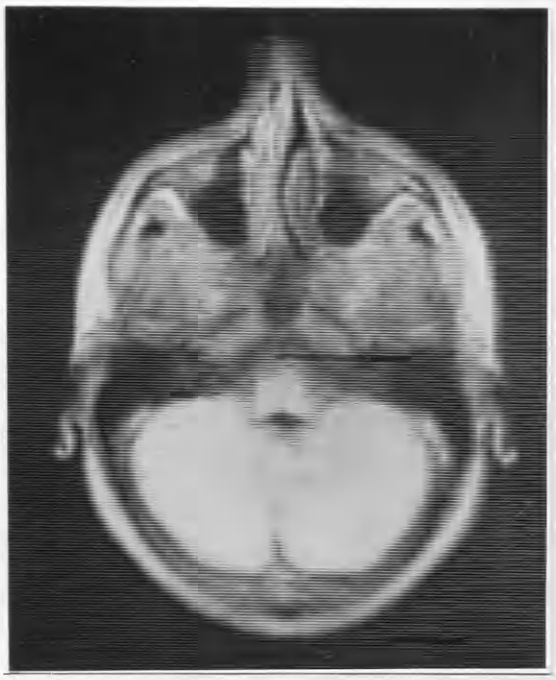
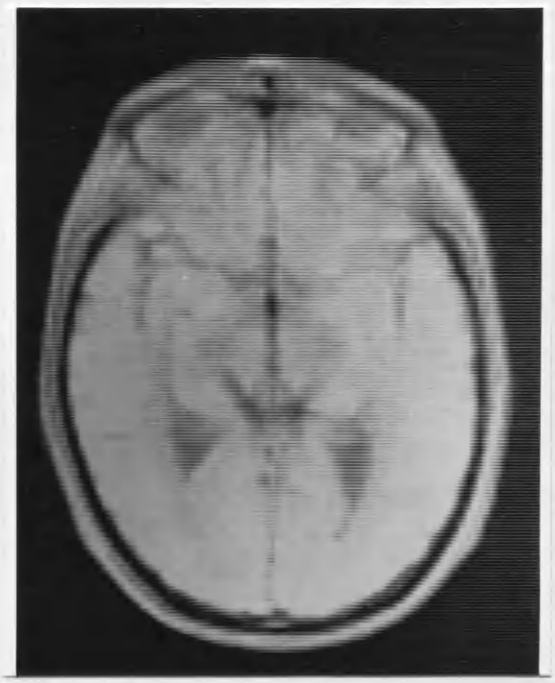


FIGURE 3

Nuclear magnetic resonance (NMR) imaging of the head of case 5 with the Miller Fisher Syndrome, performed at day 21 of the illness. Axial and sagittal views did not show any evidence of abnormality.







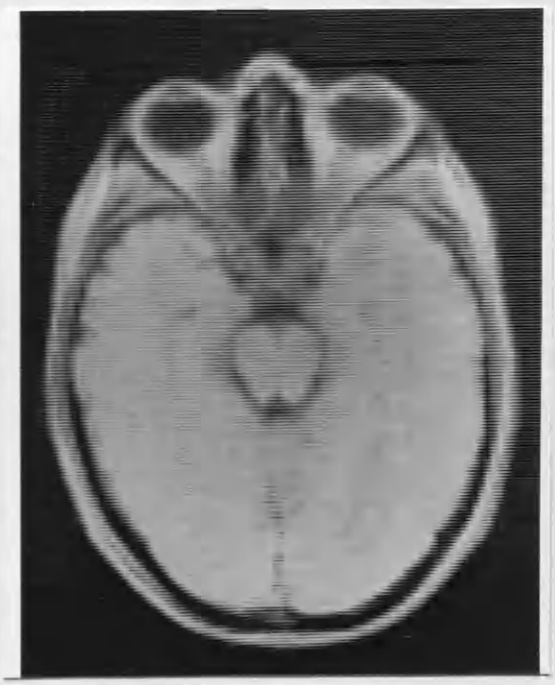


TABLE 5 : Summary of clinical data of seven patients with the Miller Fisher

Case No.	Age & Sex	Antec. illness & lat. (days)	Period	MxD (days)	OPHTHALMOPLEGIA								ATAXIA	REFLEXES
					diplopia	external	internal	ptosis	INO	MOR	Bell's phen.	OCR		
1	21 M	URTI	14	2	+	S	+	+	+	⤫	−	−	+	−
2	56 M	Flu	10	4	+	S	−	+	−	//	−	−	+	−
3	15 M	URTI	7	4	+	C	+	+	+	//	−	−	+	−
4	65 M	ST	5	5	+	C	−	−	+	//	−	−	+	−*
5	29 M	URTI	7	5	+	C	∓	+	−	⤫	−	−	+	−
6	57 M	URTI	11	6	+	I	−	+	−	⤫	+	+	+	−
7	35 F	Flu	28	3	+	C	−	+	−	//	−	−	+	−*

URTI : Upper respiratory tract infection

ST : Sore throat

MxD : Maximum neurological deficit

INO : Internuclear ophthalmoplegia

MOR : Mode of recovery

OCR : Oculo-cephalic reflex

N : Normal

EB : Epstein-Barr virus

For grading of degree of recovery see table 9

Syndrome ·

Cranial nerves	Weakness	SENSORY Sympt.	SENSORY Signs	assist. ventil.	autonomic	Viral titres	Recovery onset (days)	Recovery dur (mnth)	grade	relapse	scan CT	studies NMR
10	–	–	–	–	–	EB-IgM	12	6	0	–	N	
7, 10	–	–	–	–	–	–	10	4	0	–	N	
7, 10	–	–	–	–	–	–	10	6	1	–	N	
7, 10	∓	+	+	–	–	–	18	6	0	+	N	N
7	–	+	–	–	–	–	13	6	0	–	N	N
11	–	+	+	–	–	–	13	6	1	–	N	N
7, 10	+	+	+	+	–	–	15	>2	?	–	N	N

+ : Present
– : Absent
± : Mild
S : Severe
C : Complete
I : Incomplete
// : Conjugate
⫻ : Disconjugate
* : Asymmetrical

complete in 4 cases, very marked in 2 cases and incomplete in one patient. Ophthalmoplegia appeared to be symmetrical on clinical examination so that the eyes were properly aligned with no skewing in cases 1, 2, 3 and 7. In cases 4 and 5, the paralysis of the extraocular muscles was witnessed to start initially as incomplete and asymmetrical but progressed over the following few days to become complete with the eyes symmetrically aligned in the primary central position. In case 6, the external ophthalmoplegia remained incomplete and asymmetrical throughout the illness. In cases 2, 3, 4 and 7 the symmetry of extraocular muscle involvement was preserved during recovery and improvement occurred in a conjugate manner whereas in cases 1 and 5 the external ophthalmoplegia, starting symmetrically, improved in a disconjugate manner. In all the patients, however, diplopia was present throughout the illness including the period of recovery and in all, at one point nearer the stage of complete recovery, diplopia was still present despite the absence of demonstrable eye paresis on clinical examination. Internal ophthalmoplegia (iridoplegia) accompanied weakness of the extraocular muscles in 2 patients; being complete in case 3 and marked in case 1. Case 5 had transient dilatation of the right pupil but no abnormality of light or accommodation reflex. Ptosis was present in 6 patients; being severe and bilateral in cases 2 and 5, moderate and bilateral in cases 3, 6 and 7, moderate and unilateral in case 1 and no ptosis was noted in case 4. In the latter case, therefore, complete external ophthalmoplegia was not accompanied by iridoplegia or ptosis. At some stage of the illness, downward gaze was less affected than upward and lateral gaze to both

directions in cases 3, 4 and 5 and in case 3, downward gaze recovered 10 days prior to the recovery of other gazes. Nystagmus in the abducting eye on lateral gazes (dissociated nystagmus) was demonstrated at one stage in cases 1, 3 and 4. No disparity was present between the limitation of voluntary and reflex (to Bell's phenomenon and oculo-cephalic manoeuvres) eye movements in any of the 6 patients with complete or severe external ophthalmoplegia.

Cases 1 - 7 had severe gait ataxia and in all but one (case 4) this was associated with severe truncal ataxia. On the other hand, incoordination of the limbs was strikingly mild compared to the severity of the truncal and gait ataxia in all patients. No other features of cerebellar dysfunction were present in any of the 7 cases.

All 7 patients had abnormal deep tendon reflexes. In case 1, 2, 3 and 5 all tendon reflexes were absent while in cases 4, 6 and 7 only some of the reflexes were initially abnormal but all were eventually lost at the height of the illness. In cases 4 and 7, asymmetry of reflexes between the two sides of the body was noted at one stage of the illness.

Slight facial weakness was present in 5 patients; being bilateral in cases 4, 5 and 7 and unilateral in cases 2 and 3. The 10th cranial nerve was involved in 5 patients (cases 1, 2, 3, 4, 7) producing weakness of bulbar musculature and difficulty of swallowing. The accessory nerve was bilaterally involved in case number 6.

Mild sensory symptoms were present in 4 patients. This was in the form of tingling sensation in the fingers, toes, hands or forehead in cases 4, 6 and 7 or numbness of the hands and arms in

case 7. Patient 5 had some difficulty in expressing the type of sensory symptom he experienced and described it as a "strange sensation" in the fingers and gums. Sensory signs were, however, documented only in three patients and these included varying degrees of diminution or loss of the sense of vibration (cases 4, 6, 7), pinprick (cases 4, 6, 7), joint position (cases 6, 7), touch-pressure (case 7) and temperature (case 7). There was no limb weakness of any degree in 5 patients. Patient 4 had slight proximal and distal weakness of both upper limbs and case 7 had mild proximal weakness of the right lower limb. The latter patient developed respiratory muscle paralysis a few days after the onset of her illness which necessitated tracheostomy and artificial ventilation as life saving measures.

All but case 4 showed the classical albumino-cytological dissociation usually observed in patients with acute inflammatory demyelinating polyradiculoneuropathy and a significant rise of CSF proteins was demonstrated in cases 5 and 6 when the spinal fluid examination was repeated a week later (table 5). Routine haematological and laboratory studies were normal in all the patients and radiographs of the skull and chest were unremarkable. High definition CT scans of the head with and without contrast enhancement were performed 6 - 14 days after onset of the illness and repeated in one case (case 7). These included special views for the brainstem and were normal in all the patients. Nuclear magnetic resonance (NMR) brain scans with longitudinal sagittal views of the brainstem were performed in cases 4, 5 and 6 and these did not show any evidence of abnormality.

Gradual recovery ensued 10 - 15 days after onset of the

neurological illness and only a few days after the neurological deficit reached its height in all the patients. Cases 1 - 5 made a complete recovery without residual abnormality while case 6 had only minimal abnormality 6 months after onset. No follow up beyond the examination at 2 months after onset is available in case 7. Her initial rate of recovery was, however, excellent. Ophthalmoplegia and/or ataxia were usually the first to recover within a few weeks to a few months and the reflexes were last to reappear. The illness of patient 4 was a relapse three years after his first attack from both of which he made a complete recovery.

CHAPTER 3

THE NEUROPHYSIOLOGICAL METHODS USED IN THIS STUDY

Serial multimodal neurophysiological tests were performed on all seven patients starting within one week of the onset of the neurological manifestations and repeated at one month, two months, four months and six months thereafter. These investigations were employed to test both the peripheral and central parts of various pathways in the nervous system. They included the following:

1. electromyography (EMG)
2. nerve conduction (NC) studies
3. late response (H-and F-wave) studies
4. estimation of motor unit numbers and motor unit potential (MUP) analysis
5. peripheral facial nerve and blink reflex studies
6. computerised quantitative sensory threshold measurements
7. silent period studies
8. multimodality evoked potential (visual evoked potential, somatosensory evoked potential, and brainstem auditory evoked potential) studies
9. electroencephalography (EEG)
10. quantitative pupillometric and pharmacological observations on the pupils.

These neurophysiological investigations were performed in parallel with serial clinical examinations at the same intervals (chapter 2). All investigations were undertaken at a controlled room temperature of 22 $\mp$ 2°C. The limbs examined were maintained at 34 $\mp$ 1°C by a thermostatically controlled heating lamp. The

results of each test were compared with the range of normal values for the laboratory (see appendix for normal values). Limits of normal were determined by the application of a 99% confidence limit to a non-patient control population for each test with the exception of motor and sensory conduction and MUN estimation values where a 95% confidence limit was applied in keeping with the convention in the literature.

THE NEUROPHYSIOLOGICAL INVESTIGATIONS included the following:

ELECTROMYOGRAPHY (EMG): Concentric needle EMG was performed in the right extensor digitorum brevis (EDB), the right tibialis anterior (TA), the first dorsal interosseous (1st DI) and the facial muscles. In most patients the right quadriceps femoris and deltoid muscles were also sampled. Presence or absence of spontaneous activities at rest, evaluation of the shape, amplitude, duration and number of phases in the motor unit potentials (MUPs) and assessment of the recruitment patterns on maximal voluntary activity were performed (Lenman and Ritchie 1983).

NERVE CONDUCTION (NC) STUDIES: The fastest motor nerve conduction velocity (FMNCV) and the shortest distal motor latency (SDML) for the right common peroneal nerve (CPN) and right median and ulnar nerves were obtained recording from surface elctrodes over the target muscle by the conventional techniques initiated by Simpson (1956). The amplitude and duration of the compound muscle action potential (CMAP) were also measured using supramaximal stimulation of motor nerves. Sensory nerve action potentials (SNAPs) were elicited orthodromically in the right median and ulnar and antidromically in the right sural nerves. For

each SNAP measurement, 64 evoked potentials were averaged using supramaximal surface stimulations. Sensory latencies were measured from the onset of the stimulus artifact to the peak of the negative deflection of the evoked nerve potential. SNAP amplitudes were measured from peak to peak. For median and ulnar SNAPs, the method used by Gilliatt and Sears (1958) was followed. The sural nerve was stimulated at a point 14 cm. proximal to the malleoli and lateral to the tendo Achilles and the potential recorded by surface electrodes at the lateral aspect of the foot immediately inferior and anterior to the lateral malleolus. The distance between the pair of recording electrodes was 4 cm.

LATE RESPONSE STUDIES: Conventional nerve conduction techniques are traditionally applicable to the distal segments of the peripheral nerves while late response studies test the proximal nerve segments as well as the neurones in the CNS. Of potential interest in this respect are the F-wave (Magladery and McDougal 1950) and H-reflex (Hoffmann 1922) studies which were performed separately.

F-wave studies were performed with stimulation at the wrist for the median and ulnar nerves, and at the ankle for the common peroneal and tibial nerves. At these sites a supramaximal stimulation was applied through a pair of surface electrodes 3 cm apart with the anode placed distal to the cathode to avoid anodal block of the antidromic impulse (Kimura 1983b). The recording electrode was placed over the motor point of the target muscle and the reference electrode over the tendon of that muscle. The amplifier gain was set at 200 μV per cm and the sweep usually at 10 ms per cm. Latencies of the F-waves were measured from the

stimulus artifacts to the beginning of the evoked potential in response to supramaximal stimulation. As latencies may vary in the normal subjects by a few ms from one stimulus to the next, at least 10 F-waves were identified for each study and the shortest latency was accepted as the F-wave latency. In addition to the minimal latency, the longest latency was also measured to assess the degree of scatter among consecutive F-waves. The minimal latency of F-wave is representative of the fastest motor conduction to and from the spinal cord (Kimura 1983b).

The H-reflex was recorded from the soleus muscle by surface elctrodes, with the patient supine on the examination bed. The active electrode was placed 2 cm distal to the point of insertion of the gastrocnemius muscle on the Achilles tendon and the reference electrode 5 cm distal to the same point with both electrodes being placed along the longitudinal axis of the calf. A ground electrode was placed between the stimulation and recording sites. The knee was supported by a soft cushion and semiflexed at about 120 degrees and the angle of the ankle joint was kept at about 110 degrees. The H-reflex was recorded as a triphasic potential with initial positivity in response to submaximal electrical stimulation applied by surface electrodes to the tibial nerve at the popliteal fossa. Careful observation of stimulus condition was maintained to obtain a maximal and reproducible waveform. The latency of the H-reflex was measured from the stimulus artifact to the onset of the initial negative deflection.

MOTOR UNIT NUMBERS AND MOTOR UNIT PARAMETERS: The composition and placement of the surface electrodes over the extensor

digitorum brevis (EDB) muscle, the properties of the stimulating electrodes over the anterior tibial nerve at the ankle, and the details of the rate and strength of stimulation used to evoke motor unit potentials have been described by Ballantyne and Hansen (1974a) from this department. The amplification and display systems, the computer handling of data for the estimation of motor unit numbers in the EDB muscle, and the computer derivation of the parameters of the electrically evoked motor unit potentials have also been reported (Ballantyne and Hansen 1974 a,b).

Briefly, motor unit potentials (MUPs), recorded from surface elctrodes over the EDB muscle, are evoked sequentially by finely graded incremental stimulation of the anterior tibial nerve at the ankle. Recruitment of up to 15 motor units can be recognised by a combination of visual and computer analysis of the muscle action potential increments displayed on the oscilloscope screen. The first MUP is displayed in isolation on the oscilloscope, the potential of the second is incorporated in a compound muscle action potential containing MUPs 1 and 2. As each new potential is added to the preceding one, the compound muscle action potential so constituted is stored in a computer memory (template). Template 1 contains MUP 1, template 2 contains the sum of MUPs 1 and 2, template 3 contains the sum of MUPs 1, 2 and 3, and so on. Up to 15 templates can be stored. The number of motor units (MUN) in the EDB muscle is calculated from the formula:

$$MUN = \frac{A\,(M)}{A\,(N)} \times N$$

where A (M) = the area of the supramaximally evoked muscle action potential and A (N) = the area of the compound muscle action potential containing N MUPs.

By a process of template subtraction, the computer also displays the first and sequentially recruited MUPs in isolation. For example, subtration of template 1 from template 2 will leave MUP 2 in isolation, subtraction of template 2 from 3 will leave MUP 3 in isolation, and so on. The latencies, durations, amplitudes and areas of individual MUPs are then measured. Amplitudes and areas are provided by the computer while latencies and durations are measured manually from a computer printout (Ballantyne and Hansen 1974b). All potential recordings are from surface electrodes over the EDB muscle.

FACIAL NERVE MOTOR CONDUCTION AND BLINK REFLEX STUDIES: Direct facial motor response (D-response) and blink reflex studies were also performed on all 7 patients to test the facial nerves and blink reflex pathways on both sides. For recording the D-response, the facial nerve was stimulated transcutaneously with the cathode placed just anterior to the mastoid process. Recording from the ipsilateral orbicularis oculi muscle was made using surface electrodes. The active electrode was placed on the lower lateral aspect of the orbicularis oculi muscle, the reference electrode on the temple and a ground electrode under the chin. The subject was lying supine on the bed with eyes open.

For blink reflex studies the same arrangement of recording and ground electrodes was used. The supra-orbital branch of the trigeminal nerve was stimulated with the cathode placed over the supraorbital foramen on one side and simultaneous recordings were

made from the orbicularis oculi muscles on both sides. The same supramaximal intensity of stimulus was applied on each side to compare relative excitability of the reflexes elicited by either side stimulation and to produce maximum and stable responses. At least 10 stimulations on each side were applied and the shortest latency of the direct (R1) and indirect (R2) responses were recorded from the stimulus artifact to initial deflection of the evoked potentials. The amplifier gain was set at 500 μV per cm and the sweep at 10 ms per cm for blink reflex and at 1 mV per cm and 2 ms per cm respectively for D-response studies.

QUANTITATIVE STUDIES OF SOMATIC SENSATION: Quantitative measurement of thermal thresholds (Jamal et al 1985 a,b; Jamal 1986) and of vibration perception thresholds (Goldberg and Lindblom 1979) was performed using recently introduced techniques.

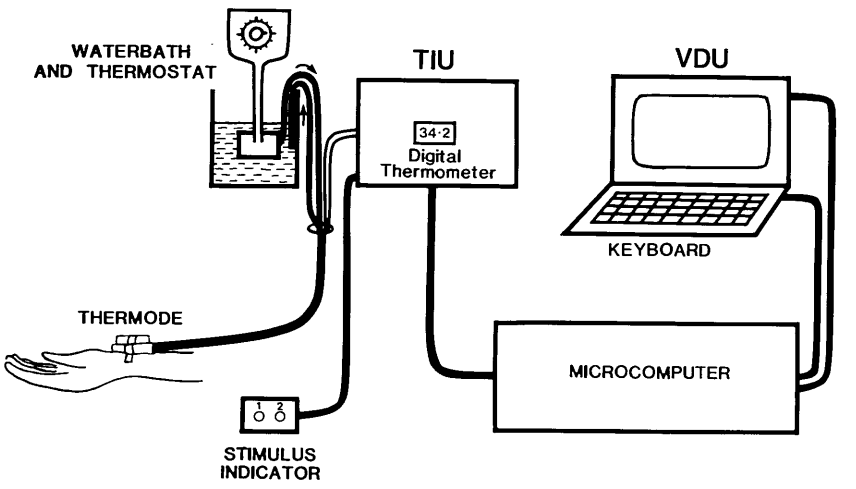
Thermal Thresholds Measurement: Heat threshold (HT) and cold threshold (CT) values were determined for the volar aspect of the right wrist just proximal to the distal wrist crease and for the medial aspect of the right ankle behind the medial malleolus. These were expressed in temperature change from the basic skin temperature (before application of the stimulus) using a microcomputer controlled system and the two-alternative forced-choice method of psychophysical analysis. The method has been described in detail previously (Jamal et al 1985a, Jamal 1986). The components of the system are shown in figure 4 and the following is a summary of the technique. The microprocessor system controls the stimulating probe (the thermode) and performs the forced-choice trials. The thermode is constructed from an array of semiconductor thermo-electric elements with a stimulating

FIGURE 4

Components of the Thermal Threshold Tester used for the measurement of thermal thresholds in this study. (Jamal et al 1985a, reproduced with permission).

TIU : Thermal Interface Unit

VDU : Visual Display Unit


WATERBATH
AND THERMOSTAT
TIU
VDU
34·2
Digital
Thermometer
KEYBOARD
THERMODE
MICROCOMPUTER
1
2
STIMULUS
INDICATOR

surface area of 12.5 cm^2 and operates on the Peltier principle. On the background of a constant skin temperature (34-35°C), the thermode applies a quantified thermal (heat or cold) stimulus to the skin tested. The subject is placed in a comfortable position and the thermode is applied to the area of the skin tested with a standard pressure. A number of trials are performed. In each trial, the subject is presented with two periods during which a null stimulus and an actual thermal stimulus are applied and the periods are indicated to him/her by two lights illuminated in sequence. The order of assignment of the actual and the null stimuli to the period is randomised by the microcomputer and is unknown to the subject and the examiner. At the end of each trial the subject must choose that period during which he/she felt or thought he/she felt the stimulus. Depending on the response, the computer will alter the stimulus strength applied during the next trial according to the up-and-down transform rule (UDTR) (Wetherhill et al 1966). The stimulus power is kept constant such that the rate of change of temperature at the skin surface is 1°C/s. The strength of the thermal stimulus is altered by changing its duration of application. The threshold is calculated as the mean of at least 12 separate trial values in accordance with the UDTR. The investigation is carried out in a quiet room temperature of 22 $\mp$ 2 °C. HT is determined first followed by CT. The time required to determine both HT and CT for one site is usually 15-20 minutes.

Vibration Threshold Measurement: Vibration perception thresholds (VPT) were measured in all subjects on the dorso-medial aspect of the middle of the right first metatarsal bone where the

overlying subcutaneous tissue is thin. The technique, its physiological basis and normal values have been described by Goldberg and Lindblom (1979). Briefly, the vibration stimulus intensity is assessed from the displacement of the skin in micrometers and not from the voltage applied to the vibrameter as in earlier techniques. The degree of displacement of skin is the physiological stimulus to the vibration sensitive receptors (Lindblom and Lund 1966; Goldberg and Lindblom 1979). The apparatus (SOMEDIC AB VIBRAMETER type III) consists of an electromagnetic vibrator with a 13 mm diameter probe which vibrates at right angles to the skin. The amplitude of the skin displacement (the vibration amplitude) is measured indirectly by an accelerometer with continuous digital display. The vibrator was held against the skin with a force of 500 $\mp$ 100 g by reference to a force indicator on the Vibrameter. The subject is placed in a comfortable position, the right leg is supported by pillows to prevent stimulus spread and a suprathreshold test stimulus is applied to familiarise him/her with the sensation produced. The apparatus can deliver two standardised rates of increase in stimulus intensity, slow or fast. The amplitude of vibration is increased using one of these alternatives and the subject is instructed to indicate when he/she feels the stimulus. The vibration amplitude at this time is recorded. The procedure is repeated at the alternative rate of increase of stimulus intensity. The average of three trials is the VPT. In cases where there is more than 10% variation between the values, further trials are performed until 3 consecutive readings are within the 10% limit.

Vibration amplitudes in the range of 0-399.9 micrometers at 100 Hz can be produced by the apparatus. The VPT determinations are made in a quiet room. On average less than five minutes was required for each VPT determination.

SILENT PERIOD (SP) STUDIES: SPs were recorded from various muscles innervated by different segmental levels in response to transcutaneous electrical stimulation of the respective mixed nerve supplying the same muscle. These included the abductor pollicis brevis (APB) and the abductor digiti minimi (ADM) muscles in the upper limb and the flexor hallucis (FH) and the gastrocnemius-soleus muscles in the lower limb.

The electromyographic SP, first described by Hoffmann (1922), is defined as *"a transitory, relative or absolute decrease in the EMG activity, evoked in the midst of an otherwise sustained muscle contraction"* (Shahani and Young 1973). There are many methods to evoke a SP including the application of a supramaximal electric shock to the skin or to a peripheral nerve supplying that muscle, tapping the tendon of the muscle or by a sudden decrease in the load against which the muscle is contracting (Merton 1951; Shahani and Young 1973).

Square wave electric stimuli of 0.1 ms duration were applied through surface electrodes to the appropriate mixed nerve. Amplitudes of these stimuli were submaximal to the compound muscle action potential (CMAP). This procedure was followed so that the SPs recorded were of a *"proprioceptive"* and not of a *"cutaneous"* origin (Shahani and Young 1973; Ropper and Shahani 1983). SPs were recorded during a period in which the muscle tested sustained an isometric background contraction of about 0.5 - 1.5 kg. The

evoked responses were picked up by surface electrodes and stored on one channel of a storage oscilloscope and measurements were performed using automatic cursors. The setting of filter band width was at 1 Hz - 6kHz, the sweep duration at 400 ms and the amplifier gain at 500 μV per cm. Measurements were made from at least 10 superimposed traces. The stimuli were delivered at a rate not faster than one every 10 seconds. The SP was measured as the interval between the stimulus onset and the reinstitution of the EMG activity (S-EMG) as suggested by Shahani and Young (1973).

For SP studies of the APB and ADM muscles, the subject was lying supine with the arm extended and properly supported. The subject was asked to activate the muscle tested (abduct the thumb in the case of the APB and abduct the little finger in the case of the ADM against an elastic band) so that the EMG activity maintained a minimum continuous recruitment monitored through the oscilloscope. The respective mixed nerve (median for the APB and ulnar for the ADM) was then stimulated at the wrist using a bipolar surface stimulator with the cathode placed distally. For the measurement of SPs in the lower limb, the subject was made comfortable over a bed in the prone position. The ankles were hanging over the edge of the bed and were supported by a pillow. For the gastrocnemius-soleus studies, the active recording electrode was placed in the midline between the two heads of the gastrocnemius muscle with the reference electrode on the Achilles tendon and the posterior tibial nerve was stimulated in the popliteal fossa. For the FH studies, the active electrode was placed one cm behind and one cm below the navicular tubercle (medial side of the foot) and the reference electrode on the large

toe and the tibial nerve was stimulated at the ankle behind the medial malleolus. Studies were performed while the subject plantar flexed the foot, for the former, or the great toe for the latter, against a steady pressure so that the EMG activity maintained a minimum continuous recruitment monitored on the oscilloscope.

EVOKED POTENTIAL STUDIES: Large fibre somatosensory, auditory and visual modality peripheral and central pathways were also assessed by studying their respective evoked potentials to sensory stimulation of these systems from surface electrodes placed on the scalp and in the case of somatosensory evoked potentials from electrodes placed over the spinal cord and the extremities. The 10-20 international system of electrode placement on the scalp was used (Jasper 1958). Stick-on EEG cup electrodes were employed for recording. These were applied with special glue and were filled with standard electrode gel. The scalp beneath the electrode was abraded with the same blunt-tip needle used to inject the conducting gel until the electrode impedence was below 2000 ohms. Repeat trials were superimposed for every evoked potential determination and waveform validity was ensured.

SOMATOSENSORY EVOKED POTENTIAL (SEP) STUDIES: SEPs to transcutaneous electrical stimulation of the median nerve at the wrist and the posterior tibial nerve at ankle were recorded. Rectangular voltage-constant stimuli were delivered at a frequency of 3 per second with a pulse duration of 0.1 ms. Stimulus intensity was adjusted to produce a small twitch in the thenar or foot muscles and this was kept the same for each patient on serial

studies. Recordings were performed using EEG disc electrodes from Erb's point, the spinous processes of the second and seventh cervical vertebrae and the contra-lateral somatosensory cortex (one cm behind the 10-20 international system C3/C4 positions) in upper limb SEP studies. In the lower limb, recording electrodes were placed over the third lumbar and the 12th thoracic vertebrae and on the vertex (two cm behind the 10-20 international system Cz position). Each of these electrodes was referred to a common mid frontal (Fz) reference electrode. For each SEP, 512 signals were averaged. Filter sets were at 5 Hz and 6 kHz for upper limb SEP recording and at 5 Hz and 250 Hz for lower limb SEP studies. Analysis time was set at 50 ms in the case of median SEPs and at 100 ms in the case of posterior tibial SEPS. Potentials were averaged on at least four channels simultaneously. The subjects were studied while lying in a semi-supine position and special attention was paid to their relaxation by close observation of the analogue signals on an oscilloscope. An automatic artifact rejection facility was used to exclude signals with relatively large artifacts.

From median nerve stimulation, the SEPs studied were the Erb's potential (EP) recorded from the Erb's point electrode, the spinal potential, the most prominent of which is the N13 and also N11 peaks from the Cv7 electrode and the N20 potential recorded from the contralateral somatosensory cortex. In posterior tibial SEP studies, the earliest negative response over the T12 and L3 spine levels and the earliest positive cortical potential recorded from the Cz electrode were identified. Signal latencies were measured from the stimulus artifact to the peak negativity of the

responses. Interpeak latencies were measured between EP and N13 potentials (EP-N13 conduction time) and the N13 and N20 negative peaks (N13-N20 conduction time). Amplitudes were measured from the preceding positivity to peak negativity for EP and from baseline for N13, N20 and P40 potentials.

BRAINSTEM AUDITORY EVOKED POTENTIAL (BAEP) STUDIES: The BAEPs were recorded in a quiet room. All patients were studied while lying in the supine position with appropriate head support necessary to minimise postural muscle activity in the neck and head. Sweeps with excessive artifacts were automatically rejected and not averaged. Click stimuli at a rate of 10 per second and an intensity of 90 dB were applied to the subject monaurally. In some patients in addition, an intensity of 65 dB on the top of hearing threshold level was used. Masking white noise was presented to the unstimulated ear at 50 - 60 dB. The far field potentials were recorded in a bipolar fashion between the earlobe ipsilateral to the ear stimulated and the vertex using a forehead ground electrode. A filter bandpass of 100 - 3000 Hz was used. 1024 signals were averaged for 10 ms post stimulus duration. At least two repeat trials were superimposed and a grand sum of these was obtained on which all the measurements were performed. Latencies were measured from the stimulus artifact to the positive peak of each wave to the nearest 0.1 ms. Waves I, II, III, IV/V and V were identified and their latencies measured. Interwave latencies I - III, I - V and III - V were also determined. Absolute and interwave latencies of the two sides were compared. Amplitudes were measured from the peak to the following descending trough. Wave I/V amplitude ratio was always

measured and compared in both sides.

PATTERN REVERSAL VISUAL EVOKED POTENTIAL (PRVEP) STUDIES:

Averaged PRVEPs were recorded from stimulation of either eye to 128 checkboard pattern reversal at a rate of one per second (Halliday and McDonald 1981). A single channel recording based on one active mid occipital electrode placed 5 cm above the inion was employed in some patients. In others a multichannel recording based on a transverse row of three occipital electrodes was employed. The central electrode was again placed 5 cm above the inion and the additional pair of electrodes were placed 5 cm on each side. All these were referred to a common mid frontal electrode. The ground electrode was placed on the vertex. Response measurements were performed only on the recording from the mid occipital-frontal montage as the largest amplitude responses are usually recorded from the central occipital position (Halliday 1982a). Filters were set at a bandwidth of 1-300 Hz. One hundred signals were averaged with an automatic artifact rejection facility being employed. The amplifier gain was calibrated before each recording of the PRVEP using the same filter setting. Each eye was stimulated separately with the other eye covered and the subject was asked to fixate on a small point in the centre of the screen which was one metre away during the test.

Parameters of the triphasic wave form were measured using an automatic cursoring facility. The major positive (P100) peak latency was measured. Its peak to peak (between the immediately preceding negative wave to the peak of P100) amplitude was measured. The form and distribution of the potential was also

noted. All these parameters were compared to those obtained from stimulation of the contralateral eye. The PRVEP test always followed a visual acuity measurement with a Snellen chart.

ELECTROENCEPHALOGRAPHY (EEG): Serial 16 channel EEG recordings each of at least 20 minutes duration were performed in each patient using an array of 21 electrodes (disc stick-on type) placed on the scalp using standard methods (Binnie et al 1982). The EEGs were visually assessed by at least two observers.

PUPILLOMETRIC STUDIES: Pupillary diameter and reflex abnormalities were quantitatively studied in case 3 using an improved photographic method recently described with control values from this department (Ramsay and Woodruff 1987). The following provides a summary of the method. The photographic apparatus included a Minolta X700 camera body programmable to take photographs at given intervals with a flare free flash illumination of 0.016 second duration from a Minolta PX 360 flash gun. Since this duration is shorter than the light reflex latency (0.2s) (Lowenstein and Loewenfeld 1962), isolated measurements of pupillary diameter were not affected by flash illumination of the eye (Ramsay and Woodruff 1987).

The patient's eyes were photographed while seated at an ophthalmic table and the vertical pupillary diameter was then measured from the enlarged negative and corrected to real values using the appropriate magnification factor. Each measure of pupil diameter was expressed to the nearest 0.1 mm. Sequential exposures, timed to monitor changes in pupillary diameter in response to an abrupt transition from light to dark (the darkness reflex) or to sudden alteration of visual fixation point (the

accommodation reflex), were taken.

The pupillary darkness reflex was assessed by taking a train of 8 flash exposures at 5 second intervals, the first two of which were taken in bright light (provided by a light with a conical reflector, cone base diameter 15 cm, and a 100 watt light bulb with the opening of the reflector 70 cm from the subject's face); the light was then extinguished at the instant of the second exposure so that the following 6 exposures were taken in darkness. Two additional flash exposures were then taken in continuing darkness 30 and 60 seconds after the last of the 8 exposure train. The patient was asked to hold his gaze on a standard fixation point (a dim red light emitting diode 270 cm away) throughout this sequence.

Pupillary accommodation reflex was assessed in a 12 flash exposure under subdued light conditions, at 2 second intervals. The patient was asked to fix his gaze on the standard fixation target until the instant of the 4th flash when he moved visual fixation to a near point 18 cm away from the eye in line with the optical axis of the camera lens with his nasal bridge. At the instant of the 8th flash he would return his gaze to the standard far fixation target 270 cm away.

Irideal neurotransmitter sensitivity was also measured using this method to study any defects of autonomic innervation of iris muscles. Abnormalities of these reflexes and sensitivity were identified at values beyond the 99 percentile derived from the application of the methods to 40 normal subjects (Ramsay 1986; Ramsay and Woodruff 1987). Irideal cholinergic parasympathetic sensitivity was assessed by measuring the degree of pupillary

constriction 30 minutes after the administration of two drops of freshly prepared 0.05% pilocarpine solution to both conjunctival sacs in an uninterrupted darkness (Cohen and Zokov 1975). In the 40 control subjects, a decrease in pupillary diameter of more than 1.4 mm in darkness in response to 0.05% pilocarpine was abnormal at 99% CL (Ramsay 1986). Irideal adrenergic sensitivity was assessed by measuring the degree of pupillary dilatation one hour after the administration of 2 drops of freshly prepared 1% phenylephrine solution into the conjunctival sacs in bright light (Matsumoto et al 1982). Pupillary dilatation greater than 2.1 mm in bright light in response to 1% phenylephrine is abnormal in a 20 year old subject (the figure should be corrected for age by a factor of 0.23 mm per decade) (Ramsay 1986).

RELIABILITY AND CONSISTENCY OF METHODS: The techniques used in this study have proved useful for the objective detection, registration, quantification and localisation of various disturbances of function in the central or peripheral nervous system. They have also proved to be reproducible and thus provide means of monitoring the evolution and progress of these disturbances through repeated longitudinal studies. All techniques were standardised and the same methodological procedures were applied to patients and control groups to minimise changes other than *"true"* ones. The adoption of the 99 percentile as criteria of abnormality for these tests in terms of both inter- and intra-individual variability virtually eliminates error of measurement not attributable to true change of function of the system examined.

With steady improvements of the recording apparatus, nerve

conduction studies have become a simple and reliable test of peripheral nerve function. The methodology has been adequately standardised in recent years and is widely used as an objective test for peripheral nerve lesion to precisely localise the site of maximal involvement and to follow up any improvement of the nerve function (Kaeser 1970). On repeated nerve conduction testing, the values might vary slightly in normal subjects because of the limitations inherent in the technique (Mattson and Lecoq 1968). The validity and accuracy of NC measurement and its reproducibility could, however, be greatly increased if important sources of error are attended to (Simpson 1964). These include poorly defined take-off of the evoked response, unstable or incorrect triggering of the sweep, inappropriate stimulus strength, inaccurate calibration, error in measurement of conduction distance resulting from uncertainty as to the exact site of stimulation of the nerve and the exact course of the nerve trunk and other technical errors (Simpson 1964; Gassel 1964). Standardisation of temperature of the limb examined at 34° C is important as conduction velocities vary with temperature (Gassel 1964; Paintal 1965) by about 5% per degree Celcius in an almost linear fashion (Johnson and Olsen 1960). The same segment of the nerve was tested each time since conduction velocity varies in various segments of the same nerve with proximal segments conducting faster than distal segments (Gilliatt and Thomas 1960). Care was taken that supramaximal, not submaximal, stimuli were used and these were not too excessively supramaximal as this may also give erroneous results (Pinelli 1964; Wiederholt 1970). For the SNAP studies the distance between recording and stimulating

electrodes was kept constant. Bipolar antidromic sural SNAP was measured as this allows a SNAP to be detected in nearly all normal subjects (Di Benedetto 1970; Burke et al 1974; Schuchmann 1977).

F-wave measurement represents an accurate procedure to detect abnormalities of motor conduction in the proximal segments of peripheral nerves (Eisen et al 1977 a, b; Kimura 1978b; Kimura et al 1979). It is more sensitive for identifying the presence of low grade multifocal sites of demyelination that add together in effect to produce a prolonged F-wave response as the length of the neural axis examined in F-wave studies is considerably more than that examined in conventional conduction velocity studies (Shahani and Young 1983). For these reasons F-wave studies are perhaps the most useful test in patients with polyneuropathies associated with prominent proximal motor pathology and are useful supplements to conventional nerve conduction studies in neuropathies in general (Kimura 1983b). F-wave latency measurements (from the stimulus artifact to the beginning of the evoked potential) vary in normal subjects by a few ms from one stimulus to the next (Kimura 1974, 1978b). It is, therefore, recommended that at least 10 F-waves should be recorded at one stimulus site and the shortest latency should be measured as the F-wave latency (Kimura 1983b) and this represents the fastest conducting motor fibres (Kimura 1974, 1978b). This largely circumvents the variability. Involvement of some motor axons more than others in the same nerve in some neuropathies may lead to a larger range of conduction velocities producing "*chronodispersion*" of the F-waves (Panayiotopoulos and Scarpalezos 1977; Panayiotopoulos 1979). In normal subjects the variation does not exceed 7.5 ms

(Panayiotopoulos and Scarpalezos 1977) as the motor axons have a limited range of conduction velocities (Panayiotopoulos 1979).

Repeated H-reflex determinations produce a more limited variation when recorded under controlled conditions. This constancy is due to the fact that each stimulation activates the same motor neuron pool (Kimura 1983c). Latencies of successive H-reflexes in the same individual at the same session recorded in our laboratory in 38 normal subjects did not vary by more than 1.5 (m=0.6; SD=0.3) ms and latency difference of both sides did not exceed 1.7 (m=0.5; SD=0.4) ms both at 99% CL. For these and other reasons, the H-reflex rivals the conventional nerve conduction studies in detecting early neuropathic abnormalities (Wager and Buerger 1974). The test was also demonstrated to be a sensitive indicator of mild neuropathies associated with alcoholism (Willer and Dehen 1977) and uraemia (Halar et al 1979) and of maturational changes in the proximal versus distal segments of the tibial nerve (Vecchierini-Blineau and Guihenenc 1979).

The method of motor unit number estimation introduced by Ballantyne and Hansen (1974 a,b) provided a marked improvement in accuracy and reproducibility over the earlier method of McComas et al (1971 a,b). The latter was criticised on the ground that erroneous results might occur as a result of using the amplitude alone as the denominator of motor unit number contained within a CMAP (Scarpalezos and Panayiotopoulos 1973). Ballantyne and Hansen (1974 a,b) used the area of the CMAP instead of the amplitude for the purpose of MUN estimation and computerised the technique and these led to a marked reduction in inter- and intra-individual variability. They were also able to isolate

individual MUPs by template subtraction and to measure their latencies, amplitudes, durations and areas (Ballantyne and Hansen 1974b). Since its description the method has been applied to a number of neuromuscular diseases and produced results in close agreement with their patho-physiological changes (Ballantyne and Hansen 1974 a,b,c, 1975; Hansen and Ballantyne 1977, 1978; Martinez-Figueroa et al 1977).

Blink reflex recording is a simple and reproducible procedure which accurately quantifies dysfunction in the reflex pathway (Kimura 1983 a). Determination of values for the minimal latency of the two components on the contralateral side can be useful in localising a lesion in the trigeminal and/or facial nerves or in the brainstem (Kimura 1983 a). Differentiation of these is made by the recognition of various patterns of abnormalities characteristic to the location of the lesion (Kimura 1983 a). The first component (R1) is shorter in duration and more constant in latency than the second component (R2) (Brown and Rushworth 1973). There is, however, a more marked latency variability in R2 from one trial to the next as this latency not only reflects axonal conduction but also the excitability of interneurones and synaptic transmission (Kimura 1973; 1983a). Measurement of the shortest latencies of the two components from at least 10 recordings largely reduces this variability (Kimura 1983a). The clinical value of these studies is further enhanced by comparison of simultaneous recordings from both sides and by their association with direct facial motor response studies (Kimura 1983a).

The application of computer assisted quantitative assessment of somatic sensation provides highly sensitive and reproducible

methods for the detection of mild dysfunction in the somatosensory pathway and their serial evaluation and thus assists in identifying improvements or deterioration of the particular sensory deficit during the course of an illness (Lindblom 1981; Jamal 1986). The method of Goldberg and Lindblom (1979) for VPT measurement excludes the effect of the pronounced variation in the mechanical impedence and stiffness of the various tissues under the skin and thus the variability in the damping effect of various tissues on the vibration stimulus. This is achieved by measuring the VPT in terms of the displacement of the skin resulting from the perpendicular movement of the stimulator which is the physiological stimulus to the vibration sensitive receptors (Hunt 1961; Sato 1961; Lindblom and Lund 1966). The pressure of application of the vibrameter which is another source of variability of VPT measurement (Cohen and Lindley 1938) is also standardised in this technique. Goldberg and Lindblom (1979) and Jamal et al (1986d; 1987a) demonstrated the inter- and intra-individual reproducibility of the technique in normal subjects. Its application to patients with various neurological diseases demonstrated the sensitivity of the technique in detecting subclinical dysfunction in the vibration sense pathway (Lindblom and Tegner 1985; Tegner and Lindblom 1985; Jamal et al 1986d, 1987a). The technique of thermal sensation assessment has proved to provide a high reproducibility of thermal threshold measurement with very small inter- and intra-individual variability (Jamal et al 1985 a, b; Jamal 1986; Jamal et al 1986a). this was achieved through the standardisation of many sources of variability including the basic skin temperature, the rate of

change of the stimulating temperature, the pressure of application of the thermode, the area of the skin stimulated and the use of the forced-choice psychophysical method that avoids subjects bias and excludes the effect of reaction time (Jamal et al 1985a,b; Jamal 1986; Jamal et al 1986a). In addition, thermode calibration before each threshold measurement excludes the effect of variation of skin thermal properties at different sites on the threshold measurement (Jamal et al 1985 a,b; Jamal 1986). In the technique, ninety stimulation levels, each of 0.1° C, are available. At the wrist a change of only one stimulus level is sufficient to identify a true change of thermal threshold at the 99% CL on repeated measurements on the same subject. The corresponding value at the ankle is two levels (Jamal 1986; Jamal et al 1986a). Sensitivity of the technique in detecting abnormalities of thermal pathway have been proved through its application to patients with several neurological illnesses (Jamal et al 1985 b,c; Jamal 1986; Jamal et al 1986 b,c,d; 1987 a,b,c; Jamal and Ballantine 1987 a,b; Weir et al 1987).

Assessment of the length of the silent period (SP) has occupied a central role in the study of motor physiology since its discovery by Hoffman in 1919 and its reflex nature was quickly appreciated (Denny-Brown 1928; Merton 1951; Shahani and Young 1973). The physiological basis of SP is multifactorial and complex involving antidromic conduction in motor axons, Renshaw inhibition and inputs from proprioceptive and cutaneous afferent fibres which all contribute to the formation of SP and its characters (Shahani and Young 1973). These various factors are believed to operate at spinal segmental level and "*long loop*

reflexes" (Yap 1967; Taborikova and Sax 1969). Abnormalities of SP can, therefore, occur as a result of a conduction block anywhere along the reflex pathways involved in the SP (Laxer and Eisen 1975). The second part of SP is attributed to cutaneous and/or proprioceptive inputs to the CNS (Shahani and Young 1973; Ropper and Shahani 1983). Through the application of a submaximal stimulus to a mixed nerve, the cutaneous contribution is minimised so that the proprioceptive part of the SP can be studied (Shahani and Young 1973; Ropper and Shahani 1983). SP has been studied extensively in normal subjects (Higgins and Lieberman 1968; McLellan 1973; Shahani and Young 1973). Higgins and Lieberman (1968) evaluated repeated measurements of SP and demonstrated that its variation was generally small in the same muscle of an individual, that the duration of SP was relatively constant to variations of muscle tension and that muscle fatigue was not a factor of importance in this respect.

Since their introduction the evoked potential techniques have proven to be reliable diagnostic tests that yield reproducible results in routine clinical practice. They provide an objective measure of function in their respective sensory systems and tracts and have been successfully applied in a large number of neurological diseases (Mastaglia and Carroll 1982; Chiappa and Ropper 1982 a,b; Giesser et al 1987). Their value is mainly based on their ability to demonstrate abnormalities in their pathways when these are subclinical, to objectify and quantify these abnormalities and to define with reasonable accuracy the site of the lesion (Robinson and Rudge 1978; Matthews and Small 1979; Chiappa 1980; Cohen et al 1982; Mastaglia and Carroll

1982; Chiappa and Ropper 1982 a,b). Latencies and amplitudes of the various waves recorded provide numerical data and sometimes an abnormal configuration of a waveform may provide useful information. They, therefore, provide reproducible, sensitive and quantitative extension of clinical neurological examination in addition to their value for the localisation of the lesion (Mastaglia and Carroll 1982; Chiappa and Ropper 1982 a,b). The SEP studies offer a non-invasive well tolerated method for the evaluation of the entire large fibre somatosensory pathway both in health and in neurological diseases (Desmedt 1971; Desmedt and Noel 1973; Jones 1982; Aminoff 1984; Brown and Feasby 1984b; Lancet Editorial 1987; Chiappa 1987).

Thus, the SEP studies enable us not only to assess the peripheral segments but also the inaccessible proximal segments of the peripheral sensory fibres and spinal roots in addition to the central pathways and can identify lesions at various levels of the neuraxis (Desmedt and Noel 1973; Noel and Desmedt 1975; Brown and Feasby 1984b; Lancet Editorial 1987; Chiappa 1987). Repeated SEP studies in normal subjects have shown that they are highly reproducible with very little variation in latencies of the SEP components (De Weerd 1986). In our patients latencies of EP and N13 negative peaks of median nerve SEP were corrected for arm length to enhance sensitivity since both of these latencies have been found to correlate with the height of the subject or the arm length (Matthews et al 1974; Eisen and Nudleman 1978; Hume and Cant 1978; Eisen and Odusote 1980; Ganes 1980; Chu and Hong 1985). More emphasis was placed on recording SEP to median nerve stimulation since technically satisfactory responses to peroneal

or tibial nerve stimulation are often harder to obtain and differentiation of their peripheral and central components is difficult (Aminoff 1984).

BAEP is an objective measure of the integrity and function of the auditory sensory pathway traversing the brainstem. The clinical value of the BAEP is largely based on the finding that the latencies of the individual waves are highly reproducible in the same individual and show a remarkably little variation interindividually even though amplitudes may vary considerably (Rowe 1978; Chiappa et al 1979). Factors like inattention to the stimulus (Picton et al 1974), level of consciousness (Picton et al 1974) and drugs (Stockard et al 1977b) have no effect on the early components of the BAEP. The most consistent and clinically valuable part of the BAEP is composed of 5 waves recorded within the first 10 ms after the stimulation (Stockard et al 1977a; Chiappa et al 1979). The sensitivity, specificity and inter- and intra-individual reproducibility of the BAEP are further enhanced by the standardisation of stimulus characteristics (Stockard et al 1979). In one report repeated studies of BAEP in 50 normal subjects over a period of 2-3 months showed no statistically significant changes in amplitudes or latencies with the passage of time (Chiappa et al 1979).

Pattern reversal visual evoked potential (PRVEP) unlike the flash response is very consistent response and very sensitive to pathological changes in the visual pathway even when they are subclinical (Halliday 1982b). A thorough understanding of the normal response and a clear delineation of the limits of its variability in a healthy population form a firm basis for

recognising abnormalities. Principal causes of inter-individual variability are variations in the character and properties of the stimulus, minor differences in the anatomical structures and generators of the visual pathway in different individuals and subjective behavioural factors including the cooperation of the subject in continuous fixation on the centre of the stimulating checkboard (Halliday 1982a). The intra-individual variation of the amplitude and latency of the PRVEP and the difference between the two sides are much less than their inter-individual variability. The PRVEP is, therefore, even more sensitive to pathological changes of the visual pathway when serial studies are performed or responses from both eyes are compared in cases of a unilateral lesion or a bilateral lesion involving both eyes unequally (Halliday 1982b).

The method used for the assessment of pupillary diameter, pupillary reflexes and pupillary response to pharmacological agents represent an accurate, quantitative, reproducible and sensitive technique to detect abnormalities of the pupillary reflex pathways, to characterise these abnormalities and to monitor their changes during the course of an illness (Ramsay 1986; Ramsay and Woodruff 1987). Changes in pupillary sensitivity to pharmacological agents (sympathomimetic and parasympathomimetic) are of considerable value in identifying the site of the lesion in pupillary abnormalities (Adler and Scheie 1940; Bourgon et al 1978). Repeated measurements of both the darkness reflex and pupillary accommodation reflex produced highly reproducible results in the same individual and among different individuals (Ramsay and Woodruff 1987). The greatest error of

repeated measurements of pupillary diameter was less than 3.5% of the mean value which implied a potential error of 0.09 mm at 99% CL. The measurement of the pupillary diameter to the nearest 0.1 mm, therefore, gave an accurate indication of pupillary size (Ramsay and Woodruff 1987). Application of the technique to patients with Horner and Homes-Adie's syndromes demonstrated a high sensitivity in revealing and quantifying pupillary dysfunction in these conditions (Ramsay 1986; Ramsay and Woodruff 1987).

CHAPTER 4

RESULTS OF THE NEUROPHYSIOLOGICAL TESTS

POSITIVE EVIDENCE FOR PERIPHERAL NERVE INVOLVEMENT

The results of the serial multimodal neurophysiological tests provided convincing evidence of peripheral nerve dysfunction in all seven patients with the MFS.

EMG AND NC STUDIES: No abnormal spontaneous activity at rest was found in any of the muscles tested by needle EMG at any stage of examination. Analysis of individual motor units revealed normal amplitudes, durations and waveforms. Recruitment patterns were not reduced. Facial muscle EMG revealed no signs of denervation.

The SDMLs and FMNCVs were within the normal limits in five cases for the right common peroneal, right ulnar and right median nerves (Figure 5). In the remaining two patients these values were abnormal for the median nerve but normal for the ulnar and common peroneal nerves. On subsequent tests, however, all FMNCVs increased and SDMLs decreased progressively (Figure 5). These improvements, including those from the first five patients, were significant when compared with the normal variance of multiple testing of age and sex matched controls (P values between 0.01 and 0.001). These results suggest that there may have been some dysfunction, albeit mild, in the distal segments of these nerves initially which improved on subsequent testing. These conventional motor studies test the largest diameter motor fibres of 12-20 μm and do not test the slower motor fibres (Dorfman 1984). In demyelination neuropathies, it is only when a relatively considerable degree of demyelination occur in the distal segments

FIGURE 5

Results of serial motor nerve conduction and F-wave latency measurements in 7 patients with the Miller Fisher syndrome. Note the more pronounced abnormality of F-wave latencies than the more distal conduction studies. All parameters improved to normal values with time. Horizontal lines represent upper (or lower) limits of normal at mean + 2SD (see appendix). The axes of the FMNCV are reversed so that abnormalities are shown as shifts in an upwards direction for all the parameters.

SDML = Shortest Distal Motor Latency

FMNCV = Fastest Motor Nerve Conduction Velocity

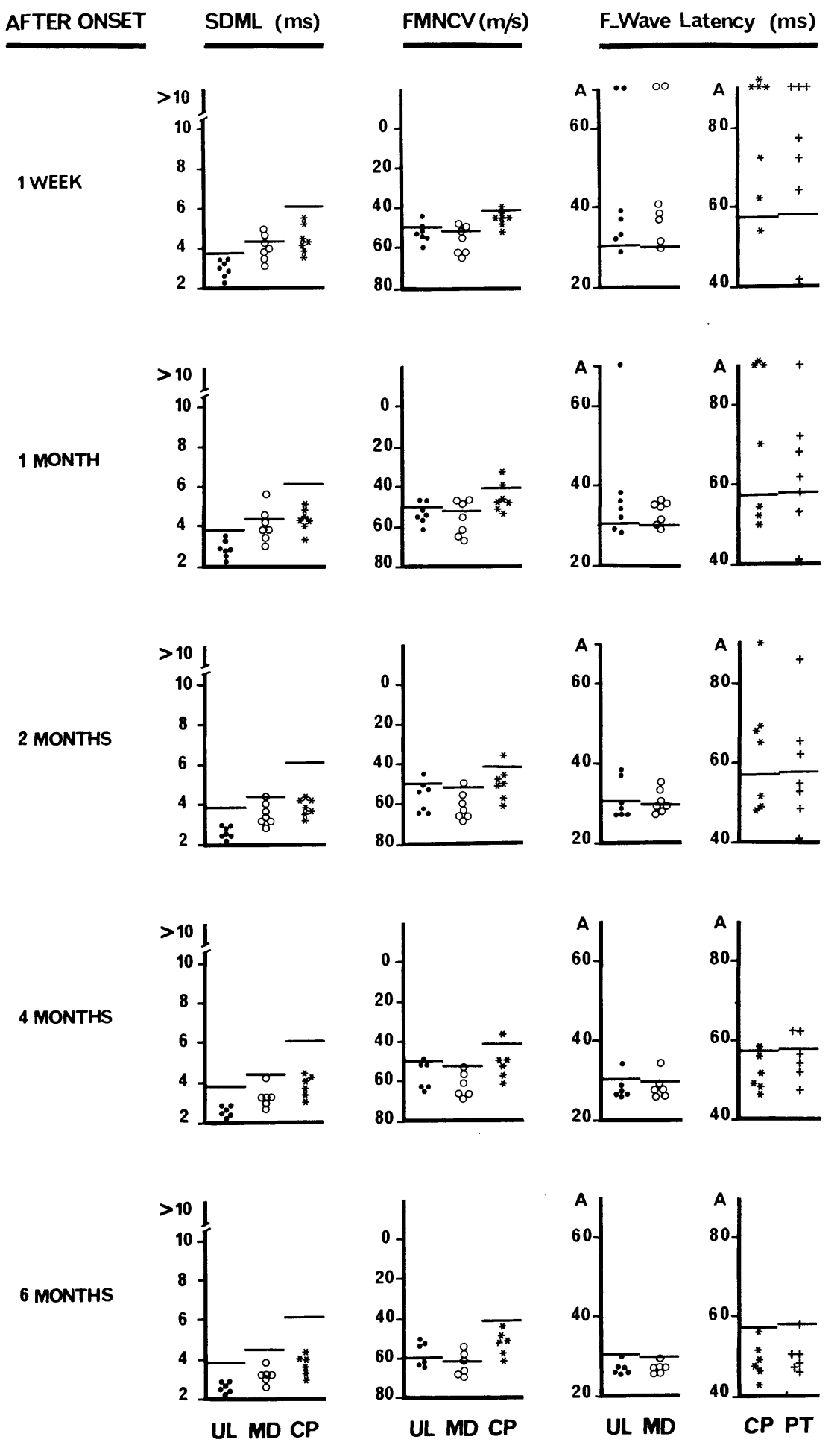
UL = Ulnar Nerve

MD = Median Nerve

CP = Common Peroneal Nerve

PT = Posterior Tibial Nerve

A = Absent


AFTER ONSET
SDML (ms)
FMNCV (m/s)
F-Wave Latency (ms)
1 WEEK
1 MONTH
2 MONTHS
4 MONTHS
6 MONTHS
>10
10
8
6
4
2
0
20
40
60
80
A
60
40
20
80
60
40
UL MD CP
UL MD CP
UL MD
CP PT

of the large diameter faster conducting motor axons that a significant delay in motor conduction and a diminution in the amplitude of the evoked compound muscle action potential (CMAP) become evident (Kimura 1984). A method for testing the smaller diameter motor axons has been described by (Hopf 1963). The method, however, does not give reproducible values and produces unreliable results (Goodgold and Eberstein 1983).

Serial studies of SNAPs for the right sural, ulnar and median nerves showed some initial abnormalities of amplitude, latency and duration (Figures 6 & 7). Thus, reduction of peak to peak amplitude, prolongation of the peak latency and abnormal dispersion of the SNAPs were seen to variable degrees in all patients initially and all these parameters progressively improved on serial measurements in a significant fashion including those SNAPs which initially had their parameters within the normal limits (Figures 6 & 7). Dispersion of the SNAP usually arises as a result of asynchronisation of the afferent volley due to segmental demyelination in the large diameter sensory fibres (Buchthal et al 1984). Demyelination will also result in diminution of the amplitude and prolongation of the latency of the SNAP (Buchthal et al 1984). The SNAP recording tests responses from the distal segments of the large diameter sensory fibres of 6 - 12 μm in diameter (Buchthal et al 1984). Its assessment provides the most sensitive indication of mild to moderate demyelination in the distal segments of peripheral nerves (Rosenfalk and Buchthal 1970). Slowed conduction and slight reduction in the amplitude of the SNAP may occur in the absence of any abnormality of conduction of the fastest motor fibres (Rosenfalk and Buchthal

FIGURE 6

Serial sensory nerve action potential (SNAP) studies in three cases of the Miller Fisher syndrome (cases 1, 2 and 3) to demonstrate the progressive improvement with time in their amplitude, peak latency and duration on serial testing. Definite abnormality in some of the SNAPs was present initially. The shadowed bars represent the range of normal negative peak latency for each SNAP.

(Jamal and Ballantyne 1987b, reproduced with permission).

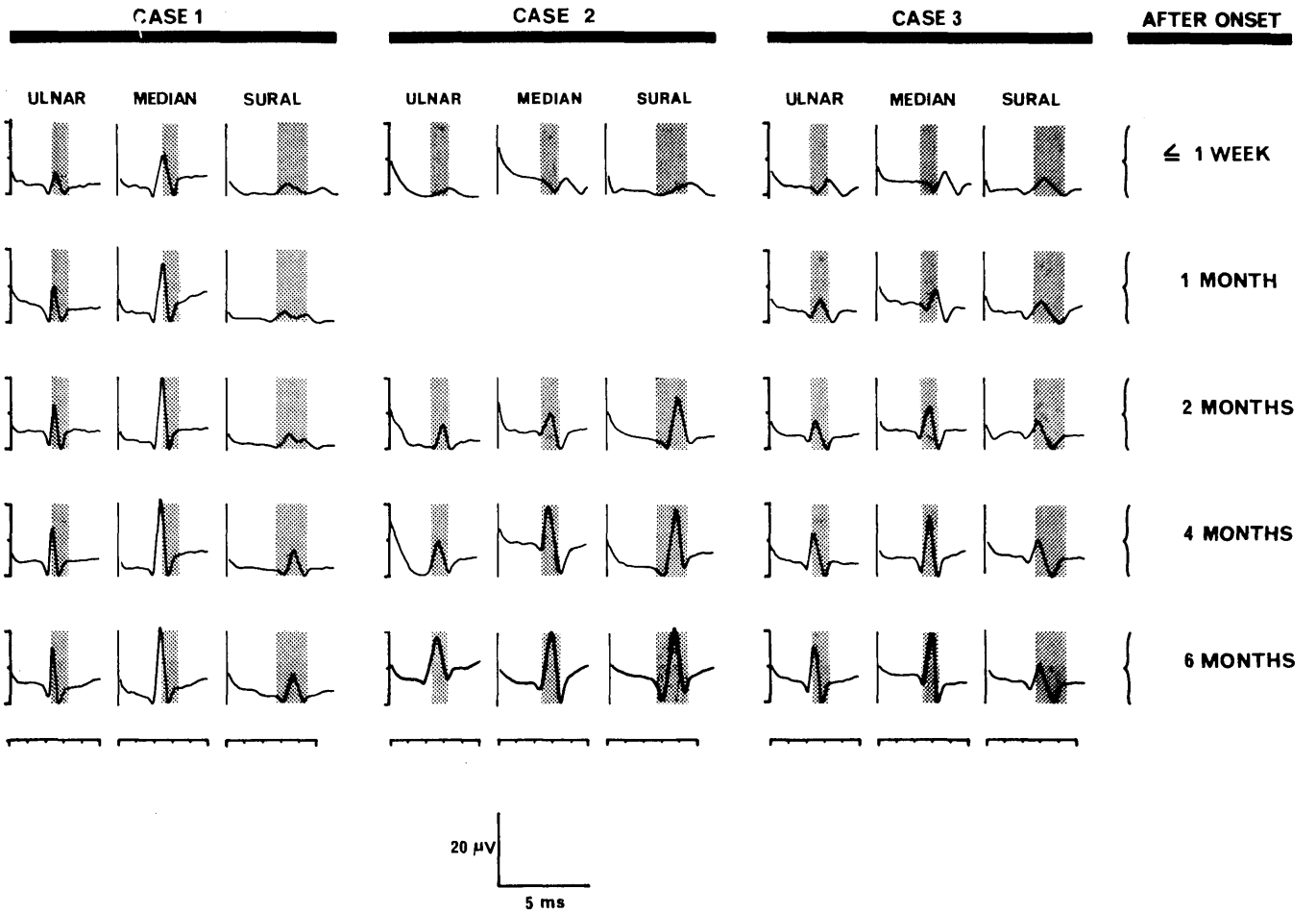

CASE 1
CASE 2
CASE 3
AFTER ONSET
ULNAR
MEDIAN
SURAL
ULNAR
MEDIAN
SURAL
ULNAR
MEDIAN
SURAL
≦ 1 WEEK
1 MONTH
2 MONTHS
4 MONTHS
6 MONTHS
20 μV
5 ms

FIGURE 7

Results of serial sensory nerve action potential (SNAP) studies in 7 cases with the Miller Fisher syndrome represented in a graphical form. Definite abnormality in some of the SNAPs was present initially but they showed progressive improvement in all their parameters with time. Horizontal lines represent upper (or lower) limits of normal at mean + 2SD (see appendix). The axes of the AMP are reversed so that abnormalities are shown as shifts in an upward direction for all the parameters.

AMP = Amplitude (peak to peak)

LAT = Latency (to negative peak)

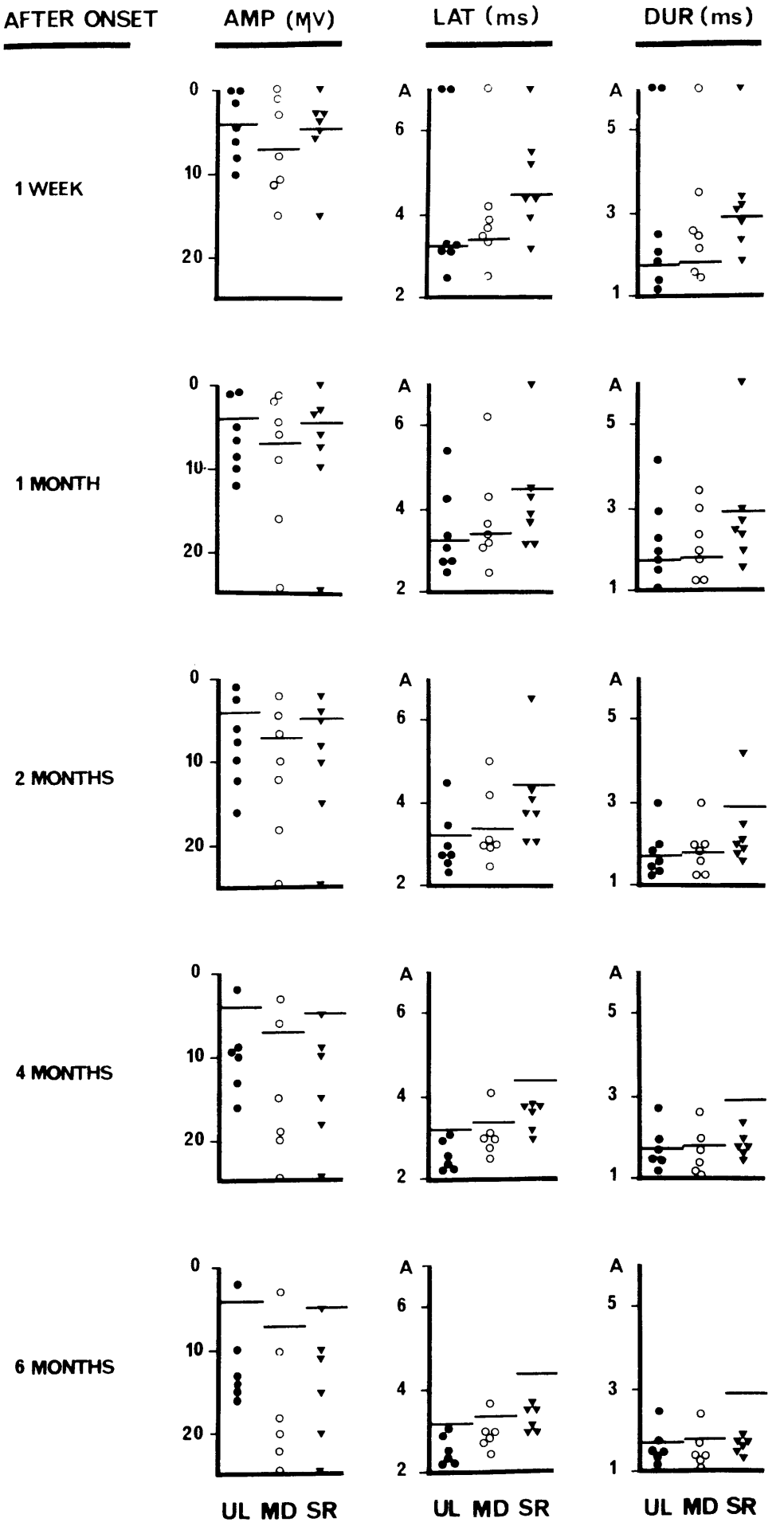
DUR = Duration

UL = Ulnar

MD = Median

SR = Sural

A = Absent


AFTER ONSET
AMP (MV)
LAT (ms)
DUR (ms)
1 WEEK
1 MONTH
2 MONTHS
4 MONTHS
6 MONTHS
0
10
20
A
6
4
2
5
3
1
UL MD SR
UL MD SR
UL MD SR

1970).

LATE RESPONSE (F-WAVE AND H-REFLEX) STUDIES: Unlike the conventional conduction studies, these tests the conduction along the entire course of the axons including the most proximal inaccessible segments.

F-wave studies showed abnormalities at the onset in all seven patients (Figure 5). Some of the F-waves were absent while others showed abnormal prolongation of their latencies and were inconsistently recorded at the onset of their illness but they rapidly and progressively improved on subsequent testing (Figure 5).

It is generally believed that the F-wave is induced by recurrent discharge (or backfiring) of the alpha motor neurones activated by antidromically travelling impulses from the site of peripheral nerve supramaximal stimulation (Kimura 1983b). It is estimated that about 1-5% of the axons stimulated are involved in the formation of individual F-waves (Fullerton and Gilliatt 1965; Kimura 1985). Hence, the F-wave latency includes the conduction time of the motor impulse to the spinal cord from the stimulation site and from the spinal cord to the target muscle. F-wave determination, therefore, assesses the proximal segment of alpha motor axons in the upper and lower limbs which is not obtainable with conventional motor conduction measurements. The much more marked abnormalities of F-wave compared to conventional motor conduction studies (Figure 5) suggest a marked block to conduction at the level of the proximal nerve segments, plexuses or spinal roots (Kimura and Butzer 1975; Shahani et al 1980; Ropper and

Shahani 1984). The considerable prolongation of the F-wave latencies, seen either initially or at some stage during recovery in all patients (Figure 5), is highly suggestive of a demyelination abnormality in the proximal segments of the peripheral nerves (kimura and Butzer 1975; Shahani et al 1980; Kimura 1983b) and the return of these latencies to normal values indicates recovery of conduction across these proximal segments (Kimura 1983b).

H-reflexes were absent initially in all seven patients (table 6). They remained absent in case 4 till one month, cases 1 and 2 till two months, case 5 till four months and cases 3 and 6 till six months after onset of the MFS after which times they reappeared and showed a progressive decrease in latency and increase in amplitude to eventually lie within normal limits (table 6). This normalisation of H-reflex latency took four months in case 4, six months in cases 1, 2 and 5 and eighteen months in cases 3 and 6 (table 6). The H-reflex was bilaterally absent in case 7 and remained so when examined two months after onset of the neurological illness (table 6).

The H-reflex, elicited by submaximal stimulation of the tibial nerve at the popliteal fossa, tests the proximal segments of that nerve (Kimura 1983c). Hoffmann (1922) believed that this was a monosynaptic reflex and this view was supported by subsequent studies (Magladery et al 1951; 1952). This monosynaptic reflex arc is composed of large diameter Ia afferent and α-motor efferent fibres both contained in the proximal segments of the posterior tibial nerve. The reflex is conducted in a portion of the neural pathway which is the same as that of the ankle jerk

TABLE 6

Serial H-Reflex Studies in seven patients with the Miller Fisher Syndrome

Case No	H-Reflex latency (ms)					
	1 week	1 month	2 months	4 months	6 months	18 months
1	A	A	40	36	35	ND
2	A	A	38.4	38	32.8	ND
3	A	A	A	A	A	34.6
4	A	39	38	33	32	ND
5	A	A	A	A	35	ND
6	A	A	A	A	A	ND
7	A	A	A			

A : Absent

ND : Not done

(T-reflex) (Kimura 1983c). The two are, however, not synonymous as in the H-reflex the afferent fibres are stimulated directly, thus bypassing the muscle spindles, and are free from any direct involvement of the fusimotor system (Messina et al 1976; Kimura 1983c). The H-reflex latency is, therefore, a measure of conduction velocity in the proximal segment of the posterior tibial nerve. Whether the abnormality of the H-reflex detected in the MFS patients is due to a lesion in the sensory or motor fibres or both is unknown. However, the absence of significant limb weakness in most of these patients and normal F-wave latency from the posterior tibial nerve in cases 2, 3, 6 and 7 with absent H-reflex initially or at some stage thereafter might favour abnormality in the afferent fibres of the reflex arc at least in these patients.

MUN ESTIMATION: MUN estimation in the right EDB muscle was performed in cases 2 and 3 at presentation and also six months from the onset of the MFS. The MUN was abnormally reduced in both cases with values of 40 in case 2 and 74 in case 3 (lower limit of normal is 98). These values rose significantly when re-estimated six months later in both cases. In case 2 it rose from 40 to 97 and in case 3 it rose from 74 to 217. Both of these changes were well outside the upper limit of normal variation derived from repeated application of the technique on different days to a normal control group in the same laboratory (Ballantyne and Hansen 1974a; appendix).

These results indicate loss of function in peripheral motor nerve fibres to the EDB muscle. Significant rises in MUN in both patients (in patient 2 to just below normal and in case 3 to

normal values) indicate a significant increase in the number of functioning motor axons to the EDB muscle in these two patients over a period of six months. This in turn indicates a progressive return of function in the peripheral motor nerve fibres probably from remyelination (see chapter 7 for further discussion). This is further clear evidence of a distal peripheral motor nerve involvement in these patients which is probably too mild in nature to be reflected on the conventional conduction studies. The findings in these two patients with the MFS are very similar to results of sequential studies in patients with the Guillain-Barre´ syndrome using the same technique (Martinez-Figueroa et al 1977; Hansen et al 1982).

FACIAL NERVE MOTOR CONDUCTION AND BLINK REFLEX STUDIES: The facial D-response was abnormally prolonged in case 2 on the right side and case 5 on both sides indicating abnormality of conduction in the facial nerve and these improved progressively on repeated measurement (Figure 8). D-responses in the cases 1, 3, 4, 6 and 7 had parameters within the normal range initially though their latencies showed some progressive improvement on subsequent studies (Figures 9 & 10). Nerve conduction studies of the facial nerve only test the peripheral segment of the nerve and cannot detect lesions localised to the proximal segment of the nerve (Kimura 1983a). The latter portion of the facial nerve is tested with blink reflex studies.

Blink reflex studies showed abnormalities on both sides in cases 4,5 and 7 and on one side in cases 2 and 3. Figure 10 illustrates the findings in case 3. The initially prolonged R1 latency mainly on the left side is shown to return to normal on

FIGURE 8

Serial direct facial motor responses (D-response) to facial nerve stimulation, and blink reflex studies to supra orbital nerve (SON) stimulation in a patient with the Miller Fisher syndrome (case 2). Recordings were made from orbicularis oculi muscles simultaneously using the same setting of recording electrodes. Shadowed bars represent the normal range of onset latency for R1 and D-response and vertical dotted lines represent the upper limits of normal onset latency for R2 responses.

D-response and R1 were abnormal on the right (R) side (the patient had right sided facial weakness) and R2 was abnormally prolonged on the same side to equal degrees on ipsi- or contra-lateral SON stimulation. These parameters progressively improved to normal values with time.

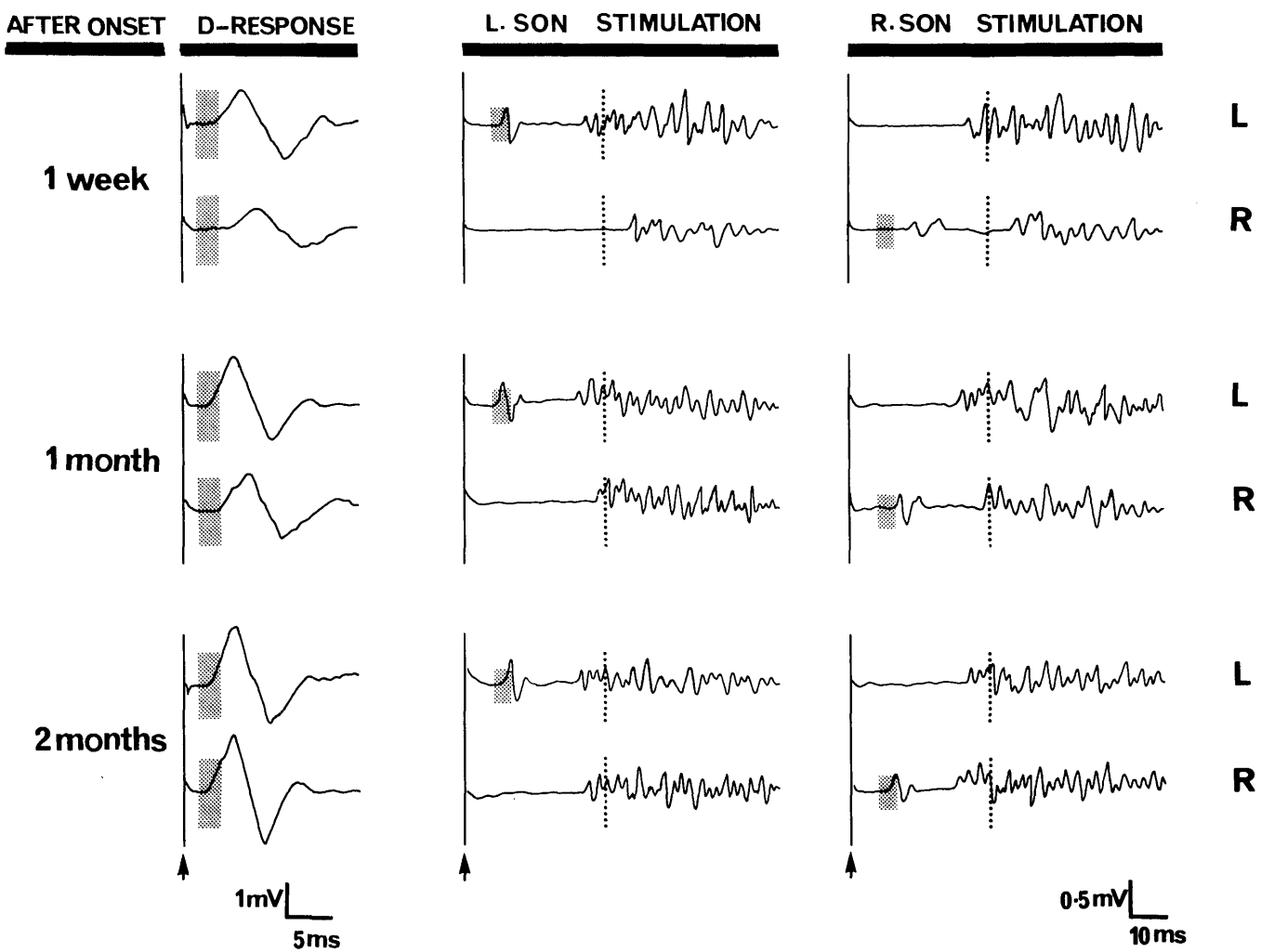

AFTER ONSET
D-RESPONSE
L. SON STIMULATION
R. SON STIMULATION
1 week
1 month
2 months
L
R
L
R
L
R
1mV
5ms
0·5mV
10ms

FIGURE 9

Serial direct facial motor response (D-R) to facial nerve stimulation, and blink reflex studies to supra orbital nerve (SON) stimulation in 7 patients with the Miller Fisher syndrome. Recordings were made from orbicularis oculi muscles simultaneously using the same setting of recording electrodes. Horizontal lines indicate upper limits of normal for each parameter. Solid dots represent patients with bilateral facial abnormalities.

The main abnormalities were in the blink reflex studies and unless bilateral, R2 only on the side of abnormality of D-R and R1 was prolonged in each case. All parameters progressively improved to normal values with time.

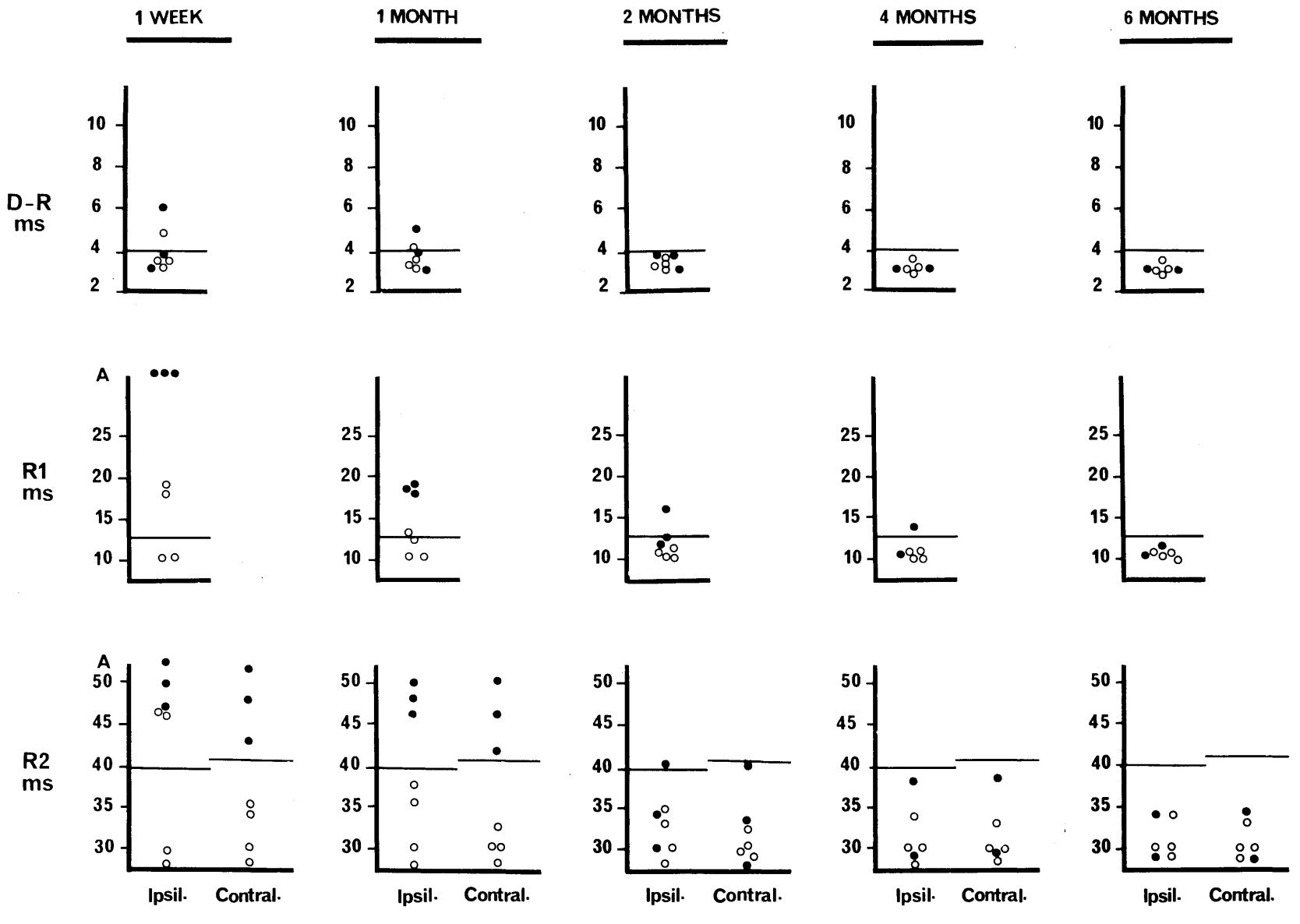
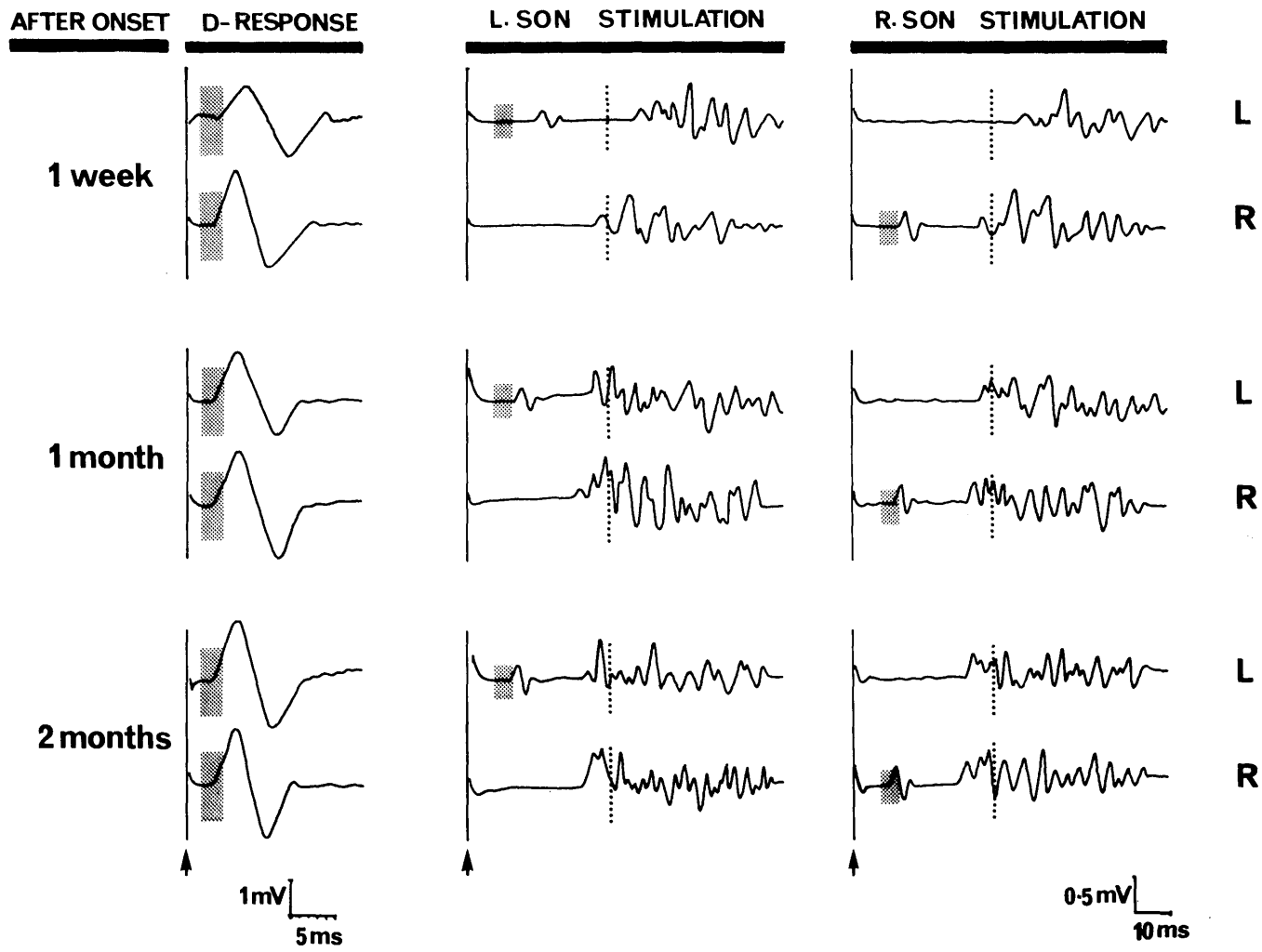

1 WEEK
1 MONTH
2 MONTHS
4 MONTHS
6 MONTHS
D-R ms
R1 ms
R2 ms
A
10
8
6
4
2
25
20
15
50
45
40
35
30
Ipsil.
Contral.

FIGURE 10

Serial direct facial motor response (D-response) to facial nerve stimulation, and blink reflex studies to supra orbital nerve (SON) stimulation in a patient with the Miller Fisher syndrome (case 3). Recordings were made from orbicularis oculi muscles simultaneously using the same setting of recording electrodes. Shadowed bars represent the normal range of onset latency for R1 and D-response and vertical dotted lines represent the upper limits of normal onset latency for R2 responses. The main abnormality is in the blink responses. The latency of R1 was abnormally prolonged on the left (L) side (the patient had left sided facial weakness) and R2 was abnormally prolonged on the same side to equal degrees on ipsi- or contra-lateral SON stimulation. These parameters progressively improved to normal values with time.

(Jamal and Ballantyne 1987b, reproduced with permission).


AFTER ONSET
D-RESPONSE
L. SON STIMULATION
R. SON STIMULATION
1 week
1 month
2 months
L
R
L
R
L
R
1mV
5ms
0·5mV
10ms

subsequent testing. The latency of R2 on the left side is consistently and about equally prolonged on ipsilateral or contralateral supraorbital nerve stimulation. All the latencies became normal in the study repeated two months after the onset of the illness. Improvement in these responses was also accompanied by some improvement of the D-responses particularly that from the left side in terms of latency and duration. Similar changes to those of case 3 were found in the studies of case 2 which showed prolongation of latency of R1 on the right side and consistent prolongation of R2 latency and reduction of its amplitude on the right side in response to either side stimulation of the SON (figure 8) . In addition, the D-response on the right side was abnormally prolonged in latency and duration. These changes in case 2 also progressively improved to lie within the normal limits in the study performed two months after the onset of symptoms (figure 8). Patients 3, 4 and 7 had abnormalities similar to those seen in case 3 (figure 10) while patient 5 showed abnormalities similar to those recorded in case 2 (figure 8). The remaining two patients (cases 1 & 6), who had no clinical facial weakness (table 5), showed no abnormality in these studies. All latencies became normal four months after the onset of the MFS (figure 9). These improvements were accompanied by clinical improvement in the facial weakness (see chapter 2).

All the existing experimental evidence supports the thesis that both components of the blink reflex are part of the polysynaptic blink reflex which is similar to other cutaneous double component reflexes recorded in man and there is no anatomical or physiological support for the original contention

that R1 component is a monosynaptic proprioceptive reflex similar to the H-reflex (Shahani and Young 1968, 1972; Shahani et al 1970). The afferent arc is provided by sensory divisions (1st and 2nd) of the trigeminal nerve whereas motor axons in the facial nerve form its efferent arc (Kimura 1983a). It is believed that the afferent impulses for the R2 component descend ipsilaterally to the spinal tract of the trigeminal nerve and ascend to make bilateral connections with facial nuclei (Kimura and Lyon 1972). The blink reflex, therefore, reflects conduction along the afferent and efferent and central brainstem pathways including the entire length of the facial nerve and especially the most commonly involved intraosseous portion of the nerve. In the latter circumstance changes in the two components of the blink reflex can be recorded at a time when conventional electrodiagnostic methods fail to reveal any dysfunction in the facial nerve.

The latency of R1 represents the conduction time along trigeminal and facial nerves and the pontine relay. R1 was prolonged in latency in all patients with abnormal blink reflex studies (Figure 9). In addition, a consistent prolongation of R2 components on the same side (s) with abnormal R1 was also seen in all patients with abnormal blink reflex studies regardless of the side of stimulation of the SON (Figures 8, 9 & 10). This prolongation of R2 was of equal degree in each patient on each side irrespective of the side of SON stimulation (Figure 8 & 10). These findings suggest an abnormality of conduction in the efferent arc (the facial nerve) of the reflex pathway (Kimura 1983a). This was confirmed in all of the five patients who had abnormal blink reflex by simultaneous recording of R2 components

from both sides, using the same electrode setting, in response to a glabellar tap which triggers the sweep of the recorder. This glabellar tap stimulates both trigeminal nerves simultaneously, each of which activates the facial nuclei on both sides (Kimura 1983a). A consistent R2 latency prolongation was seen on the same sides as seen on blink reflex studies and to the same degree, confirming that the abnormality lay in the facial nerve in each of the five patients (Kimura 1983a). D-response and/or blink reflex abnormalities were, therefore, recorded in all those patients who had clinical involvement of facial muscles and these abnormalities indicated a facial nerve dysfunction. Gradual recovery of these abnormalities accompanied clinical improvement in all patients.

QUANTITATIVE STUDIES OF SOMATIC SENSATION:

THERMAL THRESHOLD MEASUREMENT: Thermal thresholds were initially abnormally high at the ankle in all three patients tested but subsequently returned to normal values in repeated longitudinal studies (Figure 11). Wrist HT and CT were not outside the normal limits in case 1 but they showed significant improvement on subsequent studies (Figure 11). Patient 3 had his wrist CT abnormally increased initially but his wrist HT was within the normal range. Both of these, however, showed progressive and significant improvement on subsequent testing (Figure 11). In patient 2, both wrist HT and wrist CT values were normal and showed no significant change on subsequent testing from the initial values. These studies were not applied to cases 4, 5, 6 and 7 who had clinical evidence of sensory involvement (table 5).

Unlike the SNAP, VPT and SEP studies, the technique of Jamal

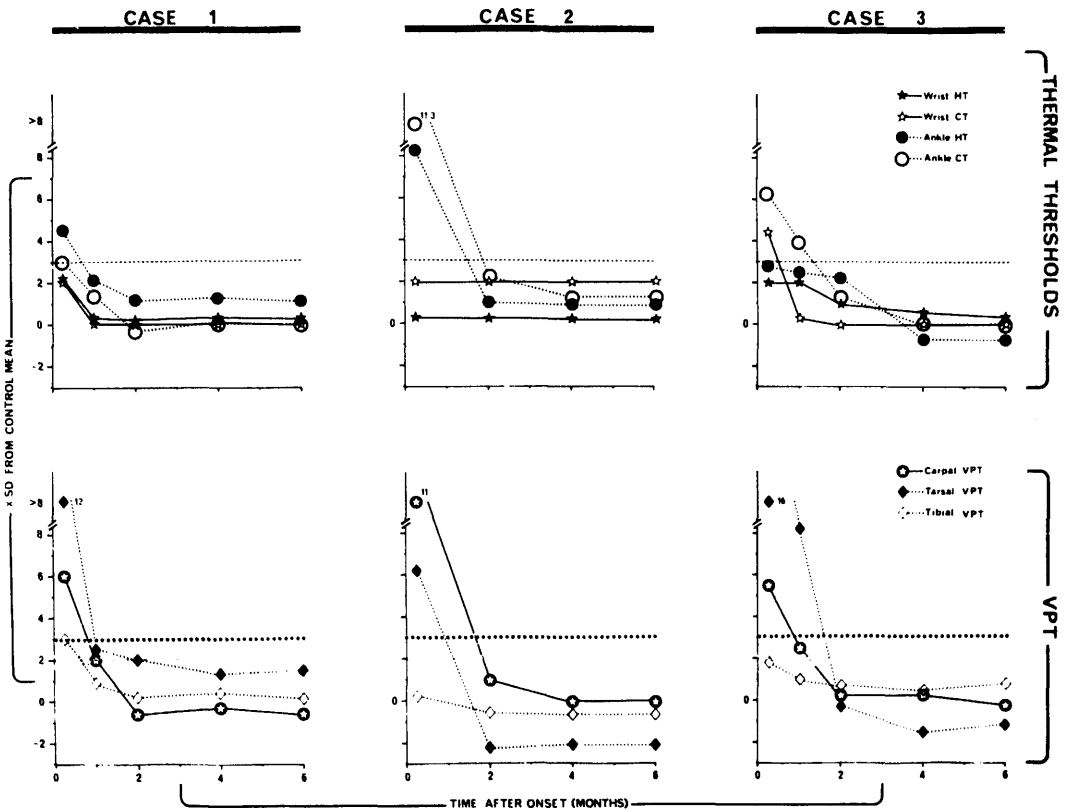
FIGURE 11

Serial thermal and vibration perception threshold (VPT) measurements in three patients with the Miller Fisher syndrome who had no clinical abnormality of sensation. Each threshold value is expressed as a figure representing the number of standard deviations (xSD) from the mean control value (represented as zero).Ordinates show these values (negative below mean and positive above mean control value for that test).The upper limit of normal threshold measurements (mean + 3SD) are indicated by transverse interrupted lines.

HT= Heat Threshold

CT= Cold Threshold

(Jamal and Ballantyne, 1987b , reproduced with permission).


CASE 1
CASE 2
CASE 3
THERMAL THRESHOLDS
Wrist HT
Wrist CT
Ankle HT
Ankle CT
VPT
Carpal VPT
Tarsal VPT
Tibial VPT
x SD FROM CONTROL MEAN
TIME AFTER ONSET (MONTHS)

et al (1985a, b) examines the small fibre thermal afferent pathways. It cannot, however, distinguish between peripheral and central involvement of the pathways (Jamal et al 1985 a, b; 1987 a; Jamal 1986). The greater and more frequent abnormality of thermal thresholds at the ankle compared with wrist in the three patients with the MFS examined, is similar to the pattern of somatic sensory abnormalities found in patients with peripheral neuropathy (Jamal et al 1985b; 1987a).

VIBRATION THRESHOLD MEASUREMENT: Vibration perception thresholds (VPTs) were measured serially on the dorsal aspect of the right second metacarpal bone, on the dorso-medial aspect of the middle of the right first metatarsal bone and the right tibial tubercle in cases 1, 2 and 3. The results are summarised in Figure 11. The VPTs were abnormally increased initially in all the three patients and returned to normal values within two months from the onset of the MFS. The VPT measurement was not performed in cases 4, 5, 6 and 7.

The vibration sense is mediated by the large diameter afferent nerve fibre pathway (Iggo 1982). Accurate quantification of this sensation, therefore, provides a sensitive index for the functional integrity of the vibration sensation pathway which is part of the large fibre afferent pathway (Goldberg and Lindblom 1979; Iggo 1982). Abnormalities of the SNAPs which occurred in all three patients with abnormal VPT (Figures 6 & 11) indicate a peripheral large fibre afferent pathway dysfunction (Buchthal et al 1984). This peripheral dysfunction was also confirmed by SEP studies (see Figures 13 & 14) which also showed no central conduction abnormality. It is, therefore, highly likely that the

VPT abnormalities in these three patients with the MFS are at least in part of a peripheral origin.

The presence of abnormalities in the thermal and vibration studies in these three cases with the MFS without obvious clinical involvement of the limbs most probably reflects subclinical dysfunction of these two pathways since loss of function of a large number of sensory fibres is necessary before any clinical abnormality of sensation appears (Ropper and Shahani 1984). Cases 4, 6 and 7 had sensory changes on clinical examination including vibration (cases 4, 6 and 7), pin prick (cases 4, 6 and 7) and temperature (case 7) sensation (table 5).

SILENT PERIOD STUDIES: Table 7 summarises the results of serial SP studies on both upper and lower limb muscles in cases 4, 5, 6 and 7. The duration and the presence or absence of SP were noted (see chapter 3) and its abnormality was determined accordingly (Shahani and Young 1973). Figure 12 shows such a recording from the abductor digiti minimi muscle in patient 4. The second half of the SP was absent initially but returned one month later. A consistent disparity between distribution of the SP abnormality and joint position sense dysfunction was present in all patients so that in any limb, abnormality of SP was accompanied by a clinically intact joint position sense while normality of the SP was accompanied by a dysfunction of joint position sense (table 7). This disparity was always associated with the presence of ataxia of gait and disappearance of this disparity was almost always accompanied by a clinical recovery of the gait ataxia in these patients (table 7, Figure 12).

A number of factors both peripheral and central are recognised

TABLE 7

Correlation of sequential examination of joint position sense and silent period studies with the severity of the ataxia in 4 patients with the Millder fisher syndrome

Case No	Parameter		1 week	1 month	2 months	4 months	6 months
4	ataxia*		++++	-			
	upper limb	JP	N	N			
		SP	A	N			
	lower limb	JP	N	N			
		SP	A	N			
5	ataxia		++++	+	+	-	
	upper limb	JP	N	N	N	N	
		SP	A	A	N	N	
	lower limb	JP	N	N	N	N	
		SP	A	N	N	N	
6	ataxia		++++	++	++	+	+
	upper limb	JP	N	N	N	N	N
		SP	A	A	A	N	N
	lower limb	JP	A	A	A	A	A
		SP	N	N	N	N	N
7	ataxia		++++	++	-		
	upper limb	JP	A	A	A†		
		SP	N	N	N		
	lower limb	JP	N	N	N		
		SP	A	A	N		

* Grading of ataxia was as follows: - none; + minimal; ++ mild; +++ moderate; ++++ severe.

† Abnormality was found in DIP joints only

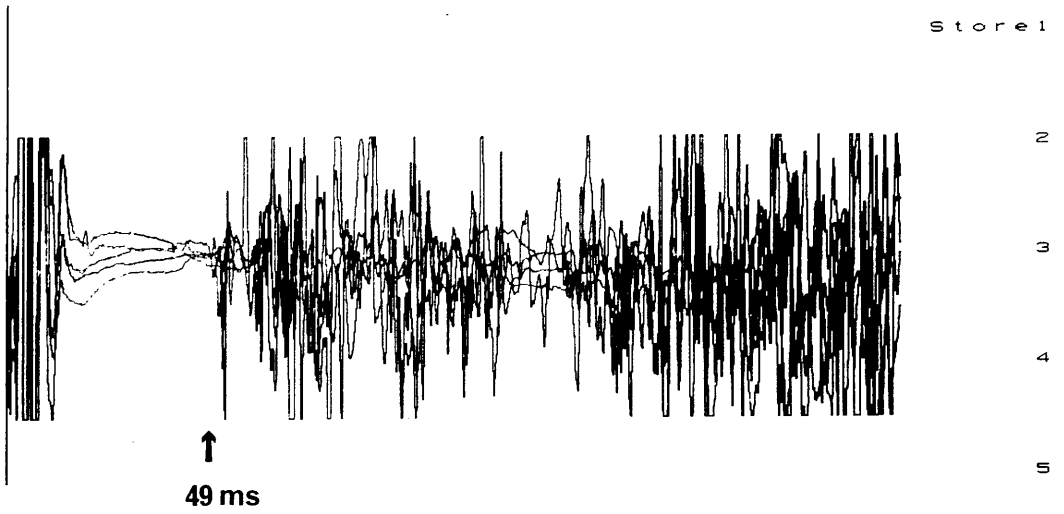
JP : Joint Position
SP : Silent Period
N : Normal
A : Abnormal

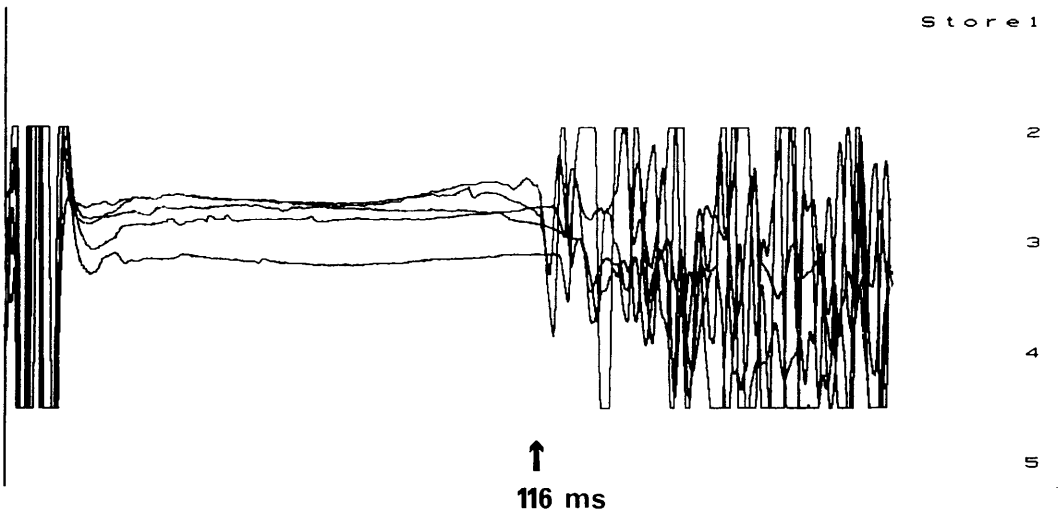
FIGURE 12

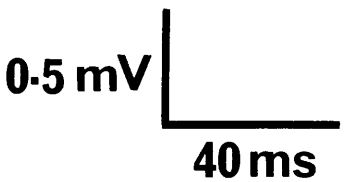
Silent periods (SP) recorded from the abductor digiti minimi to ulnar nerve stimulation at wrist with stimuli submaximal to the compound muscle action potential (CMAP) in a patient with the Miller Fisher syndrome (case 4).

At one week (top) the early part of the SP is present while the later "proprioceptive" part is absent. One month later (buttom) the SP was normal. During either study, no abnormality of upper limb joint position sense was present clinically but the patient had severe ataxia at the time of the first study. For interpretation of these findings see the text. Note that no F-wave is recorded as the stimuli were submaximal to the CMAP.

Arrows indicate the end of SP and values beneath indicate the duration of the SP measured from onset of the stimulus.Each recording represent five superimposed tracings.


Store1
2
3
4
5
49 ms


Store1
2
3
4
5
116 ms


0·5 mV
40 ms

to influence motor neurone excitability in man and thus play a role in the formation of SP in a muscle. These include the antidromic effect of a stimulus on motor axons, the Renshaw inhibition phenomenon and proprioceptive and cutaneous inputs to this "long loop" reflex pathway (Shahani and Young 1973). The first half of the SP is believed to be produced through antidromic effect on the motor axons of the stimulus and the Renshaw inhibitory phenomenon (Shahani and Young 1973). The second part of the SP (starting about 50 to 100 ms after the stimulus till the end of the SP) is produced by the cutaneous and proprioceptive peripheral input (Phillips et al 1971; Shahani and Young 1973). It is also possible that the Golgi tendon organs input contribute to the formation of the SP (Shahani and Young 1973). The second part of the SP is absent in facial muscles (Shahani and Young 1973) which were found to have no muscle spindles on careful examination in man (Gandiglio and Fra 1967) and in animals (Bruesch 1944; Bowden and Mahran 1956). The proprioceptive part of the SP which normally appears at the same time as the cutaneous part, can be selectively studied if a submaximal stimulus (to the CMAP), which mainly stimulates the proprioceptive rather than cutaneous fibres, is applied to a mixed nerve (Shahani and Young 1973; Ropper and Shahani 1983).

Abnormalities of the proprioceptive SP observed in our patients, therefore, reflect dysfunction of the large afferent proprioceptive fibre input from the muscles tested. From table 7, it is evident that this dysfunction of the proprioceptive input was not accompanied by abnormalities of joint position sensation in the same limb. This mismatching of input of information from

these two kinds of afferent units (muscle proprioceptive and joint kinesthetic units) to the cerebellum was found in a patient with the MFS by Ropper and Shahani (1983) and was proposed by the authors to be a possible underlying cause of the ataxia encountered in the MFS. These findings in our patients support this theory. A similar mismatching of afferent proprioceptive signals is thought to be partly the cause of the ataxia in spinocerebellar disease (Shahani et al 1973; Shahani and Young 1976). The same disparity in the function of muscle proprioceptive and joint kinaesthetic afferents has been found in patients with the Guillain-Barré syndrome with ataxia but not in those without ataxia irrespective of whether they had abnormalities of the SNAPs or not (Ropper and Shahani 1983).

SOMATOSENSORY EVOKED POTENTIAL (SEP) STUDIES: SEPs to median nerve stimulation at wrist were abnormal in all seven cases on presentation (Figure 13). Three patterns of abnormality were found on SEP studies. In cases 6 and 7 no SEPs could be recorded either to median nerve stimulation at wrist or to posterior tibial nerve stimulation at ankle (Figure 13). In these patients, the SNAPs including those from median nerve, were very abnormal, thus confirming the presence of peripheral dysfunction in the sensory fibres (Figure 7). Cases 1 and 3 (Figure 14) exemplify the other two types of abnormality encountered in the SEP studies. In case 1 the Erb's potential (EP) was within the normal limits but the EP - spinal (N13) conduction time was abnormally prolonged while the N13-N20 central conduction time was normal (Figure 14). In addition to these changes the EP potential of case 3 was abnormally small in amplitude and prolonged in latency (Figure

FIGURE 13

Results of serial somatosensory evoked potentials (SEPs) to right median nerve stimulation at wrist in 5 patients with the Miller Fisher syndrome*. Peripheral conduction time (EP latency: EP-N11 or EP-N13) is indicated in solid dots while central conduction time (N11-N20 or N13-N20) is shown in open circles. Control means and three standard deviations (SDs) on either side for each parameter are represented by the open bars (see appendix) . Two SD values above and below control mean for Erb's point potential (EP) latency are also shown as horizontal interrupted lines within the bars.
Abnormalities were mainly seen in the peripheral conduction time (EP - N11, EP - N13 and, to a lesser extent and less frequently, in the EP latency). No central conduction abnormality was found in any patient. The values for peripheral conduction time progressively improved with time.

* In the remaining 2 patients (cases 6 & 7), who showed gross abnormality of their median (and ulnar and sural) SNAPs, no SEPs could be recorded when attempted.

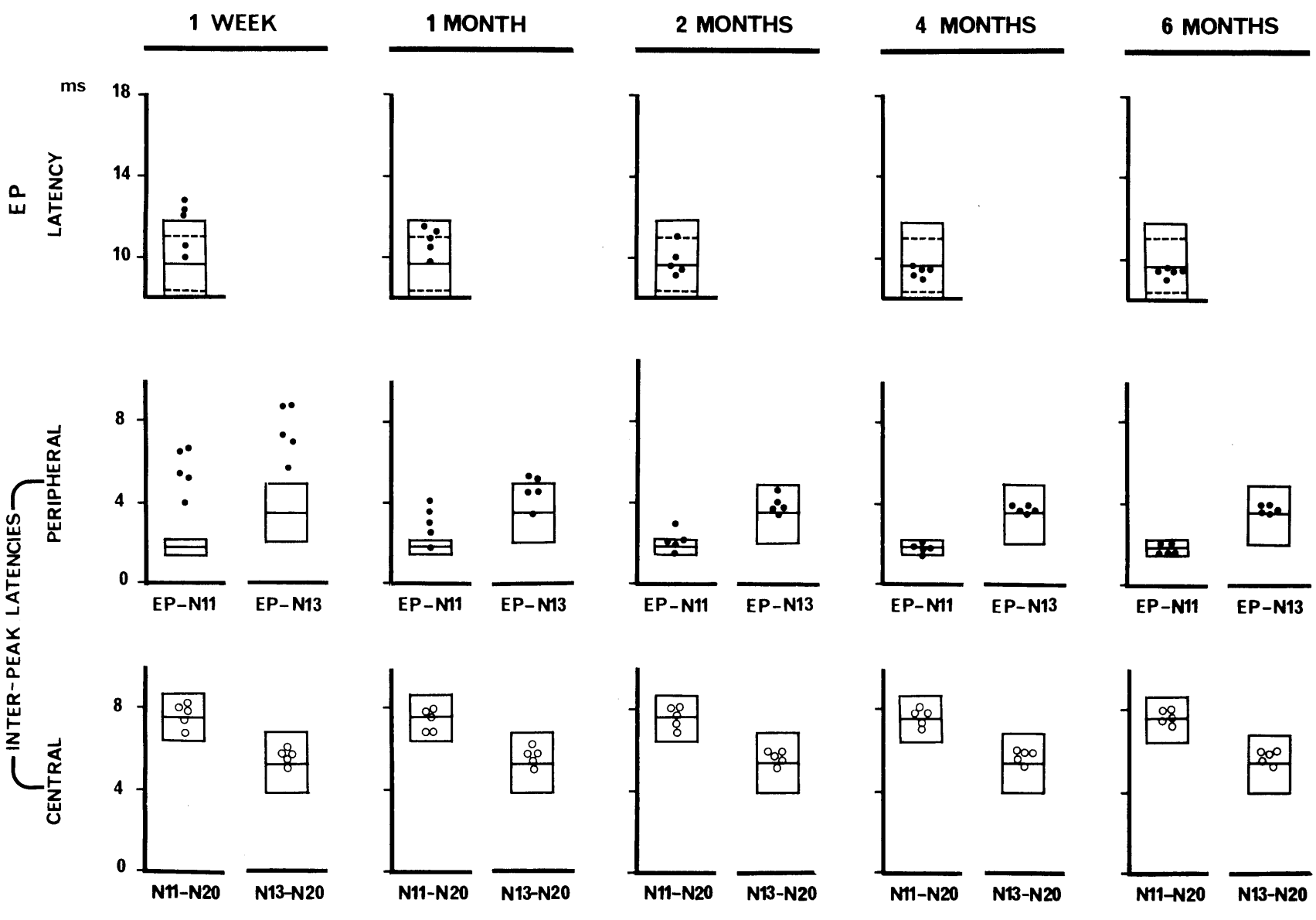
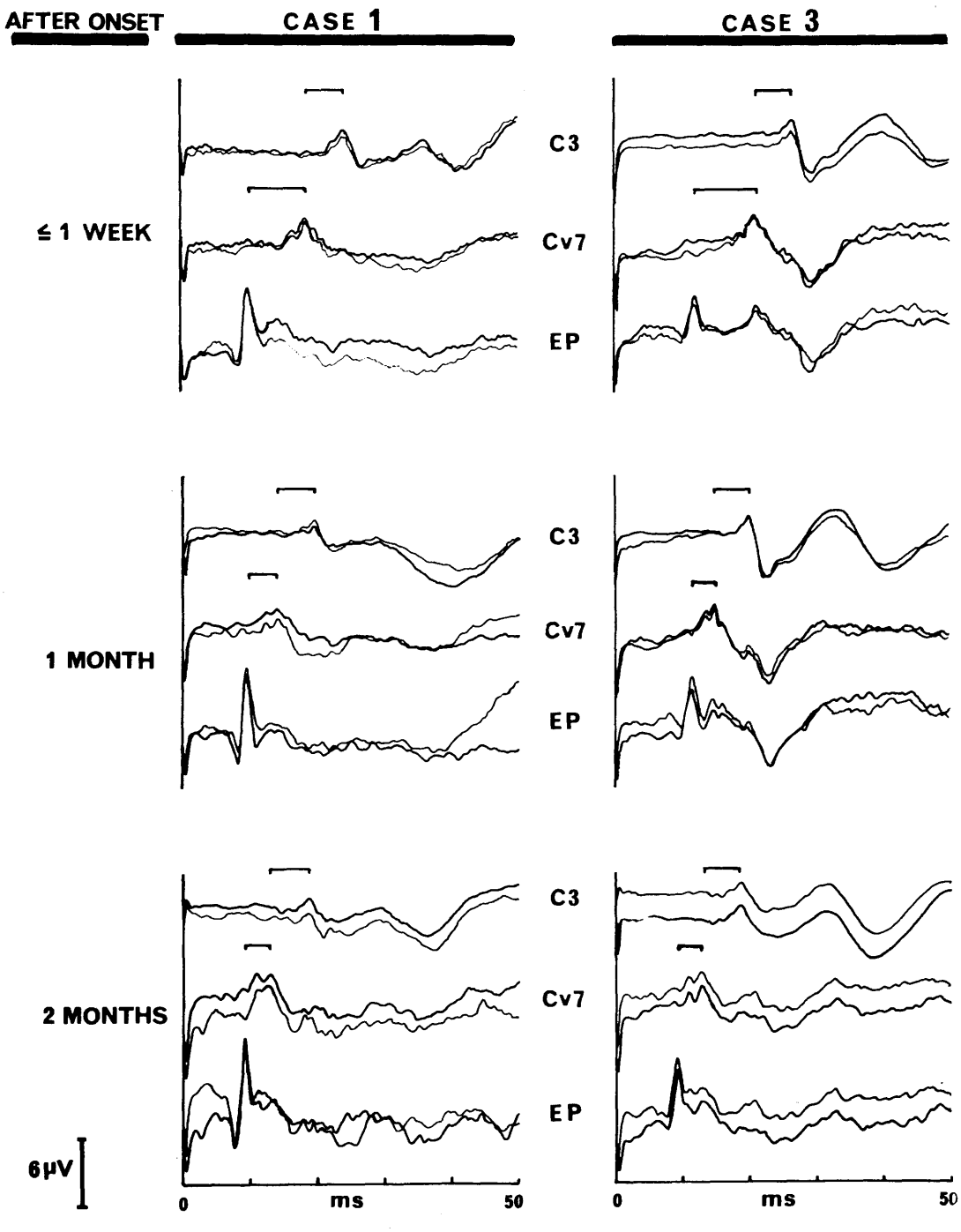

1 WEEK
1 MONTH
2 MONTHS
4 MONTHS
6 MONTHS
ms
18
14
10
EP
LATENCY
8
4
0
PERIPHERAL
INTER-PEAK LATENCIES
CENTRAL
EP-N11
EP-N13
N11-N20
N13-N20

FIGURE 14

Serial somatosensory evoked potentials (SEPs) to right median nerve stimulation at wrist in two patients with the Miller Fisher syndrome. Recording electrodes were referred to an FZ electrode and each trace is from 512 averaged sweeps. Brachial plexus - cervical spine (EP - N13) conduction time was abnormally long initially in each patient with progressive improvement on serial testing. Central conduction time was normal and stayed without significant change in each patient. Progressive improvement in the EPs confirms the mild abnormalities noted in the median SNAPs. For interpretation of these findings see the text. EP-N13 and N13-N20 are shown by horizontal bars.

(Jamal and Ballantyne 1987b, reproduced with permission).


AFTER ONSET
CASE 1
CASE 3
≦ 1 WEEK
1 MONTH
2 MONTHS
C3
Cv7
EP
6μV
0
ms
50

14). In cases 2 and 4 the SEP findings were similar to those in case 3 while in case 5 the findings were similar to those in case 1.

SEP studies test the whole length of the large fibre somatosensory pathway and provide evidence about lesions involving its various levels (Desmedt and Noel 1973; Sedgwick 1981; Lancet Editorial 1987; Chiappa 1987). They can provide direct assessment of conduction in the proximal segments of peripheral nerves, spinal roots, the centrally directed branch of the first sensory neurone, the second sensory neurone which traverses the brainstem and the third sensory neurone which terminates in the primary sensory area. Early SEPs are very resistant to alteration by anything other than structural pathology in the large fibre sensory pathway and a close relationship between the waveforms and their generators integrity usually exists (Chiappa 1987). One of the important issues in SEP assessment, which is relevant to this study, is the identification of those components that either precede or follow the arrival of the afferent volley to the spinal cord (i.e., the "spinal entry time"). In this respect, there have been some recent studies confirming that the onset latency of N11 (or P11) represents an index of the spinal entry time of the afferent volley (Desmedt and Cheron 1980; 1981; Lesser et al 1981; Chiappa 1987), whereas EP represents the passage of the volley from the axilla to the brachial plexus (Kimura et al 1978; Kritchevsky and Wiederholt 1978; Chiappa 1987). Some controversy exists as to the exact site of generation of the cervical N13. Most authors, however, believe that it represents a stable onset latency along the spinal cord formed

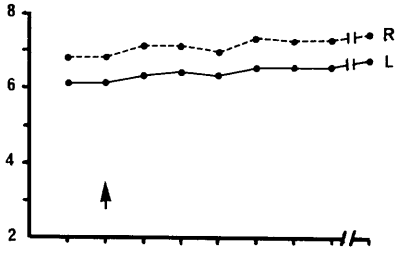
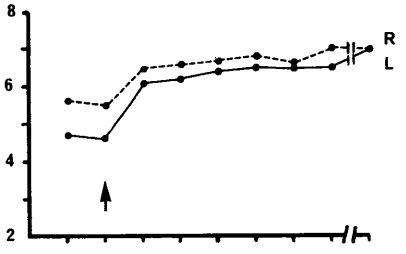
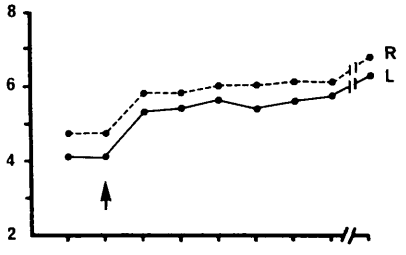
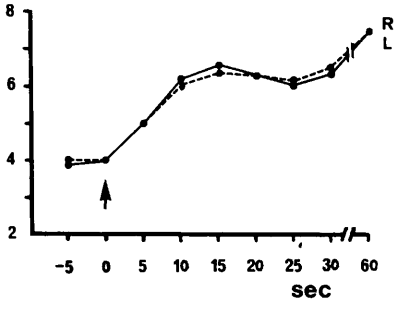
below the foramen magnum and is probably related to a fixed generator in the central part of the dorsal horn (Desmedt and Cheron 1981). Support for this view comes from the findings that the N13 amplitude drops sharply above the C3 vertebra and that in patients with high cervical transection N13 persists while the scalp farfield P14 is abolished (Mauguiere and Courjon 1981). Lesser et al (1981) suggested that N13/P13 arises from the ipsilateral dorsal column pathways at the level of cervico-medullary junction. Therefore, the view that N13 most probably arises from the cervical cord below the foramen magnum (dorsal column/horn and dorsal column nuclei) is widely accepted (Jones 1977; Hume and Cant 1978; Kritchevsky and Wiederholt 1978; Desmedt and Cheron 1981; Ganes 1982; Mauguiere et al 1983; Yamada et al 1985; Chiappa 1987). The N14/P14 is believed to be related to a generator above the foramen magnum most probably in the medial lemniscus (Desmedt and Cheron 1980; Mauguiere et al 1983; Lueders et al 1983; Emerson et al 1984; Yamada et al 1984; Chiappa 1987). As the components N11 and N13 were clearly and consistently recorded in all the recordings from the neck with a cephalic Fz reference, measurements of N11, EP - N11 and N11 - N20 latencies were also performed in addition to EP -N13 and N13 - N20 conduction time determinations in the MFS patients (Figure 13). The results again support an abnormality in the peripheral part of the large fibre afferent pathway in all these patients. The abnormality showed progressive improvement on subsequent studies (Figures 13 & 14).

PUPILLOMETRIC STUDIES: Figure 15 summarises results of the pupillary darkness reflex (PDR) studies in case 3. At the onset

FIGURE 15

Serial quantitative studies of pupillary darkness reflex (PDR) and pupillary cholinergic sensitivity using a flash photographic method (see chapter 3 for methodology) in a patient with the Miller Fisher syndrome (case 3). Arrow indicates the onset of complete darkness. Ordinates represent vertical pupillary diameter in mm. Both PDR and pupillary cholinergic sensitivity were abnormal initially and returned to normal after 6 months.

(Jamal and Ballantyne 1987b, reproduced with permission)

AFTER ONSET	PUPILLARY DARKNESS REFLEX	PC (0·05%) SENSIT·(mm)
1 week		R = 1·5 L = 1·4
1 month		R = 1·6 L = 1·6
2 months		R = 0·7 L = 1·4
6 months		R = 0·6 L = 0·7

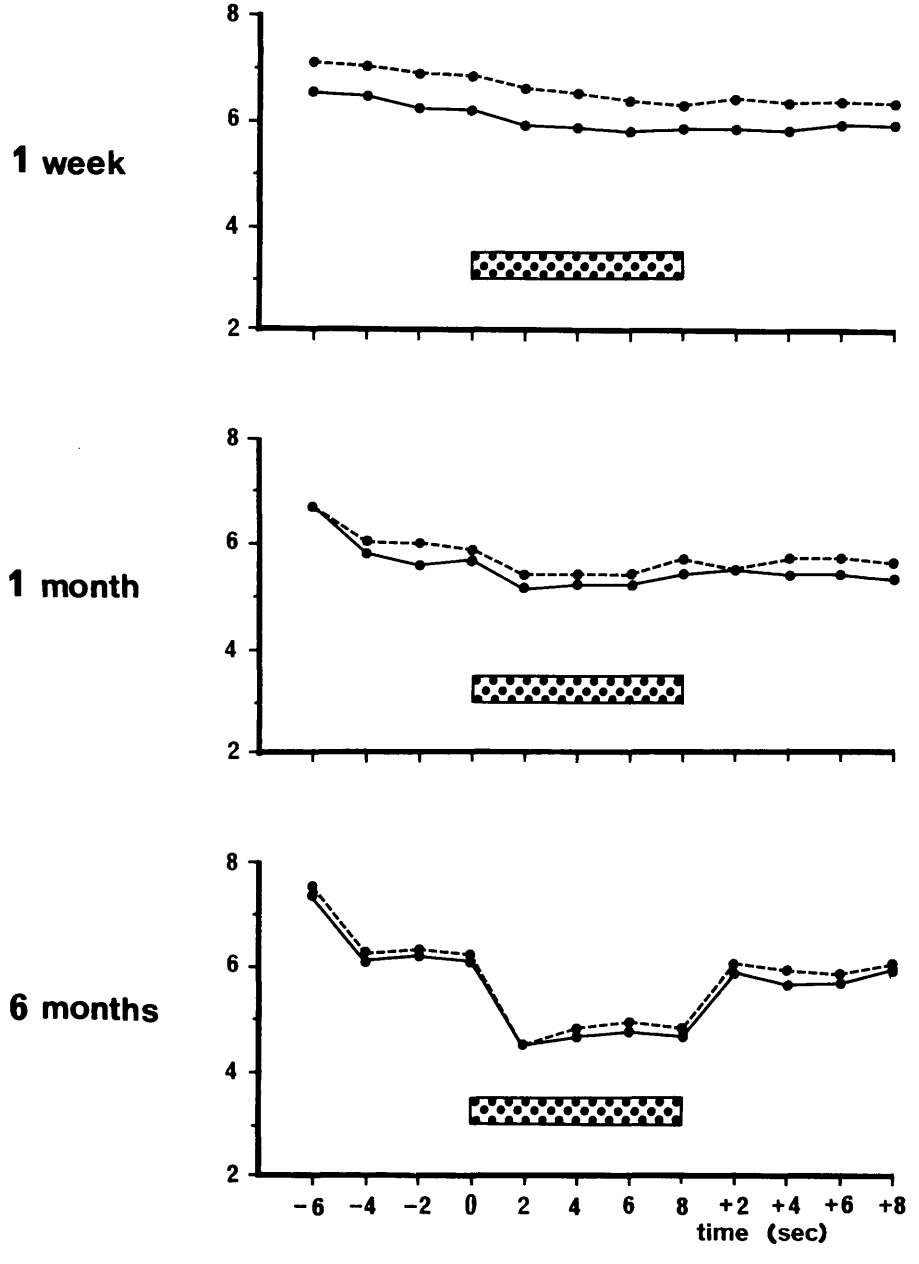
of the illness both pupils were abnormally large and as a consequence the amplitude of the PDR was diminshed. At this stage the right pupil was supersensitive to 0.05% pilocarpine while the response on the left was at the upper limit of normal (Figure 15). Within a month, however, considerable recovery had occurred in the darkness reflex but the sensitivity of the pupils to pilocarpine had increased and both pupils were supersensitive. Subsequently, a small improvement in the darkness reflex was demonstrable though anisocoria remained and the pupillary pilocarpine sensitivity waned to normal values, but significant side to side differences between the two pupils were still present at six months after the onset (Figure 15). Irideal adrenergic sensitivity was not tested in the patient as the base-line sizes of the pupils were large and this will influence its measurement (Bourgon et al 1978). Thus the measurable effect of phenylephrine on a large pupil, as in case 3, is necessarily limited since irrespective of the true adrenergic irideal sensitivity, the pupillary size prior to drug application is close to the anatomical limit for dilatation of the sphincter pupillae. Pupillary constriction to near vision in case 3, the accommodation reflex, was impaired shortly after onset but considerably improved one month later and was normal six months after the onset (Figure 16). The pupillary findings in case 1 were very similar to those of case 3 whereas in case 2 no abnormality of PDR or accommodation reflex was found but he showed a mild pupillary supersensitivity to pilocarpine which gradually improved in six months. These pupillary studies were not performed in cases 4, 5, 6 and 7.

The pupillary abnormalities seen in these MFS patients

FIGURE 16

Serial quantitative pupillary accommodation reflex studies (see chapter 3 for methodology) in a patient with the Miller Fisher syndrome (case 3). This reflex was initially impaired but returned to normal 6 months after onset of the illness.

(Jamal and Ballantyne 1987b, reproduced with permission).


1 week
1 month
6 months
8
6
4
2
−6 −4 −2 0 2 4 6 8 +2 +4 +6 +8
time (sec)

resemble those observed in patients with tonic pupil using the same technique (Ramsay 1986). The latter is thought to be caused by postganglionic parasympathetic denervation (Lowenfeld and Thompson 1967; Harriman and Garland 1968). Recovery of pupillary function noted subsequently accompanied improvement of the other peripheral nerve dysfunction parameters. The neuropharmacological results with supersensitivity to pilocarpine is consistent with a post-ganglionic parasympathetic lesion (Pilley and Thompson 1975; Keane 1977; Okajima et al 1977). Postganglionic parasympathetic oculomotor nerves are among the few fibres of the postganglionic autonomic nervous system which are myelinated (Warwick 1954). It is likely that the patients had a dysfunction in these fibres similar to those observed in the other peripheral nerves.

CHAPTER 5

PATIENTS WITH GUILLAIN-BARRÉ SYNDROME

Twenty patients with the Guillain-Barré syndrome (GBS) were studied to compare their clinical and neurophysiological course with those in the MFS patients. These GBS patients were included on the basis of clinical criteria, CSF examination and lack of additional pathology which might have produced polyneuropathy (see below). Clinical and neurophysiological assessments were performed at intervals similar to those in the MFS patients; within the first week (and/or within three weeks) from onset of the GBS and thereafter at intervals of 1, 2, 4, 6, 12 and 18 months from the onset of the neurological illness.

All the 20 patients fulfilled the criteria for the diagnosis of acute GBS (Asbury et al 1978; Asbury 1981). The criteria in summary required demonstration of weakness of multiple limbs (from mild weakness of legs to complete paralysis of all extremity, facial, bulbar and trunk muscles), areflexia or hyporeflexia, relative symmetry and mild sensory symptoms and signs. These symptoms were required to be of acute onset with progression during the initial phase of the illness followed by improvement after a plateau phase. Only those in whom the disorder progressed to a peak neurological deficit within four weeks or less were included so that patients with subacute or chronic relapsing course were excluded since they may have a different clinical syndrome with different pathogenesis to GBS (Prineas 1970; Prineas and McLeod 1975). Some workers have not excluded patients with normal CSF proteins or raised cell counts (Marshall 1963; Wiederholt et al 1964; Masucci and Kurtzke 1971) whereas

others included only patients in whom there was a rise in CSF protein and a cell count of less than 10 cells per cu.mm. in their studies on the GBS (Guillain 1936; De Jong 1940; Osler and Sidell 1960; McFarland and Heller 1966). All of the 20 patients in this group had a rise in CSF protein and the highest cell count was 8 mononuclear leukocytes per cu,mm., thus, all of the patients in this series exhibited CSF features which strongly support the diagnosis of the GBS (Asbury, 1981). Diabetes mellitus, chronic renal failure, vitamin B12 deficiency, acute porphyria, monoclonal gammopathy, systemic lupus erythematosus and other connective tissue autoimmune disorders, lymphoma, lead intoxication and other causes of polyneuropathy were excluded by proper laboratory investigations. Those patients with a history of excessive alcohol intake, nutritional deficiency or on drugs likely to cause peripheral nerve disorder were also excluded.

CLINICAL DATA

Table 8 summarises the clinical data in these 20 patients. Their ages ranged from 13 to 67 (mean = 41; SD = 18) years. There were 12 male and 8 female patients with a ratio of 3:2. A preponderance of male to female patients in this syndrome has been reported in many series with male incidence varying from 56 to 72 percent (Eiben and Gersony 1963; Marshall 1963; Wiederholt et al 1964; Ravn 1967). An antecedent illness was reported by 15 patients (75%) within a month prior to onset of the GBS (table 8). This was in the form of an upper respiratory tract infection in eight patients, a sore throat in three patients, a flu-like illness in three patients and a gastrointestinal disturbance in one patient. The latent period between the antecedent illness

TABLE 8

CLINICAL DATA IN 20 PATIENTS WITH THE GUILLAIN-BARRÉ SYNDROME

Case No.	Age & Sex	Antec. illness		MxD	Weakness		Sensory				auto-nomic	refl-exes	Cranial nerves	assist. ventill.	time	CSF			Recovery		
							Symptoms		Signs												
		type	lat. per. (days)	(days)	UL	LL	UL	LL	UL	LL					(days)	Protein g/l	cells in c.mm	others	onset (Wks)	duration (mnths)	grade
1	53 M	URTI	14	13	+	+	Pr	N Rh H C	T P	T P	–	–	7	–	9	0·76	0	–	4	4	1
2	31 F	ST	21	9	+	+	N Pr	N Pr	T P	T P	+	–	7	+	7	1·75	3	–	5	4	0
3	55 M	–		2	+	+	N	N H C	T P V	T P V J	–	–	7	–	13	1·8	0	–	4	18	2
4	44 M	ST	8	12	+	+	N Rh H C	N Rh H C	T P V	T P V J	–	–	7,10	–	15	1·32	6	–	5	18	1
5	24 F	URTI	14	20	+	+	N Pr	N Pr	P V	T P V J	+	–	10	+	6	0·85	0	–	5	12	1
6	13 F	–		10	–	+	N Pr	N Pr	–	T P V J	–	–	7	+	20	2·3	8	–	3	18	0
7	58 M	–		12	+	+	N Rh Pr	Rh	–	–	–	–*	7	–	17	1·9	0	–	2	6	0
8	53 M	URTI	21	26	+	+	Rh C	Pr	–	–	+	–	–	–	14	0·58	0	–	5	18	1
9	23 F	Flu	7	14	+	+	Pr	Pr	–	–	–	–	–	–	11	1·5	1	–	8	18	0
10	43 M	Diarrhoea	14	5	+	+*	N	N Pr C	–	–	+	–	–	–	8	0·6	5	–	14	6	0
11	19 F	URTI	10	4	+	+	N Pr Rh H	N Pr H	T P	T P V J	+	–	7,10	+	4	1·78	3	–	3	6	0
12	56 F	URTI	20	16	+	+	-	–	–	–	–	–	–	–	9	1·45	0	–	4	4	0
13	34 F	–		3	+	+*	–	N Pr H C	–	P J	+	–	–	–	10	0·8	5	–	2	4	0
14	26 M	Flu	18	10	+	+	Pr H C	Pr H C	–	P V J	–	–	7	–	14	2·85	2	–	6	18	4
15	61 M	Flu	21	3	+	+	Pr	Pr H C	T	T P V J	–	–	10,11	–	18	1·65	4	–	2	18	3
16	62 M	URTI	12	6	+	+	–	–	–	–	–	–	7,10	–	14	0·78	0	–	2	6	0

17	67 M	–		6	+	+	–	Pr	–	P J	–	–	7,10	–	13	1·56	0	–	3	18	3
18	63 M	URTI	13	11	+	+	–	–	–	–	–	–	–	–	16	2·15	4	–	7	6	0
19	19 F	URTI	28	5	+	+	–	–	–	V	–	–	–	–	9	0·9	0	–	2·5	4	0
20	21 M	ST	14	7	+	+	N	N	–	V	–	–	7,10	–	8	0·61	0	–	3	4	0

For grading of recovery see table 9

MxD	:	Maximum neurological deficit
UL	:	Upper limb
LL	:	Lower limb
URTI	:	Upper respiratory tract infection
ST	:	Sore throat
+	:	Present
–	:	Absent
*	:	Asymmetrical involvement

Pn	:	Pain
Pr	:	Paraesthesiae
N	:	Numbness
H	:	Abnormal heat sensation
C	:	Abnormal cold sensation
T	:	Touch
P	:	Pinprick
V	:	Vibration
J	:	Joint position

and onset of the neurological manifestation ranged from 7 to 28 (mean = 15.7; SD = 5.7) days. Similar incidence of antecedent illness and duration of latent period have been reported in many large series (Marshall 1963; Ravn 1967; Ropper and Shahani 1984).

Although motor weakness dominated the clinical picture at a later stage, sensory disturbances were more common than motor weakness as initial symptomatology. The former occurred as first symptoms in twelve patients; in the lower limbs in five, in the upper limbs in two and in both upper and lower limbs in five patients. They consisted of pain, paraesthesiae and, less commonly, numbness. The remaining eight patients had motor weakness at the onset; confined to the lower limbs in five, to the upper limbs in one and to all extremities in two patients. Higher incidence of sensory than motor disorder as the initial symptom has been reported in many series (Haymaker and Kernohan 1949; Marshall 1963; Eiben and Gersony 1963; Ravn 1967; Eisen and Humphreys 1974). At the peak of the illness, motor weakness dominated the picture in all patients and the power of different muscles ranged from 0 to 5 on the MRC scale. Proximal muscles were disproportionately involved more than distal muscles in 10 (50%) patients, proximal and distal muscles were about equally involved in 7 (35%) patients and in 3 (15%) patients distal muscles were weaker than proximal muscles. Weakness was more marked in the lower limbs in 11 (55%) patients, in the upper limbs in 1 (5%) patient and in the rest (40%) both upper and lower limbs were affected to about equal degrees. Eight patients remained ambulatory but all required various degrees of assistance for

walking while the remaining twelve patients were unable to walk at the peak of their illness.

Sensory disturbances were common at the time of maximum neurological deficit (table 8) and these occurred in a distal fashion similar to those observed in other neuropathies. Symptoms in order of frequency of their occurrence included paraesthesiae (13/20), numbness (11/20), altered thermal sensation (8/20) and pain (5/20). Objective evidence of sensory dysfunction was present in thirteen patients, one without any sensory symptom (table 8). There were four patients with sensory symptoms but no signs.

At least one cranial nerve involvement was observed in 13 (65%) patients and the most frequently involved was the facial nerve being bilateral in six and unilateral in five patients (11 patients, 55%). The 10th cranial nerve was involved in seven patients; being the only cranial nerve involved in one, associated with 11th nerve involvement in one and with facial nerve involvement in the remaining five patients.

The deep tendon reflexes were absent at the peak of the illness in all the patients. Asymmetrical reflexes were observed in one patient at some stage of the illness. No extensor plantar reflexes were seen in any of the twenty patients. Four patients required assisted ventilation for a period of 7 to 30 days due to respiratory muscle involvement, the onset of which was at 4 - 10 days from the onset of the GBS. Autonomic dysfunction occurred in six patients and features included instability of blood pressure (five patients), sweating disturbances (four patients), bladder dysfunction (two patients) and cardiac arrhythmia (two

patients). The clinical features in these patients including incidence and distribution of muscle weakness and sensory disorders, frequency of cranial nerve involvement, reflex abnormalities, respiratory muscle paralysis and autonomic dysfunction are similar to those described in other series (Haymaker and Kernohan 1949; Hagan and Baker 1953; Eiben and Gersony 1963; Appenzellar and Marshall 1963; Marshall 1963; Wiederholt et al 1964; McFarland and Heller 1966; Ravn 1967; Prineas 1970; Lichtenfield 1971; Eisen and Humphreys 1974; Pace 1976; McLeod et al 1976; Frison et al 1980; Smith and Smith 1980; Ropper and Shahani 1984).

Lumbar puncture and CSF examination was performed in all patients at 4 - 20 (mean = 11.8; SD = 4.3) days after onset of symptoms. The CSF protein was raised above 0.61 (range = 0.61 - 2.85; mean = 1.37; SD= 0.68) g/l and this was not associated with a cellular response (range = 0 - 8; mean = 2; SD = 0.8 cells per cu.mm) in all the patients (table 8).

The degree of disability of patients was graded from 0 to 5 according to certain criteria set out in table 9 so that the degree of disability at the peak of the illness, the extent of clinical recovery and the neurophysiological parameters could be easily correlated with each other. Clinical improvement occurred in all patients but this improvement showed variability (table 8). Complete clinical recovery was seen in 12 (60%) patients (grade 0; table 9) and this occurred in 4 to 18 (mean = 7.2; SD = 5.1) months. Four (20%) patients regained normal motor power and lost all other symptoms but with abnormality of reflexes (grade 1, table 9) and one patient (5%) had in addition to some abnormal

TABLE 9

Criteria for grading the disability status in patients with acute inflammatory demyelinating polyradiculoneuropathy*

Grade	Criteria	Number at peak of the disability
0	Normal	0
1	No symptoms but minor abnormalities on neurological examination (e.g., absent tendon reflexes, impaired vibration sense, sluggish pupillary responses... etc.)	0
2	Minor disabilities apparent in the activities of daily living + some sensory symptoms + more obvious abnormalities on examination (slight weakness or wasting, sensory signs)	0
3	Moderate disability but no assistance needed with walking, unable to do manual work (e.g., household, shopping etc)	4
4	Substantial limitation in daily activities and assistance is needed with walking	3
5	Unable to walk and confined to wheelchair or to bed ∓ respiratory muscle paralysis	13

* Adapted from McLeod et al (1976) and Brown and Feasby (1984a)

signs minor disabilities in daily activity (grade 2, table 9). The remaining patients had more substantial residual disability. This was moderate (grade 3, table 9) in two patients (10%) and relatively severe (grade 4, table 9) in one patient (5%). None of the patients died. Most other series report a favourable outcome in at least 80% and complete recovery in about 60 - 70% (Marshall 1963; McFarland and Heller 1966; Ravn 1967; Pleasure et al 1968; Prineas 1970; Eisen and Humphreys 1974; McLeod et al 1976; Loffel et al 1977; Ropper and Shahani 1984). Some residual abnormalities have been noted in about 20% and this may be severe in 8% of the cases (Pleasure et al 1968; Ropper and Shahani 1984). In the present series, no correlation was found between the extent and/or rate of recovery and the various clinical criteria including age, sex, type and degree of neurological deficit and the level of CSF protein.

RESULTS OF NEUROPHYSIOLOGICAL STUDIES

All patients had serial neurophysiological studies. The initial study was performed within three weeks after onset; in eight patients the first assessment was done within the first week and these had the tests repeated again at week three. In the remaining twelve patients the initial assessment was performed during the second or third week. Thereafter these tests were performed at intervals of 1, 2, 4, 6, 12 and 18 months after onset of the neurological illness.

ELECTROMYOGRAPHY (EMG): Needle EMG was performed in the right extensor digitorum brevis, tibialis anterior, quadriceps femoris, first dorsal interosseous, extensor digitorum communis, biceps and deltoid muscles in all patients serially. The main

objective of these studies was to detect and quantitate the occurrence of fibrillation and positive wave potentials. This was done in a semiquantitative fashion as follows: +1 occasional, +2 moderate and +3 frequent fibrillation potentials. The data were combined and expressed as an average for distal and proximal muscles. Fibrillation potentials were frequent in 3 (15%) patients, moderate in 4 (25%) patients and occasional in 2 (10%) patients. In the remaining 10 (50%) patients, no fibrillation was seen at any stage of the illness. The fibrillation potentials occurred between the second and third week on average, simultaneously in proximal and distal muscles in all patients, but on average they were slightly more in the distal than proximal muscles and in lower limb than in upper limb muscles. They were maximum before or at one month examination and following the examination at two months they gradually diminished and disappeared after a few months in six patients while the remaining four patients continued to show fibrillation at 18 month examination.

There is overwhelming pathological evidence that the initial and predominant lesion in the GBS is segmental demyelination (Asbury et al 1969; Wisniewski et al 1969; Miyakawa et al 1971; Prineas 1972; Hart et al 1972; Carpenter 1972). Segmental demyelination is not associated with anatomical denervation of muscle fibres as axonal continuity with muscle is maintained and fibrillation potentials usually indicate that the axons have lost their connection with the muscle fibres (Adams et al 1962; Robert and Osler 1970). Electrophysiological evidence of axonal disruption is found in 20% - 64% of patients with the GBS

(Pleasure et al 1968; De Jesus 1974; Eisen and Humphreys 1974; Brown and Feasby 1984a). Quantitative electrophysiological studies of the number and dimension of motor units in the EDB muscle have confirmed the presence of definite axonal damage in the majority of patients with the GBS (Martinez-Figueroa et al 1977). A decrease in the number of functioning motor units due to axonal damage and a compensatory increase in the size of surviving motor units, presumably by a process of collateral reinnervation following denervation have been demonstrated and this may be reversible or permanent depending on the severity and reversibility of the axonal damage (Martinez-Figueroa et al 1977; Hansen et al 1982). These findings are supported by pathological observations that axons as well as myelin sheath may be damaged in patients with this syndrome (Haymaker and Kernohan 1949; Finean and Woolf 1962; Asbury et al 1969; Wisniewski et al 1969; Miyakawa et al 1971; Carpenter 1972; Prineas 1972; Oppenheimer and Spalding 1973). Axonal degeneration is believed to occur at any time during the progression of the disease and this averages 2 - 3 weeks and rarely exceeds 4 weeks (Arnason 1984). The EMG evidence of axonal degeneration simultaneously in both proximal and distal muscles in this group of patients would suggest that this process occurs randomly along the axon or at the distal nerve endings. The subsequent decrease in the amount of abnormal spontaneous activity in those patients with axonal disruption probably reflects reinnervation from collateral sprouting and/or axonal regeneration (Wohlfart 1957; 1958). Collateral sprouting will also explain the increase in size, duration and amplitudes of the motor unit action potentials (MUAPs) in these patients

(Martinez-Figueroa et al 1977; Hansen et al 1982; Jamal et al 1986d). The precise relationship between the two morphological abnormalities of segmental demyelination and axonal degeneration in the GBS is uncertain. Madrid and Wisniewski (1977) suggested that axons could be damaged in a non-specific manner by the inflammatory process but whether this is the only explanation or there is an alternative one is as yet unknown.

Subjective analysis of maximal recruitment pattern and motor unit potential parameters were also performed in these patients. The recruitment pattern was reduced in all muscles with clinical weakness and subsequently improved in a fashion almost parallel to the clinical improvement except in those patients with moderate to severe axonal degeneration where its improvement occurred later or was incomplete. MUAPs were noted to be of increased duration and amplitude and more frequently polyphasic than normal in 11 patients, 10 of whom had evidence of denervation on EMG. Changes in the MUAP parameters occurred, on average during the examination at 1 month and in some patients at 2 months and the greatest percentage of abnormality was seen at the examination performed 4 months after onset with a tendency to return towards normal thereafter. In all of the 11 patients, apart from 3 with severe axonal involvement, MUAP parameters had returned to normal by the examination at 18 months. These findings are comparable to those reported by Ballantyne and his colleagues (Martinez-Figueroa et al 1977; Hansen et al 1982) and are consistent with the theory that surviving axons reinnervate denervated muscle fibres and then undergo a process of remodelling as regenerating axons reach the muscle fibres.

Incomplete and/or prolonged recovery accompanied EMG evidence of denervation while those with no or little EMG evidence of denervation had relatively good improvement in a shorter period of time (Figure 17). Other workers have reported that fibrillation and other EMG evidence of denervation are associated with an incomplete and prolonged recovery (Pleasure et al 1968; Eisen and Humphreys 1974; McLeod et al 1976; Raman and Taori 1976; Peterson et al 1982; Brown and Feasby 1984a; Feasby et al 1986).

NERVE CONDUCTION (NC) STUDIES: Table 10 summarises the frequency of abnormalities of conduction studies. Abnormality of one or more SDML was present in 17 patients (85%) at some stage of the illness. FMNCV was abnormal in one or more nerves at some stage of the illness in 14 patients (70%) all of whom had an abnormality of one or more SDML. In 3 patients (15%), therefore, an abnormality of one or more SDML was present without an associated abnormality of FMNCV in any of the three nerves tested throughout the illness. No abnormality of SDML or FMNCV was seen at any stage in 3 patients (15%). These 3 patients, however, showed proximal conduction abnormality (see below). Two patients had at least one SDML abnormal at the first week examination while in another 11 patients the abnormality occurred at the examination 2 - 3 weeks after onset. In the remaining 4 patients an SDML abnormality appeared for the first time at the 1 month examination. Similarly, slowing of FMNCV in at least one nerve occurred for the first time at 1 week examination in 3 patients, at 2 - 3 weeks examination in 9 patients and at the 1 month examination in 2 patients. As a group the mean abnormality of

FIGURE 17

Mean time to clinical recovery from onset of the illness in 20 patients with the Guillain-Barre´ syndrome correlated to median nerve motor and sensory conduction abnormalities and evidence of denervation on needle electromyography (EMG). The mean time taken by all patients to recover is shown by the darkest bar in the histogram (those with incomplete clinical recovery at 18 months are included as this figure). The dotted bars in the histogram represent the mean time to recovery in those patients who had values outside the limit of 60% of the normal control mean for the specific parameter measured in conduction studies or those with evidence of denervation on EMG. White bars in the histogram represent the mean time to recovery by the remaining patients including those with no abnormality of the specific parameter measured. It is clear that only EMG findings correlated significantly with mean time to clinical recovery. Similar correlation was found with conduction parameters of other nerves.

FP = Fibrillation Potentials (for grading see the text)

SDML = Shortest Distal Motor Latency

FMNCV = Fastest Motor Nerve Conduction Velocity

SNAP = Sensory Nerve Action Potential

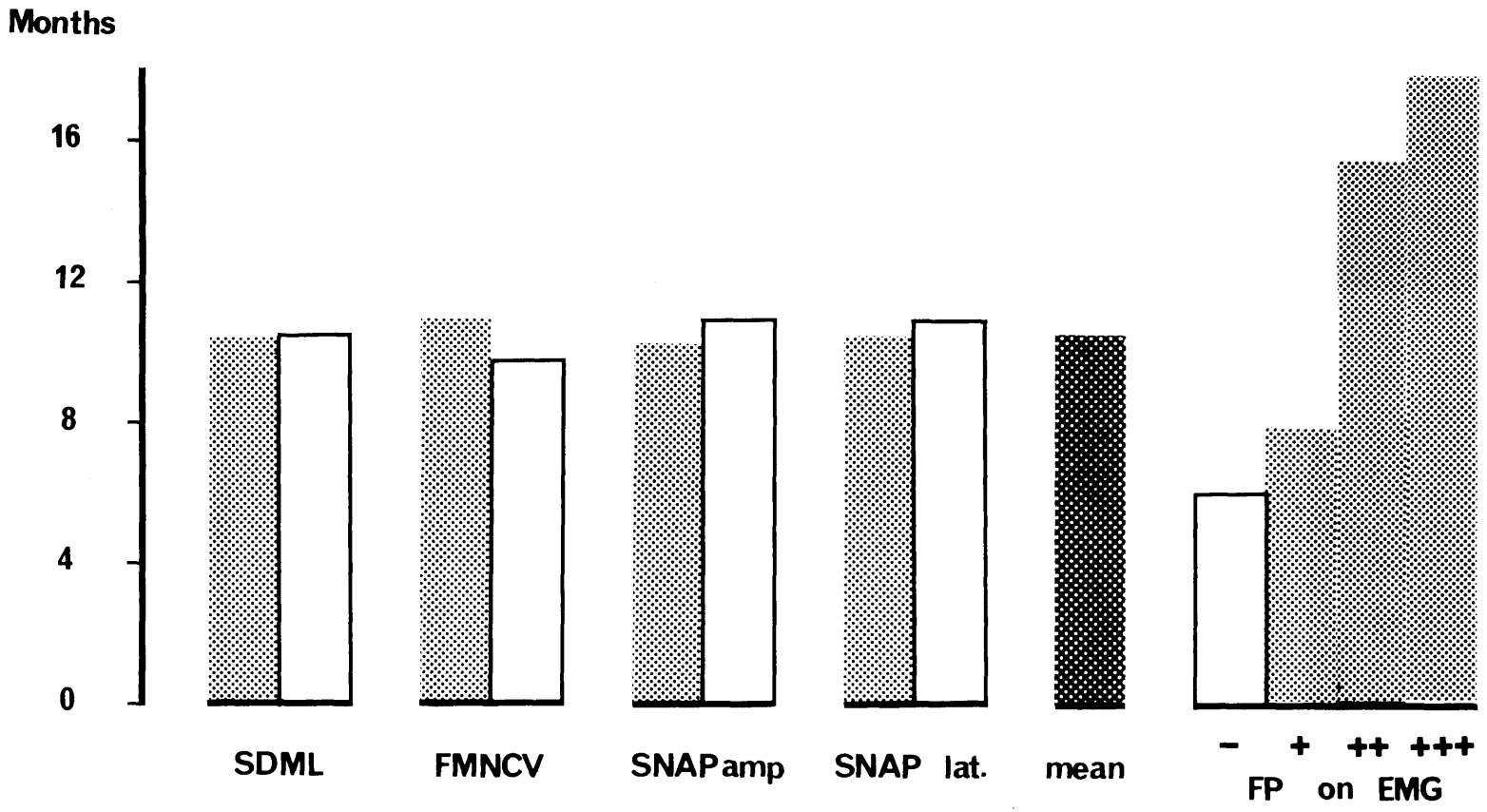

Months
16
12
8
4
0
SDML
FMNCV
SNAP amp
SNAP lat.
mean
–
+
++
+++
FP on EMG

TABLE 10

Time sequence and frequency of abnormality of nerve conduction studies in 20 patients with the Guillain-Barré syndrome during the first month after onset

Parameter		Number of patients with abnormal values*				(95% CL)
		≤ 1 week†	2-3 weeks	≥ 3 weeks	1 month	Total
SDML	median	2/8	10	12	4	16
	ulnar	2/8	9	11	4	15
	peroneal	2/8	11	13	2	15
	one or more	2/8	11	13	4	17
	all three	0/8	10	10	2	12
FMNCV	median	2/8	9	11	2	13
	ulnar	2/8	9	11	2	13
	peroneal	3/8	9	12	2	14
	one or more	3/8	9	12	2	14
	all three	1/8	8	9	2	11
F-wave latency	median	6/8	13	19	1	20
	ulnar	6/8	13	19	1	20
	peroneal	6/8	11	17	3	20
	tibial	6/8	11	17	3	20
	one or more	6	13	19	1	20
	all four	6	11	17	3	20
SNAP	median	1/8	10	11	5	16
	ulnar	2/8	9	11	6	17
	sural	0/8	6	6	5	11
	one or more	2/8	10	12	6	18
	all three	0/8	6	6	4	10

† only 8 patients were examined one week from onset of the neurological illness.

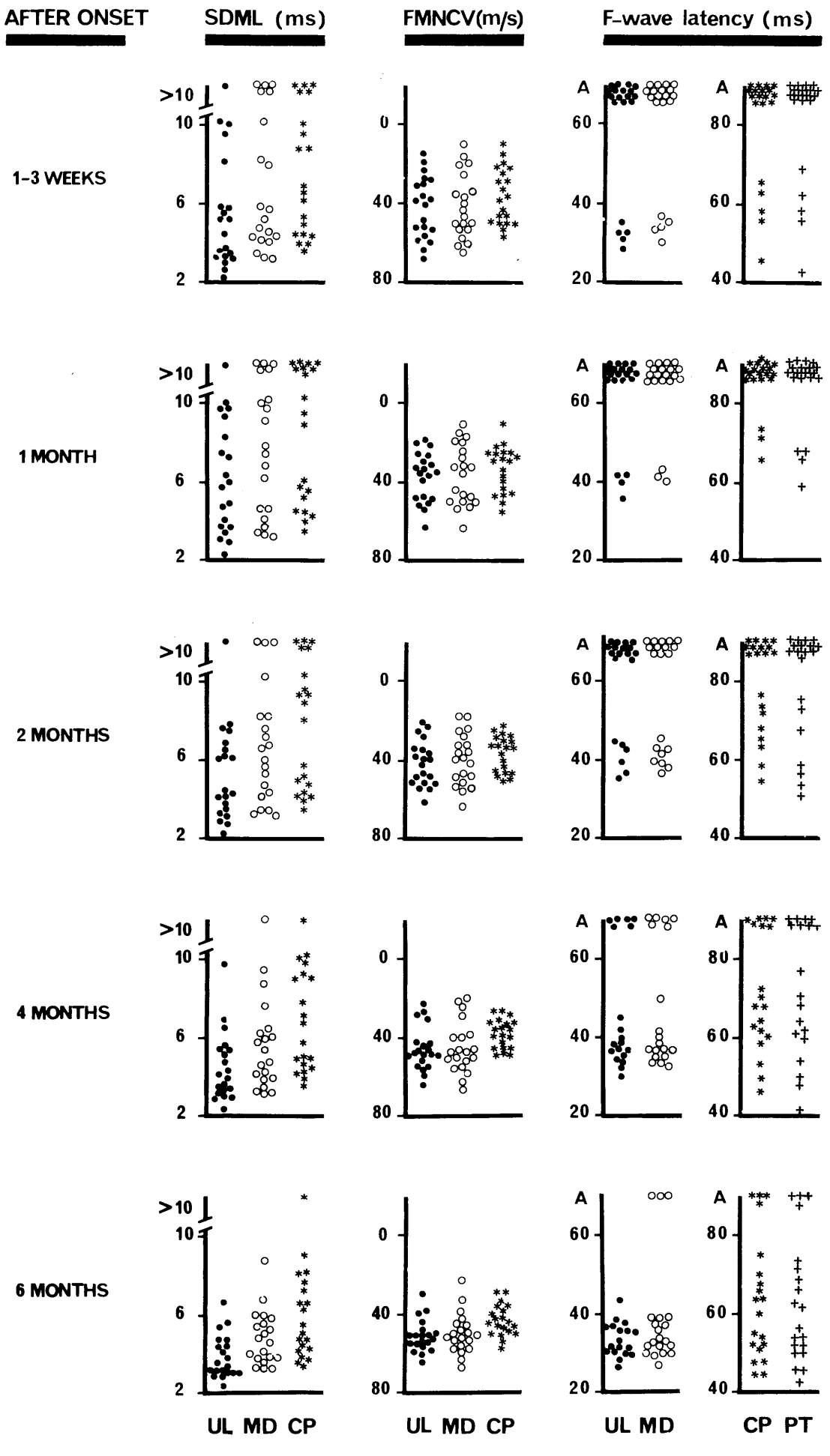
* figures indicate number of patients showing their abnormality for the first time during the periods specified.

SDML = shortest distal motor latency
FMNCV = fastest motor nerve conduction velocity
SNAP = sensory nerve action potential

SDML and FMNCV studies peaked at the examination performed 2 - 3 weeks after onset of the GBS (Figure 18).

An abnormality of the latency and/or amplitude of one or more SNAPs was present in 18 patients (90%) at some stage of the illness (table 10). It occurred at week 1 in only 2 patients while in 10 patients the abnormality occurred at 2 - 3 weeks and in 6 patients at the one month examination. At any one stage, the highest incidence of SNAP abnormality did not exceed 85%. Median (16 patients, 80%) and ulnar (17 patients, 85%) abnormalities were in general more common than sural (11 patients, 55%) SNAP abnormality (table 10) . No patient had an abnormality of sural SNAP without ulnar and/or median SNAP abnormality while a total of 7 patients (35%) had ulnar and/or median SNAP abnormality with normal sural SNAP studies. SNAP abnormalities were in general infrequent at first week examination (2 patients), more common at 2 - 3 weeks examination (10 patients, 50%) but most common at 1 month examination (16 patients, 80%) . In general the mean abnormality of SNAPs peaked at the 1 month examination. In one patient, there was neither motor or sensory conduction abnormality throughout the course of his illness. Again abnormalities of proximal conduction were demonstrated in this patient by late response and SEP studies (see below).

The sensory and motor nerve conduction studies in this group yielded results similar to others reported in the literature. The combined data for the studies performed within the first three weeks of the onset are similar to those of other studies performed about the same time (Lambert and Mulder 1964; McLeod 1981; Albers et al 1985). In the majority of these patients with the


AFTER ONSET
SDML (ms)
FMNCV(m/s)
F-wave latency (ms)
1-3 WEEKS
1 MONTH
2 MONTHS
4 MONTHS
6 MONTHS
>10
10
6
2
0
40
80
A
60
40
20
80
60
40
UL MD CP
UL MD CP
UL MD
CP PT

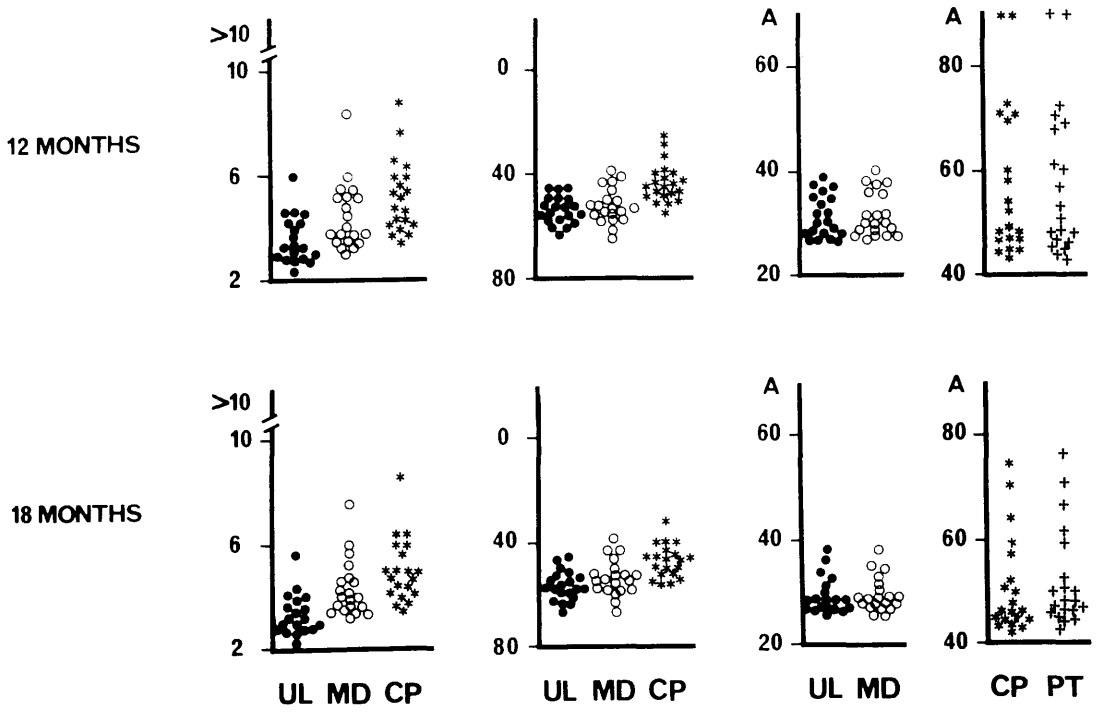


FIGURE 18

Results of serial motor nerve conduction and F-wave latency measurements in 20 patients with the Guillain-Barre syndrome. Improvement in all the parameters occurred with time.

SDML = Shortest Distal Motor Latency
FMNCV = Fastest Motor Nerve Conduction Velocity
UL = Ulnar Nerve
MD = Median Nerve
CP = Common Peroneal Nerve
PT = Posterior Tibial Nerve
A = Absent

GBS, conduction was reduced proportionately in the distal and the more proximal portions of the nerves (see table 10), thus confirming that the disease is usually diffuse and that the underlying pathology is segmental demyelination (Asbury et al 1969; Carpenter 1972; Prineas 1972, 1981; Hart et al 1972; McLeod et al 1973). There was, however, a noticeable variability of the frequency and pattern of involvement of the nerves from patient to patient and from nerve to nerve in the same patient. This is presumably due to the fact that pathological changes in the distal segments may be patchy (Asbury et al 1969; Prineas 1981) and thus the slowing of nerve conduction in the distal segments accessible to conventional studies may be irregular (Bigot and Goulon 1970; Kaeser 1970). As was the case in the three patients in this study, other workers have also found evidence of greatly prolonged SDMLs in some patients in whom NC studies in the more proximal parts of the nerves were normal or only mildly slowed (Bannister and Sears 1962; Lambert and Mulder 1964; Bergamini et al 1966; McQuillen 1971; Eisen and Humphreys 1974; Kimura and Butzer 1975; McLeod et al 1976). Normal conventional conduction studies have been encountered on serial studies in 14 - 20% of patients with the GBS from other groups even at the peak of neurological deficit and the percentage of normal studies may be even higher in the early stages (Peterman et al 1959; Lambert and Mulder 1964; Humphrey 1964; Bigot and Goulon 1970; McQuillen 1971; Eisen and Humphreys 1974; Kimura and Butzer 1975; McLeod et al 1976; McLeod 1981). In the first 14 days, NC studies may be within the normal in the majority of cases with the GBS (Lambert and Mulder 1964; Humphrey 1964; Bergamini et al 1966;

Eisen and Humphreys 1974; Brown and Feasby 1984a) but after this period slowing becomes more common (Eisen and Humphreys 1974; Kimura and Butzer 1975; McLeod et al 1976; Brown and Feasby 1984a). In the present study (see below) and in other studies (Kimura and Butzer 1975; Brown and Feasby 1984a; Albers et al 1985) major conduction abnormalities were noted in the most proximal or radicular segments of the nerves. Median and/or ulnar SNAP have been reported to be more abnormal than sural SNAP (McLeod 1981). One or both of median or ulnar SNAP were found to be absent in 58% of patients (Eisen and Humphreys 1974) but some abnormality in the latency and/or amplitude of an SNAP was reported to be present in 76% of a large series (McLeod 1981).

There was no significant relationship between the degree of slowing of FMNCV, prolongation of SDML or SNAP abnormality and the severity of the GBS or the degree or rate of improvement in the present group. Similar results have been observed in other studies (McLeod et al 1976; McLeod 1981; Ropper and Shahani 1984). The lack of correlation may reflect the variability in the nature and distribution of the pathological changes in the peripheral nervous system in this syndrome (Asbury et al 1969).

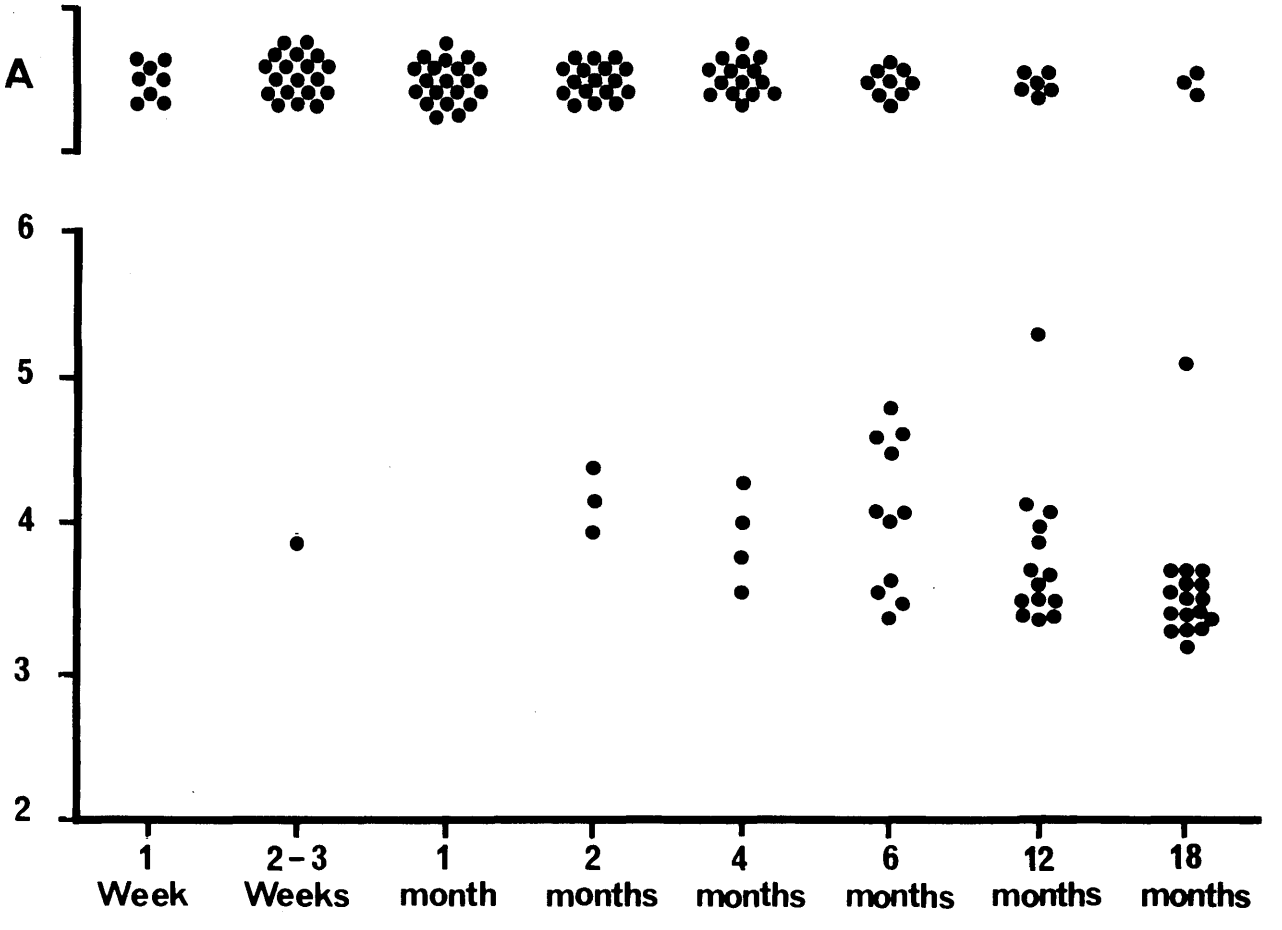
LATE RESPONSE (F-WAVE AND H-REFLEX) STUDIES: All the 20 patients in this series had either abnormally prolonged F-wave latencies or absent F-waves of all four nerves tested at some stage of their illness (table 10). F-wave abnormality was present in at least two nerves of 19 patients (95%) and in all four nerves tested in 17 patients (85%) within the first three weeks of their GBS (table 10). In one patient (5%) the first F-wave abnormality was evident 1 month after onset. F-wave abnormality was also relatively frequent during the first week after onset so that from among 8 patients examined at this stage all F-waves were abnormal in 6 patients (75%). F-waves were absent in all four nerves in 3 patients (15%) whose FMNCV and SDML values were within the normal range and remained so throughout their course of illness. Figure 18 summarises the frequency of abnormality and sequence of evolution of F-wave studies over 18 months in the 20 patients with GBS.

Prolonged H-reflex latency in one patient and absent H-reflex potential was demonstrated in the remaining 19 patients when examined within three weeks from onset of their illness (figure 19). In all 8 patients who were examined at week one the H-reflex was absent. In the only patient with prolonged H-reflex latency at the first test 16 days after onset, the reflex was lost when re-examined 2 weeks later. Improvement of the H-reflex occurred on serial studies in 17 patients (85%) but in the remaining 3 patients (15%) the reflex was still absent bilaterally when examined 18 months later. In 3 patients, the H-reflex reappeared with an abnormal latency at 2 months but became normal within 4 - 10 months afterwards. In one patient, the reflex reappeared at 4

FIGURE 19

Serial H-reflex studies in 20 patients with the Guillain-Barré syndrome. The ordinate represents H-reflex latency. The H-reflex reappeared and subsequently improved over 18 months in most patients.

A = Absent


A
6
5
4
3
2
1 Week
2-3 Weeks
1 month
2 months
4 months
6 months
12 months
18 months

months and became normal 8 months later. In 7 patients it reappeared at 6 months and all but three had their H-reflex latency returned to normal 6 - 12 months later. The H-reflex reappeared at 12 months in 3 patients and in another 3 patients at 18 months after onset. Three of these 6 patients only had their H-reflex latency within the normal range at 18 months examination. A total of 6 patients, therefore, had their H-reflex present but with prolonged latency at 18 month examination in addition to another 3 patients whose H-reflexes remained absent until this stage (figure 19). In 10 patients (50%) there was abnormal side difference of more than 1.5 ms in the H-reflex latency at some stage during improvement.

In these patients with the GBS, late responses were abnormal, and in many cases these were absent altogether, very early in the course of the disease at the stage of maximum paralysis. This is most probably due to conduction block over the more proximal segments of the peripheral nerves. Late response studies have been used by many workers as means of measuring proximal conduction in the GBS and they have demonstrated that these responses may be abnormal when conduction in the more distal segments is normal or borderline (Kimura and Butzer 1975; King and Ashby 1976; Kimura 1978a; Lachman et al 1980). Among 9 patients with mild GBS in whom both M- and F- responses were recordable, Kimura and Butzer (1975) demonstrated abnormal F-waves in 4 patients in whom FMNCV was normal or only mildly slowed in the first 4 weeks of the illness. In 4 other patients from the same group, both FMNCV and F-wave latency were slow and only the remaining one patient showed slowing in FMNCV but with nearly

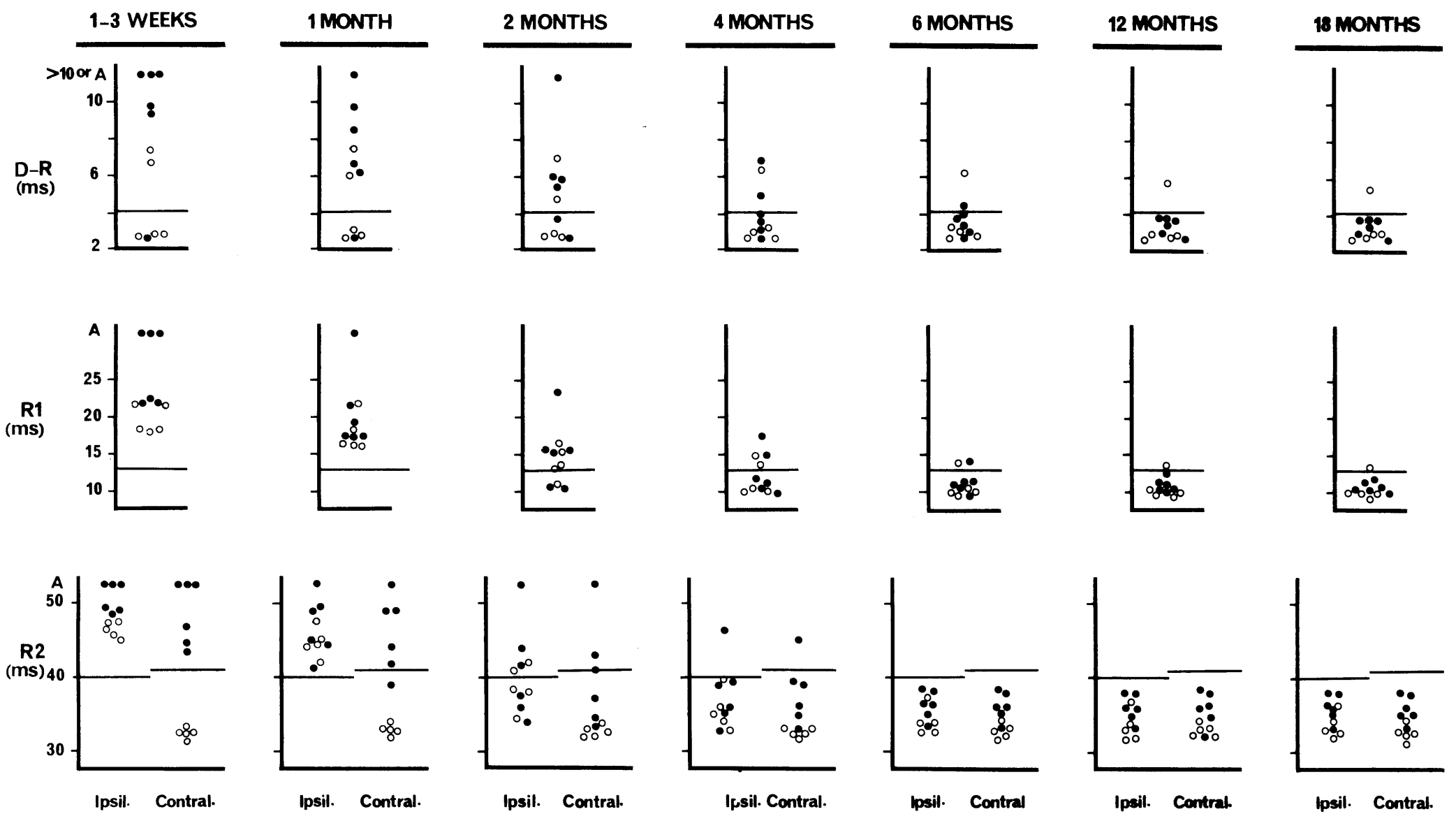
normal F-wave latency. The authors concluded that slowing of conduction in the proximal and radicular portions of the median and ulnar nerves was more common than in their distal segments and that the proximal and radicular segments may be predominantly involved in some patients with the GBS. In another study Kimura (1978a) found evidence of selective and disproportionate involvement of the most proximal and radicular segments of the extremity nerves in 25% of 45 patients (126 nerves) with the GBS. As in the present study, abnormalities of F-waves were very common in the first week and the maximum was usually reached within the first 3 - 4 weeks after onset in all patients (Kimura 1978a; Albers et al 1985). The findings of the present study, therefore, confirm other observations that although conduction abnormalities are usually diffuse involving any segment of the nerve and may affect the entire length of the nerve either continuously or discontinuously, the most common and severe site of involvement is the most proximal and radicular segments of the nerve. This is consistent with the histological findings of Asbury et al (1969) that although lesions exist throughout the peripheral nervous system, segmental demyelination is usually maximal at, and may even be restricted to, spinal nerve roots and proximal nerve segments.

FACIAL NERVE MOTOR CONDUCTION AND BLINK REFLEX STUDIES: Facial D-response and blink reflex studies were performed in all 11 patients who had unilateral or bilateral facial nerve involvement (table 8). The D-response and/or blink reflex studies were always abnormal on the same side(s) as the facial weakness when tested within the first three weeks from onset of their GBS (figure 20).

FIGURE 20

Serial direct facial motor response (D-R) to facial nerve stimualtion, and blink reflex studies to supra orbital nerve (SON) stimulation in 11 patients with the Guillain-Barré syndrome who had clinical evidence of facial weakness. Recordings were made from orbicularis oculi muscles simultaneously using the same setting of recording electrodes. Horizontal lines indicate upper limits of normal for each parameter (mean + 3SD, see appendix). Solid dots represent patients with bilateral facial weakness while open circles represent patients with unilateral facial weakness.

A = Absent


1-3 WEEKS
1 MONTH
2 MONTHS
4 MONTHS
6 MONTHS
12 MONTHS
18 MONTHS
>10 or A
10
6
2
D-R (ms)
A
25
20
15
10
R1 (ms)
A
50
40
30
R2 (ms)
Ipsil.
Contral.

A substantially abnormal D-response with prolonged latency was seen in 6 patients (55%) four of whom had bilateral facial paralysis with bilateral abnormality. In one patient with bilateral facial weakness no D-responses could be obtained from either side. In the remaining 4 patients normal D-responses were recordable at normal latencies but all of these 4 patients had abnormal blink reflex studies (see below).

The direct response (R1) was either absent (3 patients; 2 with abnormally delayed D-responses and one with absent D-response) or abnormally delayed (8 patients) in all patients. This abnormality was either unilateral (5 patients all with unilateral facial weakness) or bilateral (6 patients all with bilateral facial weakness).

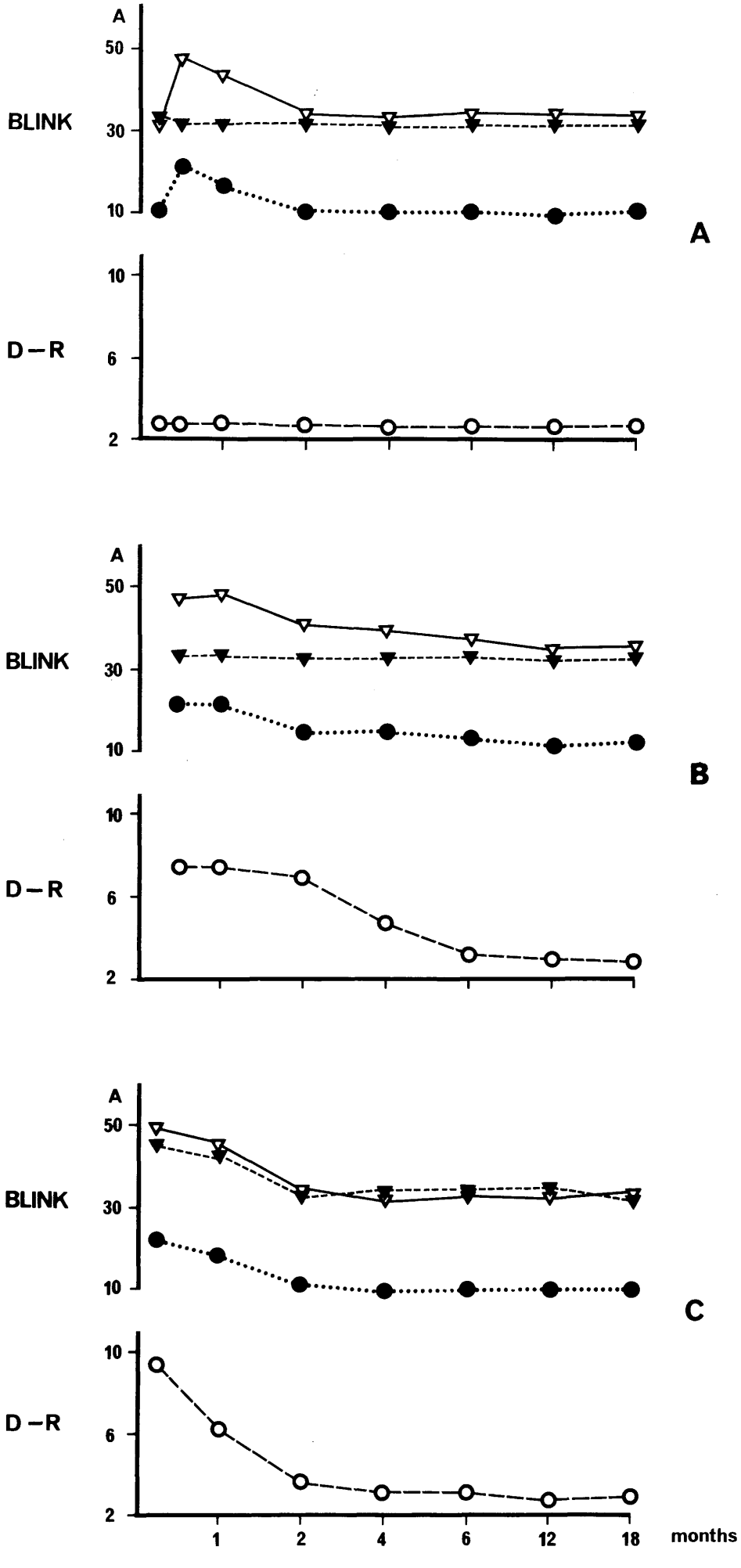
All of the R2 responses had prolonged latencies or were absent and this abnormality was proportional to that of the R1 responses in general. R2 abnormality was present only on the side of the lesion except in those patients with bilateral facial weakness in whom the abnormality was bilateral (Figure 20). The latencies of R2 responses were identical whether the ipsilateral or the contralateral SON was stimulated in all the patients, a finding highly suggestive of efferent (facial nerve) involvement (Kimura 1983a).

Two patterns of abnormality of D-response and blink reflex studies were observed in these patients. In the first pattern, no abnormality of the D-responses was noted and they remained unchanged on serial studies whereas R1 and R2 components were abnormally delayed and both progressively improved on serial testing (figure 21A). This pattern was seen in 4 patients (36%),

FIGURE 21

Types of abnormalities of direct facial motor response (D-R) to facial nerve stimulation, and blink reflex studies to supra orbital nerve (SON) stimulation in 11 patients with facial weakness associated with the Guillain-Barre´ syndrome (see figure 20). In A, the D-R remained unchanged throughout whereas R1 (solid circles) and R2 (triangles) responses on the side of the facial weakness (R2; open triangles) were both prolonged in latencies but progresively improved with time. The changes indicate that the lesion was proximal to the stylomastoid foramen in the intraosseous portion of the nerve. In B, latency prolongation was present in D-R, R1 and R2 responses on the side of facial weakness indicating that both proximal and distal segments of the facial nerve are involved. C is similar to B except that the abnormality was bilateral and hence both ipsi- and contra-lateral R2 responses were prolonged. Ordinates represent latencies of the responses in ms.

A = Absent


A
50
BLINK
30
10
A
10
D – R
6
2
A
50
BLINK
30
10
B
10
D – R
6
2
A
50
BLINK
30
10
C
10
D – R
6
2
1
2
4
6
12
18
months

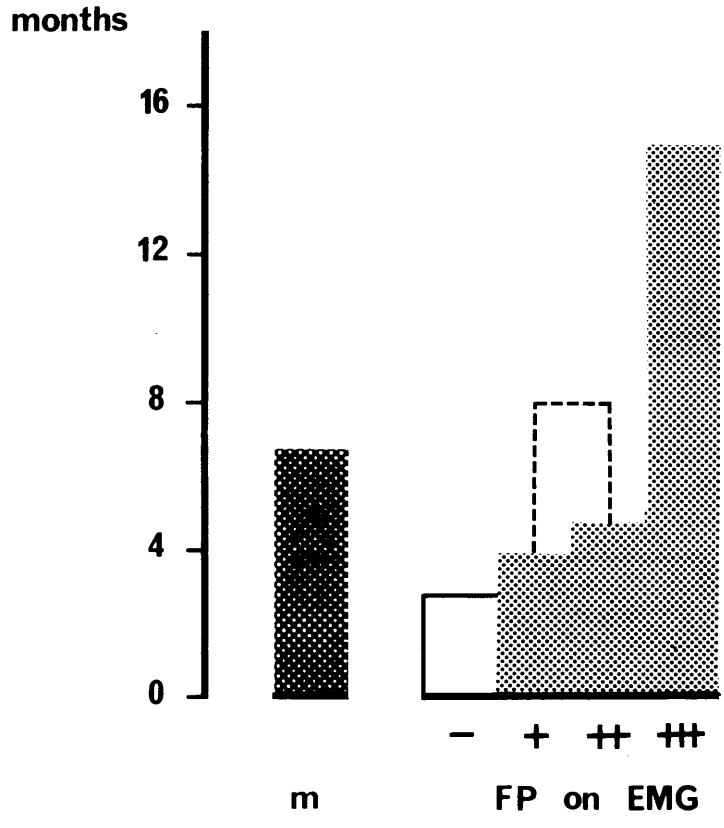
three of whom had unilateral and one bilateral facial paralysis, and it indicates that the facial nerve lesion is mainly in the proximal segments of the nerve (Kimura 1983a). The second pattern of abnormality was seen in 7 patients (64%), two of whom had unilateral (figure 21B) and 5 bilateral (figure 21C) facial weakness. In this pattern both the D-responses and R1 and R2 components were abnormal and all improved progressively on serial measurements. The latter changes indicate that the distal segments of the facial nerve are involved with or without the proximal segments (Kimura 1983a). Abnormalities similar to those observed in the present series have been reported previously in patients with the GBS (Kimura 1971; 1982; 1983a), in idiopathic facial nerve (Bell's) palsy (Kimura et al 1976; Kimura 1983a) and in other patients with a demyelinating neuropathy (Kimura 1971, 1983a).

All patients but one had their D-response and R1 and R2 response latencies returned to normal; 3 patients within 1 month, 5 patients within 4 months, 1 patient within 6 months and 1 patient within 12 months from onset of the GBS (figure 20). In the remaining one patient these abnormalities were still present though improved at the 18 month examination. The rate and extent of improvement of the facial weakness were not related to the severity of conduction slowing nor to the section of the nerve which was involved, but were closely related to the extent of facial denervation revealed by facial EMG studies (figure 22).

QUANTITATIVE STUDIES OF SOMATIC SENSATION: The origin, prevalence and nature of sensory disturbances and their longitudinal course in patients with the GBS are unclear. Although

FIGURE 22

Mean time taken by the facial weakness to recover correlated with evidence of denervation in the facial muscles on needle electromyography (EMG) in 11 patients with facial weakness associated with the Guillain-Barré syndrome. The dark bar represents the mean time to recovery from onset of the weakness (m). The interrupted line bar represents the mean time to recovery in those patients with fibrillation potentials (FPs). Grading of severity of the latter was on the same basis as that from extremity muscles (see chapter 3).


months
16
12
8
4
0
m
−
+
++
+++
FP on EMG

less common and less prominent than motor disturbances, it is evident both from this (table 8) and other series (Haymaker and Kernohan 1949; Duvoisin 1960; Marshall 1963; Ravn 1967; Eisen and Humphreys 1974; McLeod et al 1976; Ropper and Shahani 1984) that sensory disturbances including all modalities of sensation do occur in at least 86% of patients with the GBS. "Objective" sensory changes are usually reported to be less frequent than "subjective" changes in these patients (Ravn 1967). The "objective" estimate of sensory involvement in this syndrome has, however, been made by clinical examination with cotton wool for touch, pinprick for pain and a tuning fork for vibration. These clinical tests are inaccurate and not reproducible and usually underestimate both the frequency and extent of sensory involvement in neuropathies and other clinical conditions (Lindblom 1981; Jamal et al 1985 a, b; Jamal 1986; Jamal et al 1987a). On the other hand formidable problems are encountered if we attempt to relate sensory disorders in the GBS to abnormalities of peripheral sensory conduction and SEP studies. These conventional electrophysiological techniques reflect activity only in the fastest conducting heavily myelinated nerve fibres (Halliday and Wakefield 1963; Giblin 1964; Williamson et al 1970; Noel and Desmedt 1975; Anziska and Cracco 1980; Buchthal et al 1984) and are insensitive to disturbances of the small fibre population (unmyelinated and thinly myelinated fibres), the afferent pathway serving pain and temperature sensations and autonomic function (Jamal 1986; Jamal et al 1987a). Moreover, these techniques bypass the terminal parts of the large peripheral sensory fibres and their receptors and, therefore, do not register evidence of

abnormality in these terminal portions. Conduction defect in SEP and SNAP might also be present without abnormality of sensation (and vice versa) (Chiappa 1987) as Ia muscle afferents which produce no conscious sensation have a significant and possibly a dominant contribution to the production of waveforms in these studies (Gandevia et al 1984; Buchthal et al 1984). Two quantitative methods for the assessment of somatic sensation were applied to this group of patients in a serial fashion over 18 months; one to test thermal sensation to assess the function of small diameter thermal fibres and receptors and the other one to test vibration sense to asses the function of large diameter fibres and their receptors that serve this sensation. These quantitative methods are likely to accurately identify and objectify sensory disturbances in these patients (Lindblom 1981; Jamal 1986; Jamal et al 1987a).

Thermal thresholds at one of the two sites (wrist and ankle) showed abnormal elevation in 18 patients (90%) at some stage of the illness. Thermal threshold abnormalities were more frequent at the ankle (18 patients, 90%) than at the wrist (8 patients, 40%). Cold thresholds (CT) were more frequently abnormal than heat thresholds (HT) at any site in any stage of the illness. Table 11 shows the frequency of abnormality of HT and CT at each site seen within the first month from onset of the GBS compared with the 99% CL for control subjects. Variation in the pattern of abnormalities of thermal thresholds in the GBS patients was encountered in this group. All but 7 of the patients had their abnormality within the first three weeks after onset of the syndrome. The remaining 7 patients had their abnormal thermal

TABLE 11

Time sequence and frequency of abnormality of automated sensory threshold measurements in 20 patients with the Guillain-Barre syndrome during the first month after onset

Parameter		Number of patients with abnormal values* (95% CL)				
		≤ 1 week†	2-3 weeks	≤ 3 weeks	1 month	total
Thermal thresholds	wrist HT	0/8	4	4	0	4
	wrist CT	0/8	5	5	3	8
	ankle HT	4/8	6	10	3	13
	ankle CT	4/8	11	15	3	18
	one or more	5/8	12	17	1	18
	all four	0/8	3	3	1	4
VPT	carpal	4/8	13	17	1	18
	tarsal	6/8	13	19	0	19
	tibial	4/8	13	17	0	17
	one or more	6/8	13	19	0	19
	all three	4/8	13	17	0	17

† only 8 patients examined within one week from onset of the neurological illness.

* figures indicate number of patients showing their abnormality for the first time during the period specified.

HT = heat threshold
CT = cold threshold
VPT = vibration perception threshold

thresholds for the first time at the 1 month examination. It is, therefore, clear that while not all patients with the GBS were found to have abnormal thermal thresholds, the majority (90%) showed significant abnormalities (table 11). Comparison of the results of thermal threshold measurements in the GBS patients and those of normal control population (appendix) showed a significant difference between the two groups at all test sites (P between 0.01 - 0.0001).

All abnormal thermal threshold values progressively improved and in all but two patients these values returned to normal within 18 months (figure 23). This took 1 month in 1 patient, 2 months in 3 patients, 4 months in 5 patients, 6 months in 1 patient and 12 months in 1 patient. Both ankle HT and CT values remained abnormal in 2 patients at the 18 month examination.

At least at one site the vibration perception threshold (VPT) was abnormal in 19 patients (95%) within the first three weeks (table 11). Of these 19 patients, all had abnormal tarsal VPT, 18 had abnormal carpal VPT whereas 17 had abnormal tibial VPT (table 11). The prevalence of VPT abnormality was slightly less during the first week of the illness. Among 8 patients examined in this period, only 6 patients had abnormal tarsal VPT and 4 patients had abnormal carpal and tibial VPT (table 11). Comparison of the results of VPT measurements in the GBS patients and those of normal control subjects (appendix) showed the presence of a significant difference between the two groups at all test sites (P between 0.01 - 0.005).

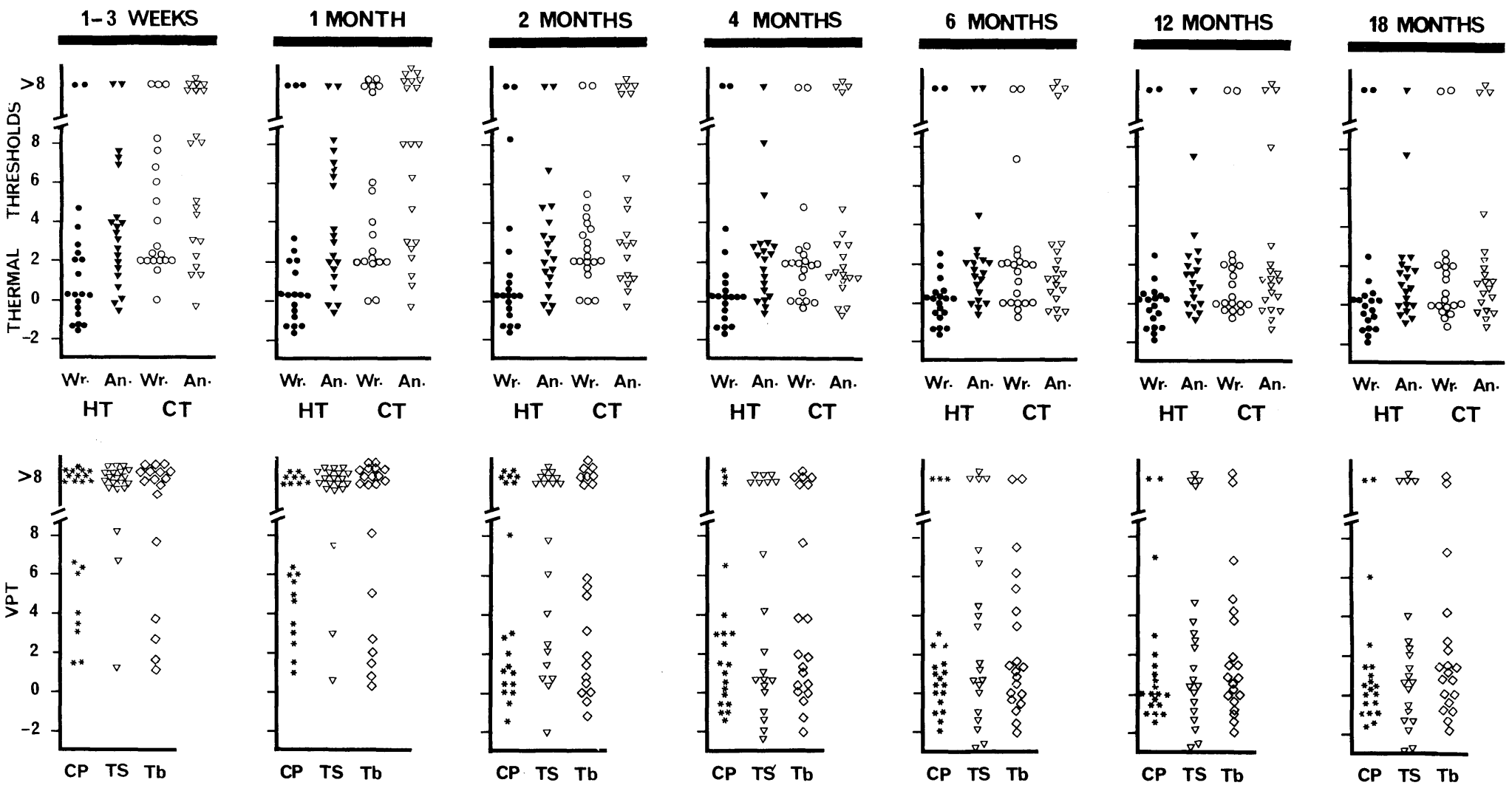
Improvement in the values of VPT occurred at all sites in all

FIGURE 23

Serial thermal and vibration perception threshold (VPT) measurements in 20 patients with the Guillain-Barre´ syndrome. Each threshold value is expressed as a figure representing the number of standard deviations (xSD) from the mean control value represented as zero. Ordinates show these values (negative below mean and positive above mean control value for that test). For normal values see appendix.

HT = Heat Threshold

CT = Cold Threshold

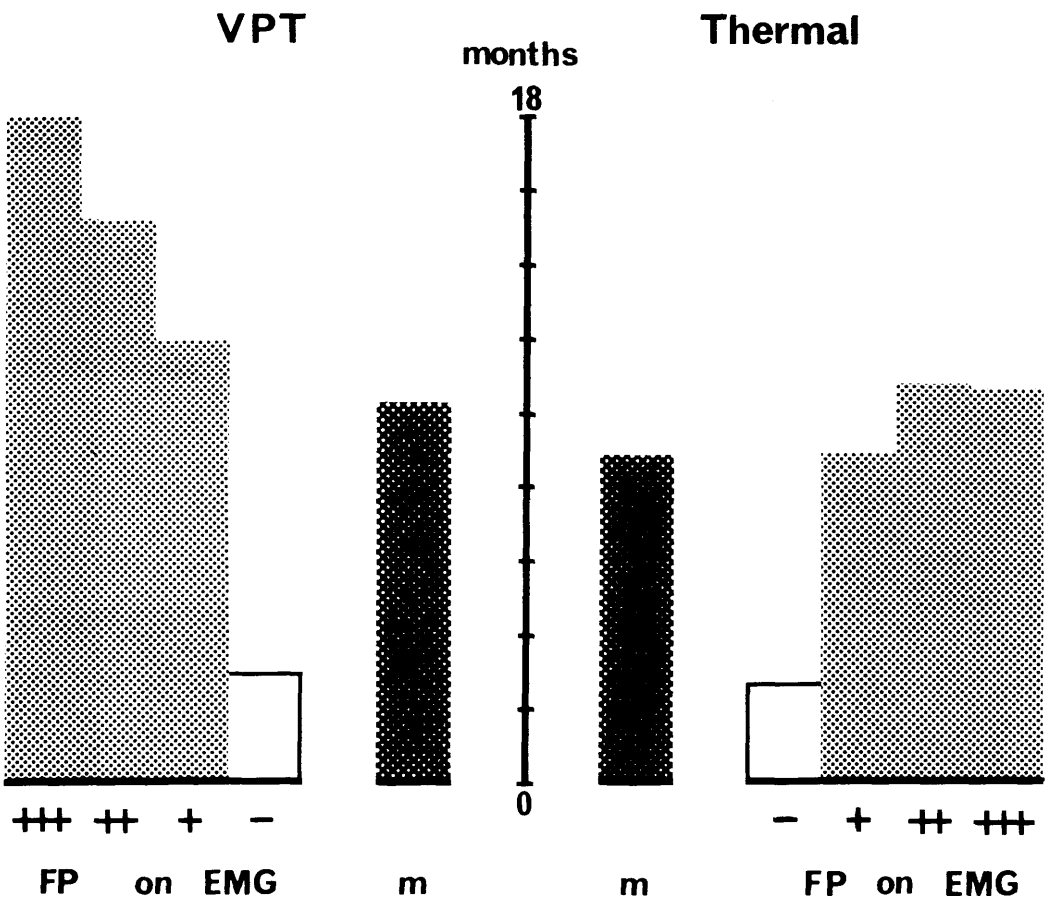

1-3 WEEKS
1 MONTH
2 MONTHS
4 MONTHS
6 MONTHS
12 MONTHS
18 MONTHS
THERMAL THRESHOLDS
>8
8
6
4
2
0
-2
Wr. An. Wr. An.
HT CT
VPT
>8
8
6
4
2
0
-2
CP TS Tb

patients on serial measurement (figure 23). All values returned to normal in 14 patients, in 5 patients within 2 months, in 4 patients within 4 months, in 1 patient within 6 months, in 1 patient within 12 months and in the remaining 3 patients within 18 months. One or more VPT value remained abnormal in 5 patients when examined at 18 months; in 3 of them all three sites, in 1 patient at the carpal and tarsal sites and in the remaining patient at the tarsal site only. The rate and extent of improvement of the elevated thermal thresholds and VPTs are related to evidence of axonal involvement on EMG studies in these patients in figure 24. Rapid normalisation of these thresholds occurred in those patients without evidence of denervation compared to those who showed denervation.

Both of the thermal and vibration sensation assessment techniques examine the peripheral and central pathways of the relevant sensory system and, therefore, a coexistant abnormality in the central pathways cannot be entirely excluded (Goldberg and Lindblom 1979; Jamal et al 1985 a, b, 1987a; Jamal 1986). There is, however, ample clinical, pathological and electrophysiological evidence which indicates that GBS chiefly affects the peripheral nervous system (Asbury et al 1969; Wisniewski et al 1969; Miyakawa et al 1971; Prineas 1972, 1981; Carpenter 1972; Oppenheimer and Spalding 1973; McLeod et al 1976; McLeod 1981). These abnormalities are, therefore, likely to have at least a significant peripheral contribution. It is now conclusively demonstrated that thermal sensation in man is induced by the stimulation of specific heat and cold receptors that transduce the physical stimuli of heat and cold respectively into electrical

FIGURE 24

Mean time to normalisation of elevated thermal and vibration perception threshold (VPT) values correlated with evidence of denervation on needle electromyography (EMG) in extremity muscles in patients with the Guillain-Barre syndrome (18 patients in the former and 19 patients in the latter) from onset of the neurological illness. Dark bars represent the mean time (m) to recovery of all patients in the respective group. For grading of severity of fibrillation potentials (FPs) see chapter 3.


VPT
Thermal
months
18
0
+++ ++ + −
FP on EMG
m
m
− + ++ +++
FP on EMG

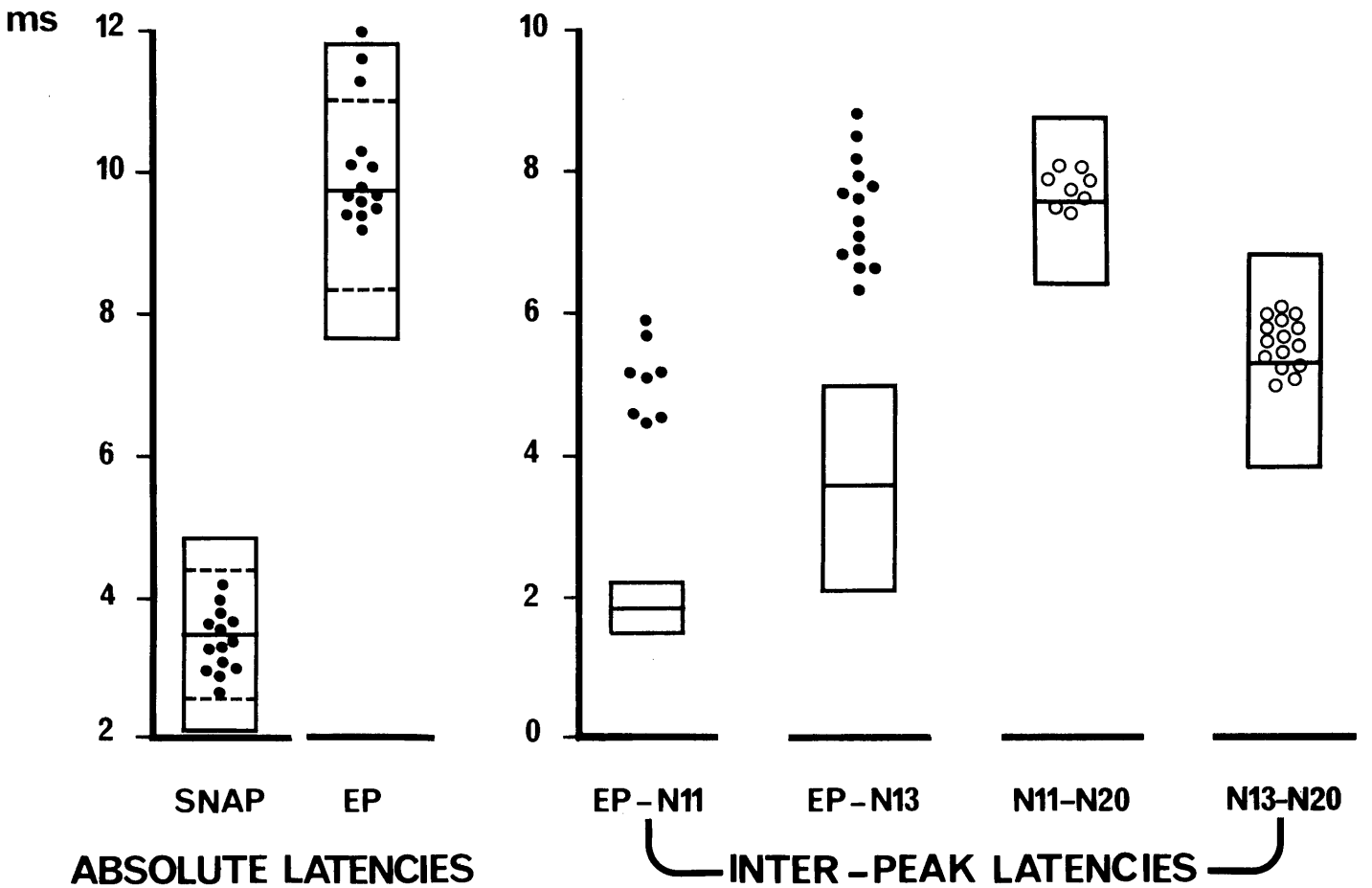
impulses (Hensel 1973; 1982; Jamal 1986). Impulses from these receptors are believed to travel in nerve fibres that exclusively fall into the Aδ and C groups (Light and Perl 1984; Jamal 1986). Thermal threshold measurements, therefore, provide a test of function and integrity of small nerve fibre population in the patients with GBS including the unmyelinated (C) fibres serving heat sensation and the thinly myelinated (Aδ) fibres serving cold sensation (Jamal 1986; Jamal et al 1987a). Vibration perception threshold measurement on the other hand provides a test to assess the integrity of the vibration sensory system which is served by large diameter sensory fibres (Goldberg and Lindblom 1979; Light and Perl 1984). Abnormality of VPT, therefore, reflects large diameter afferent fibre involvement. The greater frequency of abnormalities of thermal thresholds and VPTs in the lower limbs compared with the upper limbs in this group of patients (table 11) is similar to their pattern of somatic sensory involvement (table 8) found on clinical examination and to that found in patients with peripheral neuropathy in general. It is difficult to postulate whether these abnormalities are due to segmental demyelination, axonal degeneration or to end organ involvement.

SOMATOSENSORY EVOKED POTENTIALS (SEP) STUDIES: SEP studies were performed only once at presentation within the first three weeks in 18 patients who had abnormal SNAP studies either on presentation or in their second assessment and of these, only 12 had recordable SEPs (figure 25). In the remaining 2 patients who had all their SNAP studies normal on presentation and subsequently, the SEP studies were performed serially at the same intervals over a period of 18 months (figure 26).

FIGURE 25

Results of somatosensory evoked potentials (SEPs) to right median nerve stimulation at wrist in 14 of 20 patients with the Guillain-Barre´ syndrome, in whom SEPs were recordable. Peripheral conduction times (SNAP and EP latencies; EP-N11 or EP-N13)* are indicated by solid dots while central conduction times (N11-N20 or N13-N20)* are shown in open circles. Control means and three standard deviations (SDs) on either side are represented for each parameter by open bars (see appendix). Two SD values above and below control mean for Erb´s point potential (EP) and median sensory nerve action potential (SNAP) latencies are also shown as horizontal interrupted lines within the bars.
Abnormalities were more marked in the brachial plexus - spinal segment than more distal parts of the median nerve. As expected, no central conduction abnormality was found in any patient.

* N11 was reliably identifiable in only 8 patients on serial studies.


ms
12
10
8
6
4
2
10
8
6
4
2
0
SNAP
EP
EP-N11
EP-N13
N11-N20
N13-N20
ABSOLUTE LATENCIES
INTER-PEAK LATENCIES

In 6 patients with absent (or very abnormal) median SNAP, no SEPs were recordable. Figure 25 summarises the results of the SEP studies in the remaining 14 patients on their first test and compares them with median SNAPs studies at wrist performed in the same session. Two patients (14%) only had abnormal wrist median SNAP amplitude outside the 95% CL (but their latencies were normal). The maximum sensory conduction time between Erb's point and the cervical cord (EP - N13) was above the 3SD of the control upper limit in all patients (100%) while in only one patient (7%) the EP latency, representing conduction between wrist and Erb's point, was above the 3 SD control limit (figure 25). The central conduction time (N13 - N20) was normal in all 14 patients. These results clearly demonstrate the presence of slowed conduction across the roots and proximal parts of the brachial plexus at times when nerve conduction velocities over the more distal segments are normal in the median nerve . This is especially true in the early stages. Figure 26 shows results of serial SEP studies in 2 patients whose median (and ulnar and sural) SNAPs studies were normal throughout their illness. Both patients demonstrated an abnormal increase in their EP - N13 conduction time whereas their EP latencies, representing conduction between wrist and brachial plexus, and their central conduction time (N13 - N20) remained normal and unchanged throughout.

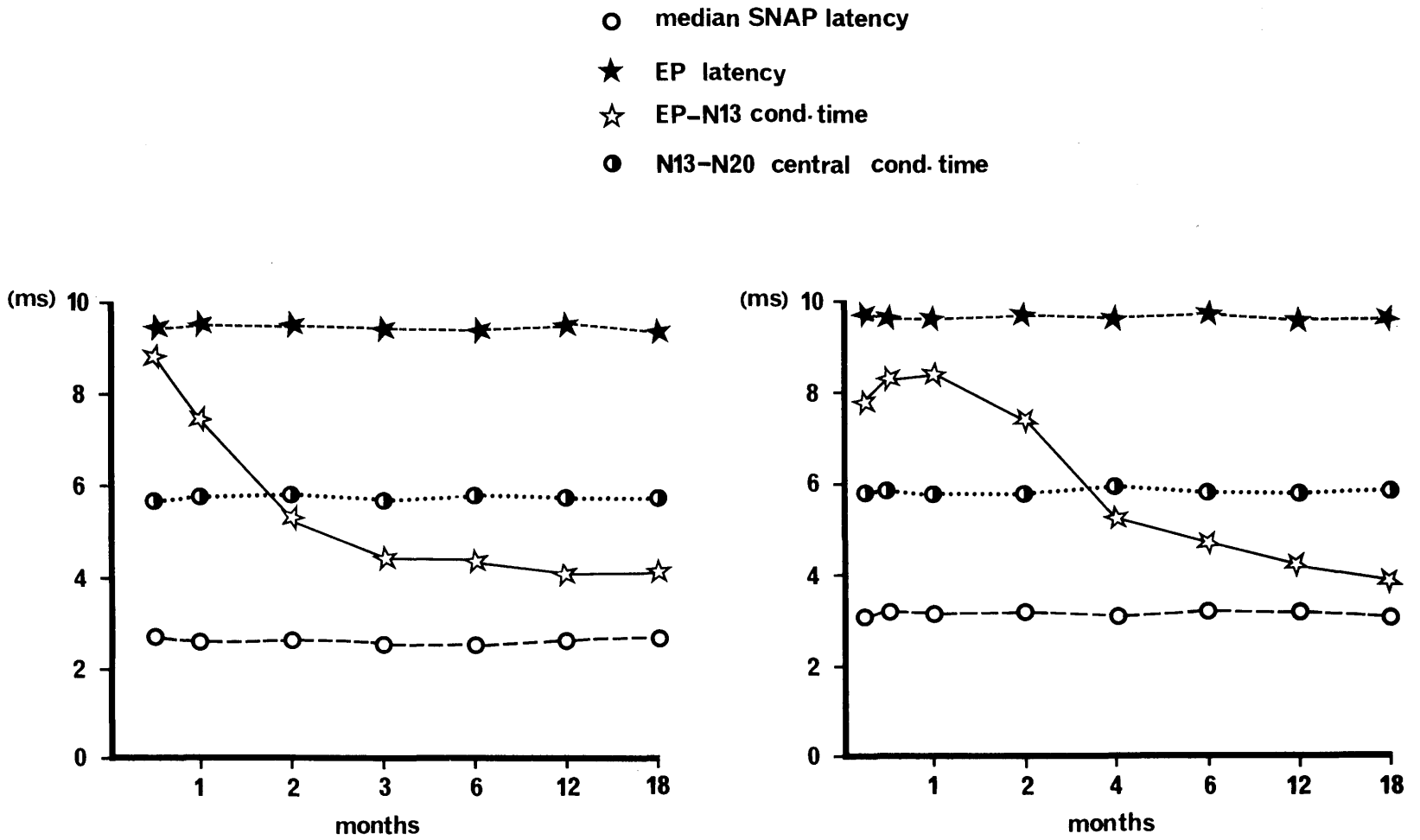
These results would suggest that conduction abnormality in the proximal segments of the large fibre afferent nerves are common in the GBS and that the proximal segment is usually the earliest site affected and in some patients may be the only segment involved. Such an abnormality in the proximal segment would of course escape

FIGURE 26

Serial somatosensory evoked potential (SEP) studies to right median nerve stimulation at wrist in two patients with the Guillain-Barre´ syndrome who had normal sensory nerve action potentials (SNAPs) for median, ulnar and sural nerves bilaterally and remained so throughout the 18 months of follow up.

Marked abnormality of conduction in the brachial plexus-spinal segment alone was present in each case. This abnormality disappeared with time.

EP = Erb´s Potential


median SNAP latency
EP latency
EP–N13 cond. time
N13–N20 central cond. time
(ms)
10
8
6
4
2
0
1
2
3
6
12
18
months
(ms)
10
8
6
4
2
0
1
2
4
6
12
18
months

detection if only conventional conduction studies were used.

IN SUMMARY, the results of the neurophysiological studies in this group of 20 patients with the GBS demonstrate the presence of conduction abnormalities in the proximal part of peripheral nerves in excess of those in the more distal segments and suggest that proximal segments are probably more liable to damage in the GBS polyneuropathy. This is especially true in the early phase of the illness. It is also clear from this study that milder abnormalities in the distal segments may be shown by serial studies. Significant sensory dysfunction, involving large and small fibre pathways, occur in the majority of patients with the Guillain-Barre´ syndrome. The study confirms previous findings of the presence of axonal disruption in addition to the segmental demyelination in some patients and the extent and severity of this axonal degeneration determines the rate and extent of improvement in these patients.

CHAPTER 6

NEGATIVE EVIDENCE FOR CNS INVOLVEMENT IN MILLER FISHER SYNDROME

Neither the neurophysiological investigations nor CT scan or NMR brain scan imaging provided any evidence of dysfunction or structural abnormality in the CNS in any of the seven patients with the Miller Fisher syndrome.

BRAINSTEM AUDITORY EVOKED POTENTIAL (BAEP) STUDIES: Auditory tracts and nuclei of the caudal and middle parts of pons which are situated ventrally in the tegmentum adjacent to the basis pontis traverse the entire length of the pons passing through superior olivary complexes and the lateral lemniscus to the inferior colliculi, on the roof of the midbrain, and the medial geniculate body (Brodal 1969). From the latter, the acoustic radiation of the internal capsule emerges to end on Heschl's gyrus on the supratemporal plane, the auditory cortex (Brodal 1969).

In BAEP studies, several waveforms are evoked on proper acoustic stimulation and these waveforms are recorded from the scalp (i.e., far field potentials) (Jewett et al 1970). These waves are generated by sequential activation of the acoustic nerve and the auditory pathway structures in the brainstem including the cochlear nuclei, superior olivary complexes, lateral lemniscus and nuclei and inferior colliculi (Jewett et al 1970; Jewett and Williston 1971). Involvement of the audiotry pathway at this level by a pathological process is likely to produce changes of BAEP components in the form of abnormality of these components or slowed conduction in the ascending pontine auditory pathway (see below).

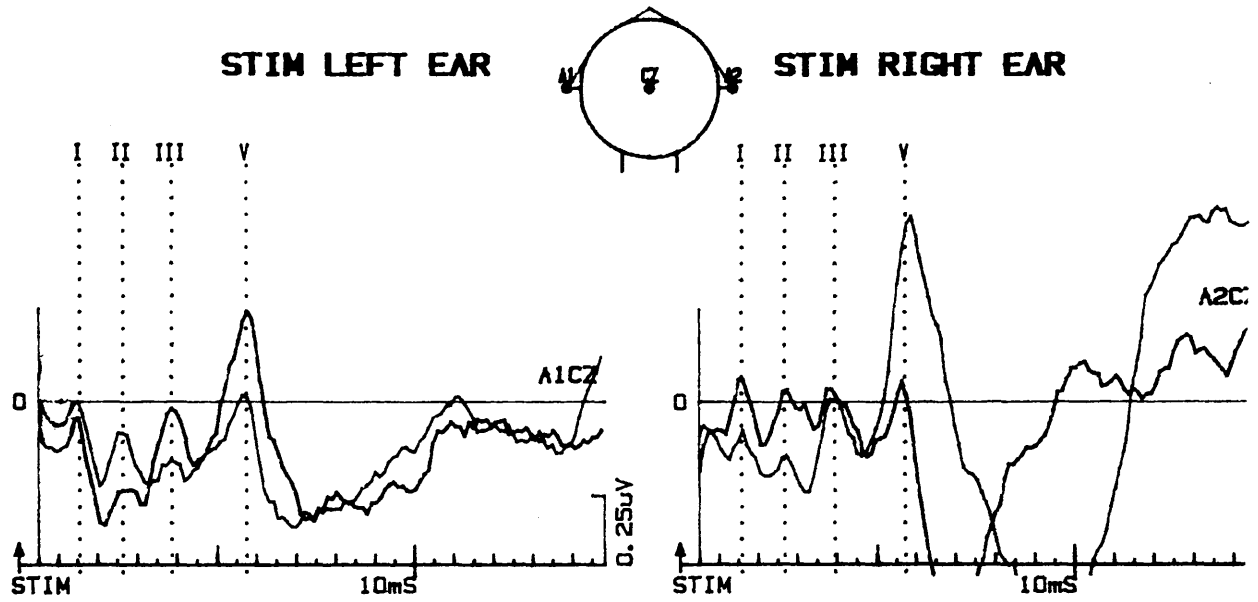
The BAEP studies have proved to be very useful in detecting and localising lesions in the brainstem even when not revealed by other tests (Stockard and Rossiter 1977). Serial recordings of the BAEP provide useful information about the evolution of brainstem lesions and their response to therapy (Stockard and Rossiter 1977). BAEP studies can be sensitive to brainstem pathologies even when they are clinially silent. (Robinson and Rudge 1978; Stockard et al 1977a,b; Chiappa 1980; Chiappa et al 1980; Eisen and Odusote 1980).

On presentation and all subsequent visits in all seven patients with the MFS waves I - V were identified with normal latencies and interwave peak latencies (I - III, III - V and I - V) and these did not change on repeated measurements (Figures 27 & 28). No significant side to side differences were noted (table 12). The ratio of wave V/I amplitude was within the normal limits in all the patients. The BAEP studies, therefore, failed to provide any evidence of brainstem involvement on presentation and on subsequent visits in all the seven cases with the MFS and such evidence reinforces the thesis that no significant brainstem pathology is present in this syndrome.

SOMATOSENSORY EVOKED POTENTIAL (SEP): SEP studies assess the entire length of the large fibre afferent pathway in man including the first order neurones, the second order neurones which traverse the brainstem and the third order neurones between the thalamus and the primary sensory cortex (Desmedt and Noel 1973; Lancet Editorial 1987; Chiappa 1987). The various peripheral and sucortical components were discussed previously (Chapter 4). The earliest cortical component in the SEPs is believed to be the N20

FIGURE 27

Brainstem auditory evoked potentials (BAEPs) in a patient with the Miller Fisher syndrome (case 5) few days after onset of the neurological illness (top) and 6 months later (bottom). Waves I, III and V are well defined and reproducible at normal peak and inter-peak latencies with no significant change. All other studies at 1, 2 and 4 months were similar to these. Similar findings were noted in all other 6 patients. For test set up see chapter 3.


STIM LEFT EAR
STIM RIGHT EAR
I
II
III
V
A1CZ
A2C
0
0.25uV
STIM
10mS

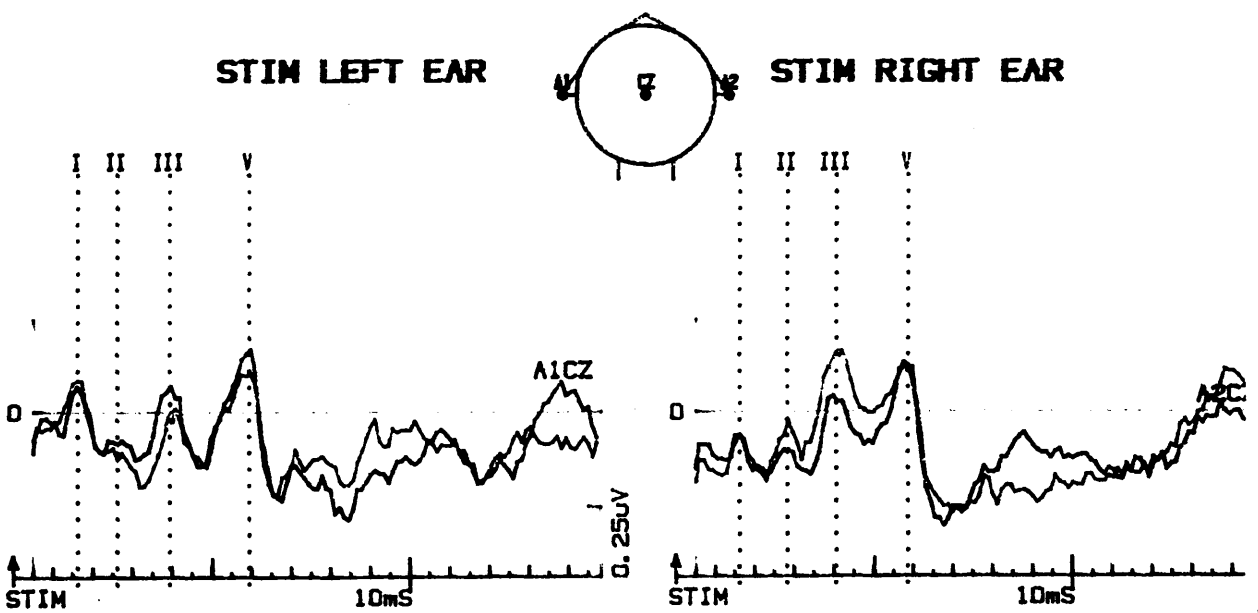

STIM LEFT EAR
STIM RIGHT EAR
I
II
III
V
A1CZ
A2C
0
0.25uV
STIM
10mS

FIGURE 28

Results of serial brainstem auditory evoked potential (BAEP) studies in 7 patients with the Miller Fisher syndrome. Control means and three standard deviations (SDs) on either side for each measurement (see appendix) are represented by open bars. These results are for the right side but similar results were obtained for the left side. Ordinates represent latencies and interpeak latencies in ms.

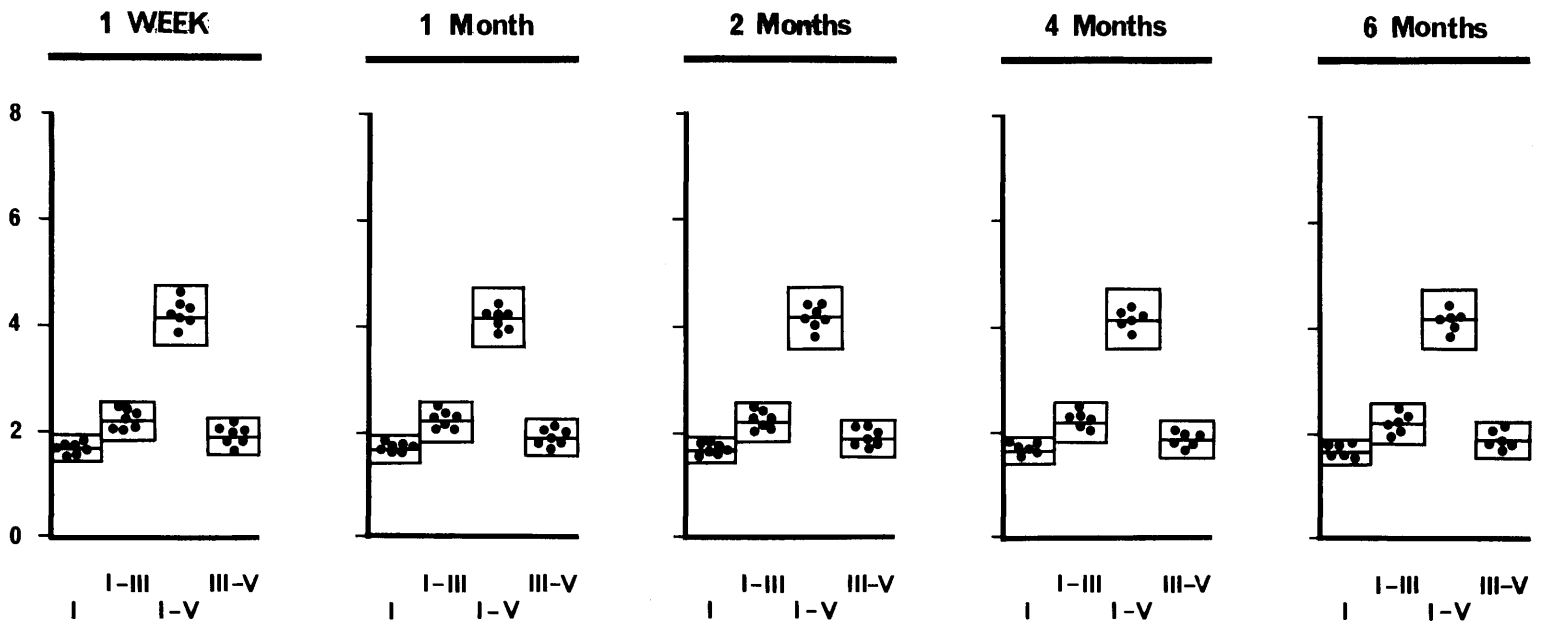

1 WEEK
1 Month
2 Months
4 Months
6 Months
8
6
4
2
0
I
I-III
III-V
I-V

TABLE 12

Side to side difference for various parameters of serial brainstem auditory evoked potentials in 7 patients with the Miller Fisher syndrome

PARAMETER		After onset of the illness					ULN
		1 week	1 month	2 months	4 months	6 months	99% CL
CASE 1	I	0.08	0.1	0.09	0.08	0.1	0.42
	I-III	0.21	0.18	0.16	0.2	0.18	0.44
	III-V	0.14	0.12	0.13	0.12	0.12	0.54
CASE 2	I	0.14	0.11	0.09	0.09	0.12	
	I-III	0.13	0.12	0.16	0.19	0.16	
	III-V	0.21	0.23	0.19	0.24	0.26	
CASE 3	I	0.22	0.24	0.26	0.24	0.24	
	I-III	0.18	0.21	0.22	0.19	0.18	
	III-V	0.24	0.21	0.22	0.21	0.23	
CASE 4	I	0.31	0.34	0.28	0.32	0.29	
	1-III	0.25	0.21	0.2	0.21	0.23	
	III-V	0.06	0.08	0.1	0.08	0.08	
CASE 5	I	0.28	0.26	0.18	0.2	0.23	
	I-III	0.16	0.18	0.12	0.16	0.18	
	III-V	0.12	0.11	0.1	0.1	0.12	
CASE 6	I	0.26	0.24	0.23	0.24	0.22	
	I-III	0.08	0.05	0.06	0.08	0.05	
	III-V	0.21	0.18	0.16	0.12	0.11	
CASE 7	I	0.26	0.28	0.26			
	I-III	0.18	0.22	0.22			
	III-V	0.34	0.36	0.38			

Values are in ms

ULN = upper limit of normal

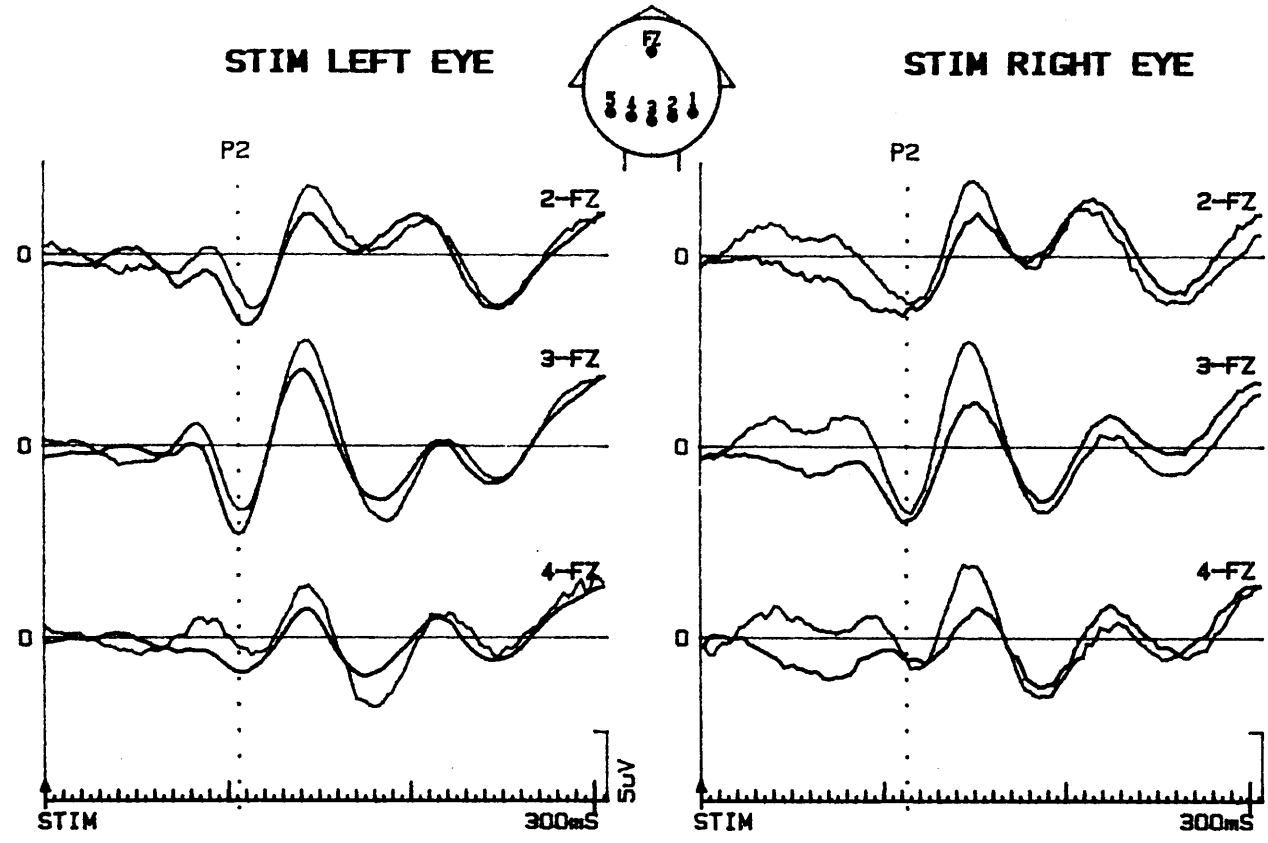
CL = confidence limit

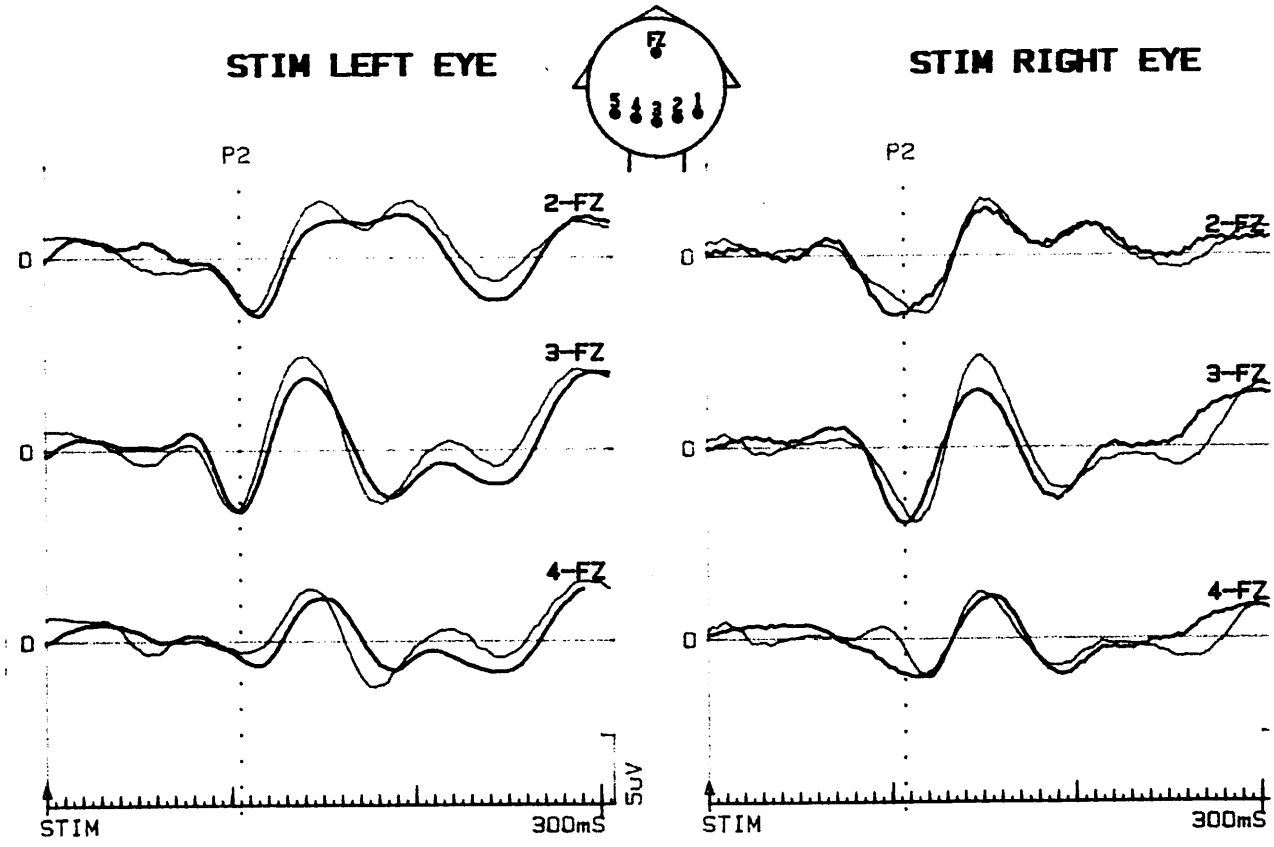
(Desmedt 1971). The N13 - N20 conduction time is believed to represent the transit time of the afferent volley from the cervical cord, traversing the brainstem lemniscal pathway to the primary sensory cortex (Desmedt and Cheron 1980). This *"central conduction time"* was used in several recent studies to investigate the CNS pathway of the SEPs recorded using a frontal reference (Eisen and Odusote 1980; Ganes 1980; Hume and Cant 1978, 1981; Kimura et al 1978; Symon et al 1979). Desmedt and Cheron (1980, 1981) suggest that the spino-cortical transit time should be estimated from the onset of the N11 which reflects the *"spinal entry time"* of the afferent volley, to the onset of the parietal N20 indicating the arrival time at cortex and that in normal adults the spino-cortical transit time is 6.4 $\mp$ 0.45 ms. Both N11 - N20 and N13 - N20 conduction times were assessed in all the five MFS patients with recordable SEP, as all the components were easily identified, and these showed no abnormality on presentation and remained unchanged on subsequent visits (Figures 13 & 14). Absence of evidence of central abnormality in the MFS cases reinforces the belief that no significant pathological changes are present in the brainstem in this illness.

PATTERN REVERSAL VISUAL EVOKED POTENTIAL (PRVEP) STUDIES: The PRVEP provides the most sensitive means at present available for detecting subclinical lesions of the optic nerve and the visual pathway which traverses the lateral geniculate body (Halliday et al 1976). In all the seven cases with the MFS the typical triphasic negative-posiotve-negative responses were identified and their latencies, amplitudes and waveforms were normal and symmetrical on presentation and subsequently (Figure 29, table

FIGURE 29

Pattern reversal visual evoked potentials (PRVEPs) in a patient with the Miller Fisher syndrome (case 4) few days after onset of the neurological illness (top) and 6 months later (bottom). All other studies at 1, 2 and 4 months were similarly normal. Findings similar to these were found in the rest of the Miller Fisher syndrome patients. For test set up see chapter 3.


STIM LEFT EYE
STIM RIGHT EYE
FZ
5 4 3 2 1
P2
2-FZ
3-FZ
4-FZ
0
5uV
STIM
300mS


STIM LEFT EYE
STIM RIGHT EYE
FZ
5 4 3 2 1
P2
2-FZ
3-FZ
4-FZ
0
5uV
STIM
300mS

13). No abnormal side to side difference in the latencies of the major positive peaks was noted in any patient (table 13).

BLINK REFLEX STUDIES: The afferent impulses for the first component of the blink reflex relay in the pons on the same side at the level of the trigeminal main sensory nucleus. R2 component is believed to be produced through the ipsilateral descent of the afferent impulses along the lateral aspect of the medulla to the spinal tract of the trigeminal nerve and then the ascent of these impulses again through medulla to make bilateral connection with the facial nuclei (Kimura 1983a). Dysfunction in this central pathway, mainly in pons and lateral medulla, is reflected on blink reflex studies as abnormalities of recognised patterns (Kimura 1983a). Blink reflex studies evoked by electrical stimulation of the supraorbital nerve or by mechanical tap of the glabella have, therefore, been used to assess brainstem function in patients with various neurological disorders (Kimura 1973, 1983a). No blink reflex abnormality of a pattern suggestive of a brainstem dysfunction (Kimura 1983a) was recorded in any of the seven cases with the MFS on presentation or on subsequent studies (Figures 8,9 & 10).

EEG STUDIES: These were normal on all ocassions in every case and did not show any evidence of a CNS dysfunction.

CT SCAN AND NMR STUDIES: Brain CT scans with and without contrast enhancement and with special views of the brainstem in all seven cases and NMR brain imaging with brainstem views in cases 4, 5 and 6 have been performed and showed no structural CNS abnormality (Chapter 2). These findings further support the lack of evidence of a CNS involvement on neurophysiological studies.

TABLE 13

Results of serial pattern reversal visual evoked potentials in seven patients with the Miller Fisher syndrome

PARAMETER		After onset of the illness					ULN 99%CL
		1 week	1 month	2 months	4 months	6 months	
CASE 1	P2 lat	102	105	101	100	103	118
	R-L diff	5	5.4	4	2	4	8.76
CASE 2	P2 lat	110	108	109	108	106	
	R-L diff	3	3.5	2.8	3.2	3	
CASE 3	P2 lat	99	101	102	100	100	
	R-L diff	2	2	3	3.5	2.6	
CASE 4	P2 lat	111	110	108	110	107	
	R-L diff	6	3	5	4	2	
CASE 5	P2 lat	109	112	108	108	110	
	R-L diff	4	5	4	4	5	
CASE 6	P2 lat	104	105	106	104	103	
	R-L diff	2	2.4	4.5	4	3.5	
CASE 7	P2 lat		112	111			
	R-L diff		4.1	4.3			

Values are in ms and P2 latencies are for the right side

ULN = upper limit of normal

CL = confidence limit

CHAPTER 7

DISCUSSION

The results of serial multimodal neurophysiological tests in the 7 patients with typical MFS (chapter 4) provide strong evidence of peripheral nerve dysfunction in this disorder. Neither the neurophysiological investigations nor the radiological (NMR and CT scan) tests revealed any evidence of a CNS abnormality (chapter 6). Improvement in the neurophysiological parameters of peripheral nerve disorder as revealed by serial studies followed or accompanied clinical recovery of peripheral nerve function in all cases.

Motor conduction velocities in the distal portions of the peripheral nerves were initially within the normal range in most patients but all subsequently increased while the shortest distal motor latencies decreased in subsequent studies in the three nerves examined in all seven patients (figure 5). These improvements were significant when compared with the normal variance of multiple testing of age and sex matched controls ($P < 0.01$) and all were in the same direction. Absence of severe conduction block in these distal segments in most patients excludes the possibility of a significant demyelination in the fastest motor fibres but the progressive improvement in their conduction velocities may be due to less severe reversible changes in these fibres. Slight degrees of demyelination or more significant demyelination in thinner fibres conducting at slower range to those tested by these conventional studies may not reflect on conduction values.

Pronounced abnormality of F-wave studies was present in all

seven patients (figure 5; table 10). The more marked abnormality of the F-waves compared with the motor conduction velocities suggests a more significant block of conduction at the level of the nerve roots, plexus or proximal segments (chapters 4 and 5). The considerable prolongation of F-wave latencies (seen initially or later during recovery) is suggestive of a demyelination of these proximal segments (Kimura 1983b) and the return of these latencies to normal values indicates recovery of conduction across these segments of the nerves (Kimura 1983b). Prolongation of F-wave latency or absence of the response are frequently seen in patients with the GBS early in the course of their illness and may be the only abnormality in their peripheral nerve motor studies (Kimura and Butzer 1975; Kimura 1978a; McLeod 1981; Ropper and Shahani 1984). In the series of 20 patients with the GBS described in chapter 5, 15% had their motor conduction abnormality almost entirely in their proximal segments and in many more,F-wave latencies were disproportionately prolonged when compared with their SDMLs and FMNCVs.

Reduction of peak to peak amplitude, prolongation of the peak latency and abnormal dispersion of the sensory nerve action potentials (SNAPs) in one or more nerves were seen in all seven patients with the MFS (Figures 6 & 7; chapter 4). All of these parameters progressively improved on serial measurements in most of the nerves tested in these patients (Figure 7). Qualitatively similar but more severe abnormalities of SNAPs were seen in 90% of the series of 20 patients with GBS described in chapter 5. In both the MFS and GBS patients there was some variability of the SNAP abnormality as to the nerves involved. Abnormal temporal

dispersion of the SNAP can be explained by multifocal demyelination of individual axons resulting in some fibres having little or no demyelination. This results in a response with a prolonged latency but which is also temporally dispersed. Bimodal SNAP may be the result of demyelination in a group of fibres more than others, thus the two groups will be separated and an initial component (representing the fastest fibres) and a trailing component (representing the slowest and mostly demyelinated fibres) are recorded as a bimodal response. Demyelination will also result in diminution of the amplitude and prolongation of the latency of the SNAP (Buchthal et al 1984).

Absence of signs of denervation in the facial and limb muscles of 7 patients with the MFS suggests that the neuropathy did not produce a significant axonal disruption (chapter 5). This lack of denervation has been observed in about half of the patients with the GBS and is usually associated with complete clinical recovery in a relatively short period of time compared to those patients with evidence of significant denervation (chapter 5). Absence of signs of denervation in the MFS patients, therefore, accords very well with the fact that complete and relatively rapid recovery occurs in the vast majority of these patients. Axonal degeneration as indicated by the presence of frequent fibrillation and positive waves usually appearing 2 - 5 weeks after onset of the illness in patients with the GBS is usually associated with prolonged and/or incomplete recovery (Eisen and Humphreys 1974; Raman and Taori 1976;Martinez-Figueroa et al 1977; McLeod 1981; Ballantyne and Hansen 1982; Hansen et al 1982; Albers et al 1985 and chapter 5). The more severe the extent of the axonal

disruption is, the less complete and more prolonged recovery is likely in these patients with the GBS (chapter 5).

The reduction of MUN estimation in cases number 2 and 3 of the MFS patients early in the course of their illness (chapter 4) most probably indicates loss of function in some peripheral motor nerve fibres to the extensor digitorum brevis muscle and the significant rises 6 months later (chapter 4) probably suggest reversibility of the underlying pathology. Similar but larger drop of the MUN values of the EDB muscle has been noted in patients with the GBS (Martinez-Figueroa et al 1977; Hansen et al 1982). The mean MUN value of the GBS patients rose from 27 at 2 months, to 58 at 3 years after onset of their illness (Hansen et al 1982). The more irreversible drop of the number of MUPs in the GBS patients was mainly attributed by the authors to axonal involvement, the extent of which would determine the degree of the reversibility of the reduction of the MUN estimation (Hansen et al 1982; Ballantyne and Hansen 1982). The drop of MUN in patients with the MFS is, therefore, likely to be due to demyelination and conduction block of individual motor axons to the EDB muscle. Complete block to conduction of the nerve impulses is known to occur in experimentally induced demyelinating peripheral neuropathy (Cragg and Thomas 1964). Studies on focal serum induced demyelination of rat sciatic nerve provided evidence that the distal intramuscular part of motor fibres is among the sites which are more vulnerable to demyelination due to increased permeability of the blood-nerve barrier to antisera at these sites (Sumner 1981). This latter finding accords with disproportionate involvement of the distal segments in some patients with the GBS (Lambert and Mulder 1964;

Chapter 5). That the drop of MUN in the patients with the MFS is more likely to be due to demyelination and conduction block of individual axons is also supported by absence of significant change in the dimension of the MUPs in patients with the MFS on serial studies. Ballantyne and Hansen (1982) found evidence of remodelling of MUPs accompanying denervation in which surviving axons reinnervated denervated muscle fibres in a process of collateral reinnervation and this resulted in alteration of the dimensions of the MUPs.

The H-reflex was absent in all 7 patients within a week from onset of the neurological illness (table 6). The reflex eventually reappeared at abnormally long latencies with subsequent return to normal values in the 6 patients who were followed up (table 6). Similar abnormalities have been found in the 20 patients with the GBS (chapter 5). Whether the abnormality of the H-reflex studies in these patients is due to a lesion in the sensory and/or motor fibres is unknown but in some patients the abnormal or absent H-reflex was associated with a normal F-wave latency from the posterior tibial nerve (cases 3, 5 & 6). At least in these patients the abnormally prolonged or absent H-reflexes are more likely to be due to disturbance in the afferent fibres of the reflex arc.

The abnormalities of blink reflex studies observed in the MFS and the GBS were similar in pattern (Chapters 4 and 5). In all the 11 patients with GBS who had blink reflex studies and in patients with the MFS (cases 2, 3,4,5 & 7; figures 8, 9 & 10) there was a consistent prolongation of the R2 component to about the same degree regardless of whether the ipsilateral or the

contralateral superior orbital nerve was stimulated. This was also confirmed in each patient by simultaneous recording of R2 components from both sides in response to a glabellar tap, which stimulates both trigeminal nerves simultaneously each of which activates the facial nuclei on both sides (Kimura 1983a). A consistent R2 latency prolongation similar to that observed in the electrically induced blink reflexes was observed in each patient. These findings strongly suggest that the abnormality of conduction lies in the efferent arc of the reflex pathway (the facial nerve). In 4 patients (36%) with the GBS and in cases 3, 4 & 7 with the MFS, abnormalities of blink reflex were not associated with abnormality of the D-response and this indicates that the proximal part of the facial nerve was the site of maximal involvement (Kimura 1983a). All patients with the MFS and all but one patient with the GBS had their D-response and blink reflex abnormalities returned back to normal within 6 months in the former and 18 months in the latter syndrome (figures 9 & 20). Clinical normalisation of the facial weakness took less time in patients with MFS and in those GBS patients who had no evidence of denervation in their facial muscles compared to those GBS patients with evidence of facial muscle denervation. Similar blink reflex abnormalities have been noticed in patients with idiopathic facial nerve (Bell's) palsy (Kimura et al 1976; Kimura 1983a) and in other patients with more generalised demyelinating neuropathies (Kimura 1971; 1983a).

An important finding of the SEP studies was the prolongation of EP-N13 conduction time with normal central (N13-N20) conduction time. The former reflects changes of conduction in the large

diameter afferent fibres in the most proximal parts of the brachial plexus and the cervical roots (Chapter 4). In addition, some patients showed abnormalities of the EP potential both in terms of amplitude and latency (figure 13). Subsequent tests showed gradual improvement of the SEP studies (figure 13). Both types of these abnormalities have been seen in patients with the GBS (Chapter 5). In 2 patients (10%) with the latter syndrome in whom sensory conduction studies in the sural, median and ulnar nerves were normal, prolongation of the EP-N13 conduction time in median evoked SEP studies was the only abnormality noted on serial assessment. Similar observations have been reported in the GBS by other authors (Brown and Feasby 1984b; Walsh et al 1984; Ropper and Chiappa 1986).

Abnormalities of the thermal and vibration perception thresholds in the patients with the MFS (Figure 11) indicate dysfunction of the small fibre thermal pathway in the former (Jamal et al 1985 a,b; 1987a; Jamal 1986) and of the large fibre sensory pathways in the latter (Goldberg and Lindblom 1979). Since both of these techniques test the integrity of both peripheral and central pathways, the site of dysfunction can only be inferred. Both subjective and objective sensory dysfunction has been noted before in patients with the MFS involving all modalities of sensation (Fisher 1956; Table 1; chapter 1). The presence of abnormalities in the MFS patients in this study by these techniques without obvious clinical involvement probably reflects subclinical dysfunction in the respective sensory systems. Loss of function in a considerable percentage of sensory fibres is usually present before any clinical abnormality of sensation

appears (Ropper and Shahani 1984). Clinical evidence of sensory dysfunction in patients with the GBS is common, albeit mild, when compared to motor abnormalities. Such an abnormality was present in 86% of the GBS in this study (Chapter 5). Clinical bedside examination of sensation underestimate both the frequency and severity of the sensory disturbances in these patients (Chapter 5). Thermal thresholds in 90% and VPT in 95% of the 20 patients with the GBS in this study were abnormally elevated (Chapter 5; figure 23). In most patients with the GBS these values returned to normal while in those with evidence of denervation the normalisation took longer time and in some patients they remained abnormal even at the examination performed 18 months after onset of their neurological illness (figure 24). The complete recovery of the sensory threshold abnormalities in a shorter time in all the MFS patients accords very well with absence of signs of denervation on EMG studies in these patients.

The pupillary abnormalities noted early in the course of the illness in the MFS (Chapter 4; figures 15 & 16) resemble those observed in patients with the Holmes-Adie syndrome (Ramsay 1986) which is thought to be caused by postganglionic parasympathetic denervation (Lowenfeld and Thompson 1967; Harriman and Garland 1968). Later,recovery of pupillary function accompanied clinical improvement and normalisation of other aspects of peripheral nerve dysfunction (Chapter 4; figures 15 & 16). The supersensitivity to pilocarpine provides indirect evidence of denervation of the iris sphincter muscles (Pilley and Thompson 1975; Keane 1977; Okajima et al 1977) and the reversibility of the supersensitivity reaction, unlike Adie's syndrome, suggest that the functional

interruption of the postganglionic parasympathetic fibres is probably due to a blockade arising from demyelination of these fibres. Postganglionic parasympathetic oculomotor nerves are among the few myelinated fibres of the postganglionic autonomic nervous system (Warwick 1954) and it is likely that the MFS patients has a dysfunction in these fibres similar to that observed in other peripheral nerves. Pupillary abnormalities are encountered in up to about half of the cases of the MFS (Chapter 1; table 1). Pupils tend to be dilated, sometimes unequally so, and have absent or limited reaction to light and accommodation (Chapter 1). Irideal cholinergic supersensitivity has been reported previously in a patient with the MFS (Okajima et al 1977). Similar abnormality has been found in a patient with the GBS who had pupillary involvement without external ophthalmoplegia (Williams et al 1979). The latter authors have also reported abnormality of adrenergic innervation of the iris in their patient by demonstrating pupillary adrenergic supersensitivity. Similar findings have been reported in the MFS (Okajima et al 1977).

Is the duration of recovery of the neurophysiological tests to normal values in the MFS patients compatible with demyelination and remyelination of the peripheral nerves? Kaeser (1962 a,b) using diphtheria toxin in animal studies found that the motor conduction velocity decreased progressively beginning one week after inoculation. The abnormality reached a plateau during the 6th to 8th week and recovered to the original values between the 18th and 20th week. Both the severity of paralysis and the dose of toxin inoculated significantly and positively correlated with the degree of slowing of motor conduction (Kaeser 1962 a, b). In

a more recent study, Saida and associates (1980) investigated in male Wister rats the relationship between remyelination and functional recovery following antiserum mediated focal demyelination. Conduction block appeared within a few hours of injetion of the antiserum.On the 7th day improvement started when low amplitude but long latency muscle action potential could be recorded and the strength gradually recovered and returned to normal by 16 days. Evidence for onset of the electrophysiological recovery was accompanied by morphological evidence for remyelination. Conduction velocities returned to normal values in about 37 days at a time when the myelin thickness was only about one third of the control nerves. Therefore, it seems likely that the recovery course of the peripheral nerve function in these MFS patients is compatible with a process of demyelination with remyelination.

The abnormality of the SNAP and SEP studies and the marked prolongation of F-wave and H-reflex latencies at some stage of the illness after being absent and their subsequent recovery, the absence of signs of denervation on EMG examination in several proximal and distal muscles and the rapid recovery of clinical disturbances of ocular movements and balance all permit the hypothesis that the pathological process underlying the peripheral nerve disorder in the MFS is, at least predominantly, of a demyelinating type. Support for this comes from some pathological studies which showed evidence of patchy demyelination of the oculomotor and other cranial and peripheral nerves (see below).

There are many clinical similarities between the MFS and the

GBS. These include the acute onset, the facial weakness, the presence of occasional peripheral weakness and slight sensory changes in patients with the MFS, the rapid clinical improvement and the albumino-cytological dissociation in both syndrome (tables 1, 4, 5 & 8; figure 1). An antecedent event usually in the form of an upper respiratory tract or exanthematous viral infection is present in about two thirds of patients with either syndrome (tables 2, 5 & 8). Abnormalities of extraocular movement in classical cases of the GBS have been reported to occur in 5-30% of cases in various series (Haymaker and Kernohan 1949; Eiben and Gersony 1963; Weiderholt et al 1964; McFarland and Heller 1966; Ravn 1967 ; Asbury et al 1969 ; Arnason 1984; Ropper and Shahani 1984) and are usually associated with other cranial nerve dysfunction and with the classical motor and sensory deficits in the extremities. Involvement of the pupils occurs only occasionally and all patients with abnormal pupillary responses have associated impairment of ocular movements but the former has been reported to occur without the latter (Williams et al 1979). There is a wide variation in the type of ophthalmoplegia in acute idiopathic demyelinating polyneuropathy. Among 50 fatal cases reported by Haymaker and Kernohan (1949), 47 (97%) had cranial nerve involvement, 12 of which had varying degrees of extraocular movement abnormalities but only one had total ophthalmoplegia. The latter case had severe involvement of other cranial nerves but had no sensory deficit or extremity weakness at any time. Out of 48 cases reported by Eiben and Gersony (1963), 35 (76%) had cranial nerve abnormality of which 5 (10%) had extraocular paresis but none had total ophthalmoplegia. In Weiderholt and colleagues

(1964) series of 97 patients, 34 (35%) had facial weakness and 5 (5%) had extraocular muscle involvement but there was no mention of total ophthalmoplegia. The series of McFarland and Heller (1966) of 100 patients contained 75 patients with cranial nerve involvement and 13 of these had paresis of the third and/or sixth cranial nerves but no mention of total ophthalmoplegia was made. In Ravn's series (1967) of 127 patients, 68 (54%) had cranial nerve involvement with only 20 patients having bilateral involvement of the third, fourth and sixth cranial nerves. Marked or total ophthalmoplegia was, however, not reported. In the study of Asbury et al (1969) of 19 autopsied patients of the GBS, all but one (95%) showed evidence of cranial nerve disorder three of which had total external ophthalmoplegia and three more had internal ophthalmoplegia with pupillary involvement but also some minor external eye movement abnormalities. In case number 3 of the latter series (Asbury et al 1969) the third, fourth and sixth cranial nerves were the site of most severe pathological involvement and the patient had total ophthalmoplegia, the sixth cranial nerves were most severely involved while the remainder of the cranial nerves showed minimum to moderate involvement histologically. In the third case with total ophthalmoplegia (case number 12) no specific mention of the state of cranial nerves was made. Asbury et al (1969) also reported cases number 7, 8 and 15 who did not have any extraocular movement deficit clinically but had histological lesions of the extraocular cranial nerves. Bignami and Servi (1963) reported on the histological changes of the cranial nerves of a patient with an acute bilateral external and internal ophthalmoplegia and who did not have any

disturbance of consciousness nor any motor weakness of the extremities.Pathological changes in the third cranial nerves were seen and secondary changes in the nerve cells of their nuclei were reported but no primary brainstem abnormality was found. In all these series,however, it was not stated whether pre- or post-ganglionic parasympathetic oculomotor nerve fibres were examined.

Ataxia of the type seen in patients with the MFS has long been known to occur in patients with the GBS (Baruk and De Lille 1934; Guillain 1936; Richter 1962; Weiderholt et al 1964). In one of the two cases reported by Richter (1962) detailed pathological findings showing degeneration of the middle root zone of the posterior column and of the Clarke's column were described. In the latter report no evidence of cerebellar or brainstem abnormality was found. Ataxia may occur more commonly (in as many as 25% of patients) in the GBS but it is often concealed by the progression of the peripheral weakness (Richter 1962).

Both the GBS and MFS patients show similar CSF abnormalities. CSF protein is elevated in the majority of patients in both syndromes (Chapter 1, 2 and 5) without significant CSF pleocytosis while gamma globulin levels are usually normal. These CSF changes common to both syndromes suggest a breakdown of the blood brain barrier rather than production of gamma globulin inside the CNS (Olsson and Patterson 1976).

Patients with transitional forms (or overlap syndromes) between the syndromes of Miller Fisher and the more classical Guillain-Barré type exist. These cases have common features and overlapping clinical manifestations of both syndromes and act as a

link between the two entities suggesting that a similar pathogenesis probably underlies both disorders. Table 14 summarises some of the clinical features encountered in 20 such intermediate cases reviewed from the literature. All these patients showed evidence of polyneuropathy of the GBS type, fulfilled all the criteria for the diagnosis of GBS and were regarded as variants of the same syndrome. Other variants of the GBS have been described. A type confined to the cranial nerves (Munsat and Barnes 1965), GBS with predominant ophthalmoplegia (Asbury et al 1969) and Ropper (1986) described several other regional variants presenting with unusual features (see below). The presence of these variants suggests that the pathological process of the GBS could be topographically selective involving certain groups of nerve fibres maximally. Some of these variants might progress to the typical picture of the GBS later in the course of the disease while others remain as abortive regional forms (Ropper 1986). It is quite possible that these various kinds reflect the severity and duration of the underlying immunological process and their selectivity as to the groups of nerve fibres involved.

In both cases described by Richter (1962) profound gait ataxia occurred at the early phase of their illness without any clinically demonstrable proprioceptive loss. In the first case severe ataxia and areflexia were present with no weakness at all and only slight sensory loss to touch and vibration but not to proprioception was present for several days initially. The second case, on which postmortem studies were carried out, had profound ataxia, especially of gait (but no nystagmus and no

TABLE 14: Clinical data of 20 patients from the literature with features

Author(s), year & case No.	Age & Sex	Antec. illn & lat. per. (days)	MxD (days)	OPHTHALMOPLEGIA						ATAXIA	REFLEXES
				diplopia	external	internal	ptosis	Bell's phen.	OCR		
Richter (1962) 1	39 M	+ 10	7	+	I	–	+			+	–
2	63 F	+ 14		+		–	–			+	–
Hopkins (1971)	49 F	+ 9	10	+	C	–	+	–	–	–	–*†
Gibberd (1970) 1	69 M		14	+	C	+	–			+	-
2	78 M		15	–	C	+	–			+	–
3	8 M		7	+	I	–	+			–	–
4	22 M		7	+	C	–	+			–	–
6	50 M			+	I	+	–			+	–†
Grunnet & Lubow (1972)	62 M	+ 14	5	+	C	+	+			+	–
Jampel & Haidt (1972)	24 F	+ 6	3	+	C	+	+	+	–	–	–
Ashworth (1973)	21 M	+ 7		+	I	–	+			–	–
Green (1976)	7 M	+ 5	7	+	C	–	+		–	–	–
Williams et al (1979)	66 F	+ 6	7	+	–	+	+			+	–
Sobue et al (1983) 1	37 F	+ 11	8	–	–	–	–			+	–
2	38 F	+ 7	8	–	-	–	–			+	–
3	51 F	+ 2	11	–	–	–	–			+	–
4	46 M	–	7	–	–	–	–			+	–
Kaplan et al (1985) 1	47 F	+ 14		–	–	+	–			+	-
2	57 M	+ 4	2	+	I	–	+			+	–
Dehaene et al (1986)	52 F	–		–	C	+	+	–	–	+	–

MxD = Maximum neurological deficit

OCR = Oculo-cephalic reflex

C = Complete

I = Incomplete

D = Distal

P = Proximal

blank spaces indicate unavailable information or unperformed test

common to the Miller Fisher and Guillain-Barre´ syndromes

Cranial nerves	MOTOR		SENSORY				C S F			RECOVERY				
	Weakness	ambulation	Sympt.	Signs	Assist. Ventill.	Autonomic	time	ptn. g/l	cells /Cmm	onset (days)	dur. (mnth)	grade	Relapse	Autopsy or Biopsy
6,9,10	–	+	+	+	–	–	20	0·54	0	10	3	1	+	–
–	–	+	+	+	–	–		1·02	0		36	3	–	+
–	P&D	+	–	–	–	–	27	1·8	35	19	8·3	0	–	–
7,10	P>D	+	–	+	–	–	28	0·8	0	28	18	2	–	–
10	P>D	–	+	+	+	–		0·17	0	(Died on day 15)			+	–
–	P>D	–	–	–	–	–				14	24	2	–	–
7	P>D	–	+	+	–	–					12	1	–	–
7,1	P>D	+	–	–	–	–		2	0	(See text)			+	–
7,9,10,11	P>D	–	–	+	+	–	17	1·65	0	12	(Died day 22)		–	+
5,7,9,10 11,12	D>P	–	+	+	+	–	19	0·49	0		4	0	–	–
6	P&D	–	+	–	+	–		1·92	0		>12⊙		–	–
7,6,10	P&D	–	–	–	+	+	4	1·5	30	28	>3⊙		–	–
5,7,10	P&D	–	–	+	+	+	9	1·42	0	16	>8⊙		–	–
–	D>P	–	+	+	–	+	10	4	2		7	3	–	–
–	D&P		+	+	–	–		1·7	3	30	7	3	–	+
–	D&P	–	+	+	–	–		1·15	3		>5	3	–	+
–	D&P	–	+	+	–	–		2·98	4		>14	3	–	+
–	∓	+	+	+	–	–					>14	1	+	+
–	∓	+	–	+	–	–				13			+	–
5,7,10,11 12	P&D	–	–	–	+		25	2·24	0	12	(Died day 13)		–	+

\+ = Present

– = Absent

$\frac{-}{+}$ = Mild

* = Arm reflexes absent, leg reflexes normal

┼ = Asymmetrical

⊙ = Continuing improvement but no follow up

for grading of the recovery see table 9

Romberg's sign) and complete loss of all reflexes with no motor or sensory deficit for several weeks before other features of muscle weakness and sensory deficit appeared.

The patient reported by Hopkins (1971) (table 14) was interesting as she was one of 9 patients who had both geographical and temporal coincidence in that all of the 9 cases occurred simultaneously in a small island. The rest of the cases (8 patients) were classical cases of the GBS in whom the cranial nerves were spared. These 9 cases were regarded as an outbreak of acute inflammatory demyelinating polyneuropathy in the small island and thus suggesting that the patient reported by Hopkins (1971) was a variant of the GBS which manifested differently in this lady (table 14). In case number 6 of Gibberd (1970) a relapse occurred 4 months after the first attack from which the patient was recovering adequately. The relapse resulted in complete paralysis of arms and legs and some sensory deficit both of which continued to recover during the relapse but interestingly no change in his pupils or ophthalmoplegia occurred.The relapse was accompanied by doubling of the CSF protein from 200 to 400 g/l. Improvement from the relapse started 7 days after its onset and in one month's time there was almost a complete return of power in the arms. When seen two months later, he was in a very good shape with only minimal symptoms and some signs. The patient described by Grunnet and Lubow (1972) started to improve 12 days after onset of the neurological illness and abnormalities of pupils, eye movements and power all started to regress when he died of cardiopulmonary failure 22 days after onset. Autopsy studies showed evidence of demyelination of the nerve roots and

oculomotor nerves which also showed axonal swelling and fragmentation while axons and myelin within the brainstem appeared normal. Pathological changes similar to those in the GBS were, therefore, confined to the peripheral nervous system with some secondary changes in the nuclei of the cranial nerves in the brainstem and anterior horn cells in the spinal cord but no primary abnormality of these structures was present. Jampel and Haidt (1972) reported their patient to have partial preservation of Bell's phenomenon despite complete paralysis of upward gaze. On the basis of this clinical finding alone, the authors assumed the presence of a central brainstem lesion. Their patient, however, had many features more likely to be attributable to a peripheral nerve dysfunction in the oculomotor system such as asymmetric involvement of the extraocular muscles when tested individually, the presence of diplopia, iridoplegia and marked bilateral ptosis, complete absence of reflex oculocephalic eye movement and other manifestations like sensory changes and weakness of extremity and respiratory muscles. The case described by Williams et al (1979) demonstrates that complete iridoplegia and paralysis of levator palpebrae superioris muscle can occur in the GBS without involvement of the extraocular muscles. The patient otherwise had a classical presentation of the syndrome with albuminocytological dissociation and electrophysiological findings. The authors demonstrated that the pupillary abnormality was due to the involvement of postganglionic parasympathetic nerve fibres through the application of pupillary pharmacological studies. In many of the intermediate cases listed in table 14 it is noted that pupils were not involved while there was

severe or complete external ophthalmoplegia. In Marshall's review (1963) of 35 patients, 6 had ophthalmoplegia but none lost pupillary responses and Haymaker and Kernohan (1949) reported that among 50 cases with the GBS 12 patients had extraocular palsies in all of whom the pupils were spared. In most cases of *"polyneuritis cranialis"* there is partial or complete external ophthalmoplegia but the pupils are not usually involved. The four cases of the intermediate syndrome described by Sobue et al (1983) (table 14) are unique in their presentation and clinical manifestations. They all had in addition to the motor weakness, which was of moderate severity, severe loss of deep sensations of touch and proprioception which was associated with severe sensory ataxia. In all of them the motor abnormalities completely regressed in 7 - 14 months but improvement of their sensory deficit and the associated ataxia was much less so that after 3 - 4 years they all still had ataxia and marked sensory abnormalities. All four patients had absent SNAPs or extremely slow conducting sensory fibres and sural nerve biopsies performed in three of them showed evidence of marked reduction in the number of myelinated sensory fibres, especially the large sized fibres, associated with active axonal degeneration. Evidence of demyelination was also found in these fibres. The authors attributed the bad prognosis of the sensory deficit and ataxia to the severe axonal degeneration shown in sural nerve biopsies. These 4 cases described by Sobue et al (1983) demonstrate that sensory symptoms could be sometimes more prominent and more persistent than motor abnormalities in the GBS. Kaplan et al (1985) reported two cases of the GBS which were unusual in the

sense that they had recurrent sensory neuropathy and external ophthalmoplegia. In the first patient, conduction abnormalities were confined to the sensory system, and sural nerve biopsy showed evidence of demyelination and remyelination with minimal axonal loss. In her latest episode, this patient had only pupillary involvement in the form of light-near dissociation without involvement of extraocular muscles or any other cranial nerve , whereas in the previous episode a year earlier she had right sixth nerve palsy with horizontal diplopia. The second patient had 10 episodes similar to the one described in table 14 and on electrophysiological studies he showed evidence of motor and sensory involvement. Kaplan et al (1985) believed that these two cases represented a variant of the GBS and that they have some features similar to the MFS. The case reported by Dehaene et al (1986) had ataxic gait very similar to that seen in the MFS, total exernal and internal ophthalmoplegia, severe bilateral ptosis, areflexia, other cranial nerve involvement and other features of typical GBS. The patient showed rapid improvement starting 12 days after onset for a period of 26 days after which he suddenly died of septicaemia and irreversible shock. On postmortem studies careful search revealed a completely normal cerebellum and brainstem, apart from mild secondary changes in the nuclei of the third, sixth, fifth and seventh cranial nerves as a result of axonal damage to these nerves. Similar changes in the anterior horn cells of the spinal cord were noted. The oculomotor, sixth and other nerves and spinal ganglia showed evidence of severe demyelination and inflammatory cell infiltration with occasional axonal involvement. The oculomotor nerves also showed some

evidence of remyelination. Demyelination was also proved to be present by immunochemistry and other quantitative methods. This patient's ataxia did not accompany any evidence of sensory deficit on clinical examination rather like patients with the MFS. The patient also showed improvement of his vertical gaze before horizontal versions, a finding usually alleged to represent a brainstem lesion by proponents of the central theory of the MFS (Jampel and Haidt 1972; Meienberg and Ryffel 1983). Ropper (1986) reported several other examples of limited regional forms of the GBS in whom they demonstrated unusual focal signs and symptoms that resembled other illnesses. He reported three patients with mild extraocular muscle weakness manifested by diplopia, marked oropharyngeal, neck, shoulder and respiratory muscle weakness with normal sensation while power and reflexes in the legs remained normal. Like clinical findings, electrophysiological changes were confined to the upper limbs. In contrast to these patients, Ropper (1986) reported three other patients in whom the areflexia, weakness and electrophysiological abnormalities were entirely confined to the lower limbs while arms, face and cranial nerves were entirely normal. In a third group consisting of 8 patients, the main abnormalities were severe ptosis, asymmetrical in three , minimal or no ophthalmoplegia nor iridoplegia and mild facial weakness early in the course of the illness. Five of these 8 patients later progressed to the classical GBS. All these patients reported by Ropper (1986) had raised CSF protein, typical electrophysiological findings and a clinical course identical to that of the GBS and all other possibilities were excluded. Ropper (1986) also described a

patient with a probable GBS in a very restricted form who presented with subacute weakness of ilio-psoas, quadriceps and bilateral facial muscles and numbness over the anterior thigh, findings that resembled mononeuritis multiplex.

Of particular interest in the context of relation between the MFS and the GBS are a few classical cases of the former who went on to develop the full picture of the latter at a stage when the ophthalmoplegia and ataxia were resolving. An example of this is case number 4 of Storey et al (1977) with the MFS. He was a 14 year old schoolboy in whom the ocular movement started to improve 5 weeks after the onset of his illness, but at the same time weakness of both hip flexors appeared and subsequently progressed to involve the upper limbs as well. Two weeks later, the ocular movement abnormalities completely recovered, whereas the peripheral neuropathy rapidly progressed to produce a quadriplegia and involvement of the respiratory muscles. These abnormalities started to improve 5 weeks later and proceeded in a progressive manner so that he was able to walk unaided, swim, and return to school 16 weeks after the onset of the illness. Of interest also is the case described by Schapira and Thomas (1986) who was a 33 year old solicitor in whom two attacks of external ophthalmoplegia, ataxia and areflexia occurred with one year interval between them. In one of them he demonstrated features not only of the MFS but also some changes associated with classical GBS such as limb weakness and distal paraesthesiae while in the other attack he demonstrated features more compatible with pure MFS.

These cases demonstrate a clear overlap between the GBS and MFS

occurring sequentially in the same patient and would thus suggest a similar pathogenesis underlying both disorders. The intermediate cases summarised in table 14, the cases described by Storey et al (1977) and by Schapira and Thomas (1986), the variants described by Ropper (1986) and the presence of cases of the GBS with pure cranial nerve involvement (Van Bogaert and Maere 1938; Massion-Verniory 1940; Munsat and Barnes 1965), of cases in whom cranial nerve abnormalities comprise the main clinical deficit (Baker 1943) and of cases in whom the cranial deficit precedes the onset of extremity weakness (Dempsey et al 1947; Haymaker and Kernohan 1949; Boshes and Sherman 1953) all point to the presence of a graded continuum of neurological involvement in the GBS.

The argument for central involvement in the MFS has mainly been based on clinical ocular findings, features of the ataxia and other clinical observations (Jampel and Haidt 1972; Keane 1977; Becker et al 1981; Al Din et al 1982, 1985; Meienberg and Ryffel 1983; Meienberg 1984). Much emphasis has been placed on the abnormalities of conjugate ocular movements and the pattern of ophthalmoplegia, recovery of upward before horizontal gaze, preservation of Bell's phenomenon despite impairment of voluntary upward gaze, the presence of horizontal dissociated nystagmus similar to internuclear ophthalmoplegia and of rebound nystagmus, tendency to preserve downward gaze compared to upward gaze, preservation of convergence with loss of voluntary adduction and the presence of mild internal ophthalmoplegia and ptosis in association with severe external ophthalmoplegia. All these signs are held to be of brainstem origin (Jampel and Haidt 1972;

Keane 1977; Meienberg and Ryffel 1983, Meienberg 1984).

The symmetry of ophthalmoplegia in some cases of the MFS is remarkable and was noted by Fisher (1956) in his description of the syndrome. This symmetry is sometimes preserved during the period of recovery of the ophthalmoplegia. This finding has suggested to many authors that there might be an interruption of a brainstem gaze pathway rather than paresis of individual nerves (Keane 1977; Meienberg and Ryffel 1983). Conjugate ophthalmoparesis, however, has been noted to occur in patients with myasthenia gravis (Walsh and Hoyt 1969; Miller 1985) and in the GBS (Ropper 1983; Dehaene et al 1986). Despite the apparent symmetry of eye involvement on clinical examination, in the vast majority of patients, this symmetry is associated with diplopia (table 1, chapter 1; table 5, chapter 2) indicating that the optic axes are not absolutely aligned. The apparent symmetry of ocular weakness may be due to the fact that"some supranuclear stimuli can keep the ocular axes approximately parallel when functioning through a relatively balanced peripheral weakness of the extraocular muscles"(Ropper 1983).

Recovery of upward gaze before horizontal version has also been noticed in a patient with GBS who had ophthalmoplegia (Dehaene et al 1986). Careful pathological studies in this patient, however, showed no evidence of a primary involvement of the brainstem but evidence of demyelination and remyelination of the oculomotor abducent and trochlear nerves (Dehaene et al 1986).

The centre which coordinates and integrates the components of Bell's phenomenon (upward turning of the eyes in response to bilateral eyelid closure) is probably an area of the pontine

tegmentum (Bielschowsky 1939; Weinstein and Bender 1943). This centre is believed to receive inputs from the cerebral cortex, cornea and retina and send impulses to both facial and oculomotor nuclei coordinating the response (Weinstein and Bender 1943). Sparing of Bell's phenomenon in the presence of severe upward ophthalmoplegia occasionally occurs in the MFS (chapters 1 & 2; Jampel and Haidt 1972; Keane 1977; Meienberg and Ryffel 1983). This observation is, however, not necessarily a central sign as it has been reported to occur in myasthenia gravis, botulism, oculomotor palsies from aneurysms or pituitary tumours and in the GBS (Ropper 1983).

The observation in some patients with the MFS of an apparent internuclear ophthalmoplegia (INO) (Swick 1974; Weintraub 1977; Keane 1977; Derakhshan et al 1979; Barontini et al 1981; Becker et al 1981; Meienberg and Ryffel 1983) suggested to these authors that it represented a disorder of the brainstem. This manifestion was encountered in cases number 1, 3 and 4 of the present study (chapter 2). INO usually occurs as a result of interruption of the medial longitudinal fasciculus with or without the presence of a concomittant damage to the subnuclei of the oculomotor complex (Smith and Cogan 1959; Cogan 1970; Gonyea 1974; King et al 1976; Jenkyn et al 1978; Baloh et al 1978). INO occurs secondary to vascular pontine lesions when unilateral while bilateral INO is almost always due to multiple sclerosis. In all three patients with the MFS in the present study who manifested INO, there were other ocular features probably more suggestive of a peripheral disorder, e.g., improvement of the eye movement abnormalities in a disconjugate manner and presence of

diplopia and marked ptosis (table 5). Similar observations were present in most of other patients reported in the literature. In patients with the MFS, it will be unusual for a central lesion to produce an INO from the involvement of the medial longitudinal fasciculus without simultaneously disturbing some adjoining brainstem structures. This is especially so if the INO is associated with a *"supranuclear"* vertical gaze disturbance. Moreover, Glaser (1956) described 3 patients with myasthenia gravis who had disturbances of ocular motility which mimicked INO and the author termed the phenomenon as *"pseudo INO"* to stress its peripheral origin. Keane and Hoyt (1970) and Lyon and Van Allen (1972) reported a few patients with myasthenia gravis having similar findings. This phenomenon is, therefore, not necessarily of central origin and may be due to a mild paresis in the adducting eye rather than a brainstem lesion.

The lesser involvement of downward gaze compared to upward version during the stage of maximum palsy (Smith and Walsh 1957; Elizan et al 1971; Keane 1977; Barontini et al 1981; Meienberg and Ryffel 1983) or the earlier recovery of downward then upward gaze (Fisher 1956; Smith and Walsh 1957; Elizan et al 1971; Derakhshan et al 1979; Barontini et al 1981) are claimed to represent a CNS disorder (Meienberg and Ryffel 1983) as they have been observed in patients with mesencephalic lesions (Christoff 1974; Bender 1980; Buttner-Ennever et al 1982). These findings have, however, been reported to be present in the more classical cases of the GBS (Ropper 1983) and some patients with myasthenia gravis (Miller 1985). In the present study, less involvement of downward gaze than all other gazes was observed in cases 3, 4 and

5 (Chapter 2) but this was associated with other clinical signs of peripheral involvement such as diplopia, marked ptosis (either unilateral or bilateral) and disconjugate weakness of other extraocular muscles at least at some stage of the illness.

Rebound nystagmus (horizontal nystagmus appearing after the return of the eyes to mid position following a sustained lateral gaze) has been reported to occur in lesions of the cerebellum or brainstem (Hood et al 1973). This has been observed in a patient with the MFS described by Meienberg and Ryffel (1983) and the authors postulated a central lesion as the underlying cause. An identical finding has, however, been reported in a patient with myasthenia gravis (Schmidt 1977). Similarly, the preservation of convergence with marked restriction of adduction thought to reflect a central disorder (Meienberg and Ryffel 1983) has been observed in myasthenia gravis (Ropper 1983).

Ophthalmoplegia with preservation of vertical gazes has been observed in the GBS along with ataxia and irideal muscle sparing (Grunnet and Lubow 1972). Autopsy studies in this patient showed no primary lesion in the brainstem but typical pathological findings of the GBS in the peripheral nerves and oculomotor nerves.

The relative preservation of the pupils compared to the severity of external ophthalmoplegia, seen in some patients with the MFS, is frequently observed in patients with classical GBS who have extra-ocular muscle involvement (Haymaker and Kernohan 1949; Marshall 1963; Eiben and Gersony 1963; Weiderholt et al 1964; Munsat and Barnes 1965; McFarland and Heller 1966; Asbury et al 1969). The reverse, however, can occur (Williams et al 1979). In

some of these cases who had detailed pathological studies, no primary central abnormality was noted (Haymaker and Kernohan 1949; Asbury et al 1969).

It is, therefore, clear from the above discussion that all of the features of ocular involvement held to represent a brainstem involvement have been observed in patients with substantiated peripheral nerve lesions or in cases of non-MFS like GBS who otherwise present with the conventional symmetrical quadriplegic paralysis and other usual features of the syndrome.

The profound degree of ataxia with absent or minimal clinical sensory and/or motor deficit in patients with the MFS has raised the question of involvement of the cerebellum or its connections in the brainstem as a possible source of this abnormality (Al-Din et al 1982; Meienberg and Ryffel 1983). Profound ataxia and areflexia out of proportion to weakness or proprioception loss with or without ophthalmoplegia are not infrequently observed in the GBS. Haymaker and Kernohan (1949) in their clinicopathological report of 50 cases of the GBS stated that *"ataxia of the affected limbs, out of all proportion to weakness, was observed from the onset in about one-fourth of the cases"*. Ataxia may occur in the GBS early in the clinical course or may even antedate the onset of involvement of the extremities (Spector 1942; Richter 1962; Munsat and Barnes 1965). It is usually associated with clinically evident impairment of deep sensory modalities and in these cases it is easily explicable on this basis. Occasionally, however, marked ataxia and dysmetria occur in the GBS in the absence of clinically demonstrable proprioception abnormality (Spector 1942; Guillain 1953; Richter

1962). The case described by Spector (1942) was a boy aged 13 years with rapid onset of leg pain and severe truncal ataxia and absent tendon reflexes but without weakness or any sensory changes until later in the course of the illness. The CSF protein was 225 g/l with no pleocytosis. The patient had complete recovery within 7 months. Richter (1962) reviewed many other cases with prominent ataxia. He reported two patients of GBS who presented with profound ataxia and supplied a detailed pathological study of one of them. It is, therefore, possible that ataxia is present in a larger proportion of patients with the GBS but it becomes quickly submerged in the advancing paralysis and occasionally the ataxia and the areflexia, which is always associated with it, are the only manifestation of the disease with little evidence of neuropathic disturbance. As to the type of ataxia in the MFS, the most severe and frequent involvement is of the gait and trunk so that walking and even sitting become very difficult but in addition, there may be evidence of a bilateral appendicular dysmetria that precludes usage of the limbs when at the same time motor power is intact and sensation is almost so. There is, however, lack of other cerebellar signs despite the striking "*cerebellar*" quality of the ataxia. Speech is usually not involved and nystagmus which is usually present in cerebellar-type ataxia is absent. The ataxia, therefore, seems to point to a widespread uniform involvement of some system of neurones (see below).

Fisher (1956) proposed that the underlying mechanism of the ataxia observed in this syndrome may involve abnormalities of afferent nerve fibres from muscle spindles. This was also

suggested by Hopkins (1971) referring in his argument to the observation of McDonald and Gilman (1968) who have shown that in ataxic cats with early experimental diphtheritic neuropathy, the primary receptors of muscle spindles have an abnormal threshold to strech while the maximum conduction velocity remains unchanged. Ropper and Shahani (1983) in further elaboration of Hopkins' (1971) suggestion, proposed a physiological mechanism for this ataxia based solely on peripheral nerve dysfunction. This proposed mechanism was investigated in 4 patients in the present series (chapter 4) and findings consistent with this hypothesis were noted (chapter 4; table 7). Ropper and Shahani (1983) based their hypothesis on the findings of intact joint position sense with absent proprioceptive silent period (SP) or in contrast, normal proprioceptive SP with diminished joint position sense. The authors then proposed a mismatching of input from muscle spindles and joint position receptors to the cerebellum as a possible cause for the ataxia rather than a lesion in the cerebellum itself or its pathways in the brainstem (Ropper and Shahani 1983). The results of SP studies carried on in 4 patients with the MFS from the present series are summarised and related to abnormalities of joint position sense and the ataxia in table 7. They showed a consistent disparity between distribution of the abnormality of their muscle spindle and joint position function at times when severe ataxia was present while such disparity disappeared when the ataxia recovered. Muscle spindle function was tested by silent period (SP) studies modified so that proprioceptive input from muscle spindles was tested primarily (Shahani and Young 1983) while joint position sense was assessed

clinically (chapter 3). In every patient the SP was found to be normal in a limb with abnormal joint position sense and in contrast, normal position sense in a limb was accompanied by abnormal SP in that limb during the acute phase of the illness when the ataxia was prominent. The mismatching became less evident as the ataxia improved and the disparity disappeared when the ataxia recovered (table 7). According to these findings it is, therefore, unnecessary to postulate a central lesion to explain the phenomenon of the ataxia in patients with the MFS. This hypothesis and these findings in this study are entirely consistent with Richter's pathological findings (1962) of degeneration of the fibre system of Clarke's column secondary to peripheral lesion in an ataxic case of the GBS (see below). It has long been appreciated that patients with unusually severe and rapidly progressing ataxia are those with damage to Clarke's column or the middle root zone through which its afferents pass (Gilpen et al 1936; Russell and Moore 1943). Oppenheimer and Spalding (1973) also showed evidence of an extensive axonal degeneration at proximal levels of peripheral afferent neurones especially in the spinal roots in a case of the GBS with sensory residues.

Most of the signs on the bases of which a CNS lesion in the MFS has been postulated by some authors can, therefore, be explained on the basis of peripheral nerve dysfunction and are found in other cases of undoubted peripheral disorders. Therefore, the assumption of an underlying central cause for these signs is not valid. It is possible that the ocular manifestations occur in some cases of peripheral nerve disorder because *"certain*

supranuclear stimuli are more powerful than others and are able to break through peripheral paresis" (Ropper 1983). To explain the findings in most patients with the MFS, including the patients described in this study, on the basis of a CNS lesion, one has to assume that the lesion has to extend from the upper midbrain to lower pons or pontomedullary junction involving the tectum, the medial longitudinal fasciculus , the oculomotor nerve nuclei selectively and its supranuclear structure, the cerebellar connections in the brainstem ,the periaqueductal region, the frontopontine fibres (recovery of vertical before horizontal gaze) and other supranuclear structures of extra-ocular and other cranial nerves. The lesion affecting the former structures has nevertheless to exclude many other structures in the close vicinity traversing the whole length of brainstem in the various regions both vertically and transversely including the medial lemniscus (normal SEP central conduction time), the spinothalamic tracts, the reticular formation (clear consciousness), the pyramidal tracts (no motor signs), the extrapyramidal pathways, the auditory brainstem structures (normal BAEP) and the central structures of the blink reflex pathway. The postulation of such a lesion with such an exceptional selectivity for certain structures and excluding others in the brainstem is extremely difficult to accept. The undisturbed consciousness, the absence of pyramidal and extrapyramidal signs and the normal CSF cell count are against encephalitis as an underlying cause for the classical cases of MFS as suggested by some authors (Green 1976; Becker et al 1981; Al-Din et al 1982; Meienberg and Ryffel 1983).

The loss of all tendon jerks in patients with the MFS is out

of proportion to the rest of the peripheral nerve deficit. This can occasionally occur in patients with the GBS early in the course of the illness before the occurrence of marked motor and sensory deficit. The loss of the deep tendon reflexes is usually generalised but other forms of topographical distribution of this abnormality may occur such as their loss in arms or in legs alone(Ropper 1986). Asymmetrical involvement of reflexes early in the course or during the recovery stage has been noted in patients with the GBS (case 7 in this study,table 8), in patients with the intermediate syndrome (table 14) and in the MFS (table 1 and cases 4 and 7 of this series). The loss of tendon reflexes disproportionate to other features of peripheral nerve deficit in the extremities in MFS and some cases of the GBS may be due to a specific and selective involvement of certain neuronal system in the same line of the presence of other forms of the GBS with topographic and functional specificity as discussed previously in this chapter such as the occurrence of pure motor forms or of other variants in which the sensory system is mainly affected. It has been demonstrated in some experimental animal models of induced focal demyelination that the smaller diameter myelinated axons are affected earlier and more completely than the larger diameter myelinated axons (Sumner 1981). It is, therefore, possible on the basis of this finding to assume that the early loss of deep tendon reflexes in the GBS may result from block of the fusimotor outflow rather than block in the large diameter type Ia afferents (Sumner 1981). On the same basis it is possible to offer an alternative explanation for the disproportionate loss of these reflexes in the MFS at least in some cases that the

causative factor produces demyelination in the smaller diameter myelinated axons of the fusimotor outflow out of proportion to that of larger myelinated axons.

Brain imaging in the MFS: Most computed tomographic scan reports in the literature (Swick 1974; Keane 1977; Price et al 1978; Barontini et al 1981; Al-Din et al 1982; Keane and Finstead 1982; Meienberg and Ryffel 1983; Jamal and McLeod 1984; Al-Din et al 1985; Vincent and Vincent 1986) and in all patients in the present series (chapter 2) showed no CNS abnormality in patients with the MFS. The 3 cases with NMR head studies revealed no abnormality of the CNS including brainstem (Chapter 2). No other NMR studies on patients with this syndrome have as yet been reported. However, abnormality of brain CT scan has been claimed to occur in some patients with the MFS and the authors attributed the manifestations of the syndrome to such abnormality (Derakhshan et al 1979; Barontini et al 1981; Al-Din et al 1982). Derakhshan and his colleagues (1979) reported a case of MFS with an enhancing lesion in the midbrain tegmentum at midline. They also found another *"lesion surrounded by oedema in the right frontal lobe"*. No abnormality was found at the level of upper, middle or lower pons. Their patient, however, had features of INO, inability to move the eyes in a vertical plane, ataxia, hyporeflexia and facial weakness. A central lesion extending from the upper midbrain to lower pons is needed to explain the former features which are hardly explicable on one lesion at the level of midbrain as shown by the CT scan. Moreover, the patient had other features suggestive of a peripheral disorder such as marked ptosis and the recovery of eye movement abnormality in a disconjugate manner. A

similar argument applies for the patient reported by Barontini et al (1981) in whom the CT scan showed *"a small area of increased contrast in the left paramedian midbrain extending until the thalamus"*. The study reported by Al-Din et al (1982) mixed 8 cases of MFS with 10 obscure cases of brainstem encephalitis. Among their total 18 cases, they reported abnormal CT scan findings in 3 patients. In 2 of them frank features of encephalitis were present including disturbance of consciousness, headache, mental changes, extensor plantar responses, abnormal EEG findings and very high CSF cell count (270 lymphocytes per c.mm) with a slight increase in the protein content while other more typical features of the MFS such as ataxia were missing. One of these two patients died from pulmonary embolism and an incomplete postmortem examination showed evidence of encephalitis in the brainstem. Their third patient with a CT scan abnormality had features more consistent with the MFS though not entirely typical. He showed *"a low density abnormality in the medulla"*. It is quite obvious that such a finding would not explain the features of the patient nor of any classical case of the MFS. It is, therefore, clear that the "lesions" reported in these patients to be present on the CT scan do not satisfactorily explain the clinical findings.

Support for the peripheral theory in the MFS also comes from some limited but interesting immunological and pathological studies.

Immunological Studies: It is generally thought that the GBS is an autoimmune disease but its precise cause and the nature of the antigen(s) against which the immune response is directed have not

as yet been determined. Overwhelming evidence, however, exists that an immunological response always accompanies the disease (Asbury et al 1969; Iqbal et al 1981; Korn-Lubetzki and Abramsky 1986). a cell mediated immune mechanism in which activated lymphocytes and macrophages contribute and decreased supressor T-cell function is consistently demonstrated, has been suggested for the tissue destruction in the GBS (McQuillen 1971; Sheramata et al 1975; Nyland et al 1981; Iqbal et al 1981; Lin et al 1982; Geczy et al 1985; Korn-Lubetzki and Abramsky 1986). There is, however, evidence that an immune complex humoral mechanism may also be operative at least in part by antibodies to nerve tissue or soluble immune complexes (Cook and Dowling 1981). This possibility is supported by demonstration of immune complexes in serum from the GBS patients in the acute phase of the disease (Goust et al 1978), detection of specific autoantibodies to peripheral nerve in serum of the GBS patients (Nyland and Aarli 1978), the evidence of successful treatment of some cases of the GBS with plasmaphoresis (Brettle et al 1978; Fowler et al 1979; Server et al 1979; Mark et al 1980; Cook et al 1980; Ropper et al 1980; Toyka et al 1980; The GB study group 1985), deposition of immune complexes in renal glomeruli in biopsies from kidney (Faber and Balslov 1970) and the demonstration of immunoglobulin and complement factors in sural nerve biopsies from patients with the GBS (Nyland et al 1981). The basic myelin proteins are different in the CNS and peripheral nerve myelin. The peripheral myelin protein and nervous system tissue contain a variety of proteins, lipids and carbohydrates that may serve as immunogens in provoking immune response and/or as antigens participating in

immunological reactions and one or more of these types has neuritogenic properties for inducing experimental allergic neuritis and may also be involved in immune mediated peripheral nerve myelin injury in humans (Whitaker 1981). Therefore, it is possible that different aetiologic agents might give rise to immune reactions that attack different sites for example in the cases of the GBS and chronic relapsing demyelinating polyneuropathy. Similarly, it is possible that the nature of the specific antigen(s) in the classical GBS, in the variants of this syndrome and in the MFS may well differ from each other. Cell mediated immunity to peripheral nerve tissue and myelin but not to cental myelin antigens have been demonstrated in a case of the MFS by both invivo and invitro methods (Behan and Geschwind 1973). This sensitivity to myelin antigens has been demonstrated also in patients with classical GBS by means of a similar invitro technique of lymphoblastic transformation (Knowles et al 1969;Behan et al 1969; Caspary et al 1971) and invivo macrophage inhibition method (Rocklin et al 1971; Behan et al 1972). There was no sensitivity to central myelin antigens either in patients with classical GBS or in the patient with the MFS. It is known that sensitivity to central myelin antigens may occur when CNS tissue is involved in allergic reactions (Behan et al 1968). Behan and Geschwind (1973) concluded that these findings suggested that their patient's illness was due to immunological involvement of the peripheral, not central nervous system.

More insight into the pathophysiological changes in the GBS has probably been provided by some studies on a new experimental animal model. Serum induced demyelination in rat sciatic nerve

following the local injection of small volumes of proper antisera followed by serial electrophysiological recordings of motor responses evoked by stimulation of the sciatic nerve at various points below and above the site of injection (Saida et al 1978 a, b; 1979 a,b; Sumner 1981) permitted a quantitative follow up of the evolving sequence of functional changes in nerve conduction. It was found that rapidly evolving conduction block accompanied the lesion, that smaller diameter myelinated axons were affected earlier and more severely than large diameter axons and that nerve roots were highly permeable to the antiserum. Local permeability of the spinal roots may explain the special liability of this site to early and pronounced abnormality in the GBS and the MFS. It was also found that distal motor nerve fibres and common sites of nerve entrapments are other points where the permeability to antisera is increased rendering these sites more vulnerable to abnormalities. The latter finding accords well with the predeliction of abnormalities of the GBS in the proximal segments (Kimura and Butzer 1975; Brown and Feasby 1984a,b; Chapter 5), in the distal segments in some patients (Lambert and Mulder 1964; Chapter 5) or at common sites of entrapment (Lambert and Mulder 1964).

Pathological Studies in typical cases of the MFS are extremely limited due to the benign nature of the illness. Knowledge about the nature and site of the pathological changes causing the clinical manifestations of this syndrome is, therefore, inadequate. Phillips et al (1984) reported their postmortem findings in a 67 year old woman with the MFS who suddenly died from bronchopneumonia. Patchy and extensive recent

segmental demyelination was found in the peripheral nerves of the extremities and some of the cranial nerves associated with scanty perivascular chronic inflammatory cell infiltration. These changes appeared to be of the same age in all the nerves. Axons were in general preserved. These findings were found in the cranial nerves seventh, tenth and eleventh. The optic nerves appeared to be normally myelinated. Proximal portions of the third, fourth and sixth cranial nerves showed no histological abnormality but their distal portions were not available for examination. The spinal cord, brainstem and cerebellum were all entirely normal histologically. Muscle examination showed evidence of atrophy typical of recent denervation. Electron microscopic examination of the affected spinal roots revealed even more prevalent myelin destruction. Lymphocytes and macrophages but no plasma cells were seen in the areas of myelin breakdown. All these features have been described in the GBS (Haymaker and Kernohan 1949; Asbury et al 1969; Wisniewski et al 1969; Carpenter 1972; Prineas 1972, 1981). During the course of her illness, this patient showed all the typical ocular and other clinical manifestations of the MFS. It has been remarked, however, by proponents of the central theory that the patient had clinical and electrophysiological evidence of relatively severe neuropathy and for this reason, did not represent a typical case of the MFS (Meienberg 1984; Al-Din et al 1985).

Al-Din et al (1985) performed a sural nerve biopsy in the sixth week of illness on a 33 year old male patient with the MFS and had found no evidence of demyelination or degeneration of peripheral nerve fibres. The authors claimed that their patient had no

evidence of peripheral disorder and that his manifestations were due to a central lesion (Al-Din et al 1985). Neurophysiological studies, however, have shown that there may be a relative sparing of the segment of the sural nerve tested compared to median and ulnar nerve sensory fibres in the GBS (Eisen and Humphreys 1974; Murray and Wade 1980; chapter 5 of this study). Quantitative histological studies of sural nerve biopsies in classical cases of the GBS have also demonstrated relatively low yield of positive results. In such a quantitative study normal densities of myelinated fibres and fibre diameter distribution were found in 6 out of 8 patients with classical GBS (McLeod et al 1976). In another study, evidence of demyelination was found only in 5 out of 8 patients with the GBS (Nyland et al 1981). These findings, therefore, indicate that a single screening sural SNAP study as is commonly done is inadequate in the evaluation of patients with the GBS and that the sural nerve may not be a suitable nerve to show evidence of demyelination even in the frank cases of the GBS. These observations would probably be also true in the case of MFS patients.

Few other pathological reports are available concerning some typical or variant cases of the GBS who had some features very similar to those seen in patients of typical MFS.Of importance in this context is the report of Richter (1962) who described the pathological findings of a patient with the GBS associated with severe ataxia and some sensory deficit but no ophthalmoplegia. The author found demyelination of the posterior columns and degeneration of Clarke's column in the spinal cord secondary to nerve root involvement but no changes in the brainstem or

cerebellum were found. Richter suggested that these peripheral changes provided the anatomical basis for ataxia.

In other patients with the GBS and ophthalmoplegia with features similar to those observed in the MFS no abnormality of the brainstem was found apart from occasional mild chromatolysis in the oculomotor neurones secondary to peripheral changes whereas the classical pathological findings were seen in the oculomotor and other extraocular cranial nerves (Haymaker and Kernohan 1949; Asbury et al 1969; Grunnet and Lubow 1972). Dehaene et al (1986) carefully studied the oculomotor nerve system in a fatal classical case of the GBS who had bilateral total ophthalmoplegia, bilateral ptosis, iridoplegia and severe ataxia in addition to other cranial nerves, extremity and respiratory muscle involvement. During recovery, which occurred before his sudden death, improvement of downward gaze preceded upward gaze and both preceded horizontal version improvement. Postmortem histological examination was made with a variety of conventional and more recent accurate and quantitative laboratory methods including immunocytochemical staining for myelin basic protein, S-100 protein (for Schwann cells) and neuron-specific enolase (NSE) and neurofilaments (NF) (to study axons) by using peroxidase-antiperoxidase technique. No evidence of a primary involvement of the brainstem, cerebellum or spinal cord was found but only mild secondary chromatolytic changes were noted in neurones belonging to the mesencephalic oculomotor complex and spinal cord neurones. The main lesion of demyelination and slight inflammatory perivascular cell infiltration was found in the third, fourth and sixth cranial nerves, spinal ganglia and

other peripheral nerves. No significant alteration of axonal morphology was found. Some evidence of remyelination especially in the oculomotor nerves was also found. These limited number of pathological studies, therefore, support the notion that peripheral nerve disorder is responsible for the clinical manifestations of the MFS. No histological evidence of interruption of the supranuclear tracts in the brainstem nor abnormality of the cerebellum is available.

Differential Diagnosis: In clinical practice, the onset of the syndrome may cause diagnostic confusion as many other illnesses which cause external and internal ophthalmoplegia may share some similarity to the MFS. Within several days, however, more characteristic features of the MFS usually appear, a negative CT scan or NMR head scan will exclude the possibility of a surgically treatable lesion and the characteristic CSF findings appear. Multimodal neurophysiological studies are likely to be useful in documenting evidence of a peripheral and in excluding a more serious central lesion and repetition of these studies serially will increase their sensitivity in detecting such peripheral abnormalities. The benign course of the illness will further substantiate the diagnosis of the syndrome. That myasthenia gravis could be confused with the MFS especially early in the course of the illness was suggested by many authors including Fisher himself (Fisher 1956; Smith and Walsh 1957; Bell et al 1970; Price et al 1978; Becker et al 1981). Myasthenia gravis is a neuromuscular defect that affects both children and adults and may have a similar constellation of eye signs with varying degrees of ptosis, ophthalmoplegia, and fluctuating axial weakness

which may be unilateral or bilateral. There is, however, always sparing of pupillary responses despite the degree of ocular dysfunction, tendon reflexes are usually normal or increased and only when the weakness is marked may be depressed, and ataxia does not occur (Simpson 1981). A tensilon test and repetitive nerve stimulation help to establish the diagnosis (Simpson 1981). Vascular disease of the brainstem, whether haemorrhage or infarction, is most unlikely to produce extensive ophthalmoplegia and ataxia without also damaging the reticular formation and thus producing profound disturbance of consciousness (Masucci 1965). Thrombosis of the basilar artery may cause unilateral or bilateral extraocular muscle weakness but the pyramidal tracts and medial lemniscus are nearly always involved too (Masucci 1965). Symptoms and signs of basilar artery occlusion usually have a very sudden onset but they can develop over a period of 3 - 4 days. In the latter case, it is usually in a stepwise, stuttering manner rather than smoothly as in the case of MFS. Bilateral involvement is uncommon in vertebral-basilar artery disease. Brainstem encephalitis is a distinct disorder in which the brainstem is the site of a possible viral infection (Bickerstaff and Cloake 1951) with definite brainstem postmortem changes (Bickerstaff 1957,1978). This syndrome has recently been confused with the MFS by some authors (Al-Din et al 1982). Brainstem encephalitis , however, has some distinctive features. In brainstem encephalitis there is acute conjugate ophthalmoplegia with nystagmus, frequent involvement of other cranial nerves involving the 5th and 8th nerves, and ataxia, but pyramidal and long tract sensory disturbances are usually present and all cases have

headache and disturbance of consciousness. CT scan may be abnormal (Al-Din et al 1982), the EEG is frequently abnormal and the CSF usually shows evidence of marked lymphocytosis but only a mild increase in the protein content. Wernicke's encephalopathy may have considerable similarity to the MFS (Fisher 1956). Patients with this encephalopathy present with abrupt onset of disturbance of consciousness, ataxia and ophthalmoplegia and a peripheral neuropathy is often present (de Wardener and Lennox 1947). The disturbance of consciousness and presence of mental changes are cardinal features of Wernicke's disease. Total ophthalmoplegia can occur but this is an exception and usually in the advanced stages of the disease (de Wardener and Lennox 1947). There is usually a history of alcoholism and/or malnutrition. Some patients with multiple sclerosis may present with features similar to those of the MFS. The evidence of dissemination in time and space and the presence of disturbance of brainstem and elsewhere in the CNS are frequently demonstrated by multimodality evoked potentials. Plaques are shown by NMR studies (Bogousslavsky et al 1986). Tumours of the brainstem and base of the skull are likely to mimic the MFS and may be difficult to differentiate clinically (Horrax and Bailey 1925; Netsky and Strobos 1952; Sarkari and Bickerstaff 1969; case 7 in this study). They may present with paralysis of conjugate gaze and ataxia but hyper-rather than hypo-reflexia is usually present together with pyramidal and long tract sensory signs. Mental changes are usually early and prominent and papilloedema usually occurs early especially if the tumour is near to the ventricular system. CT scan and NMR may show the tumour and the neurophysiological tests

may show evidence of brainstem abnormality. Though relatively rare, metastatic tumour of brainstem may also result in similar findings (Stevenson and Hoyt 1963). Botulism may present with ocular complaints due to difficulty in convergence followed by ptosis and parallysis of the extraocular muscles. The pupils become dilated and are usually unreactive and in the majority of cases there is a progression to bulbar involvement and then generalised weakness of other muscles of the body. The deep reflexes are, however, usually preserved and the patient's history and EMG changes help in diagnosis. Phenytoin intoxication may occasionally cause severe ophthalmoplegia in addition to ataxia and nystagmus in a conscious patient with minimal evidence of neuropathy (Spector et al 1976). Weintraub et al (1971) reported a case, a 48 year old woman, of acute onset of ataxia mainly of gait,diplopia, complete internal ophthalmoplegia and mild extremity sensory disturbance following exposure to a commercial insecticide containing pyrethrins and piperonyl butoxide. The condition improved afterwards. MFS can easily be differentiated from a group of progressive inherited heterogeneous disorders manifested by chronic progressive external ophthalmoplegia (Drachman 1968; Danta et al 1975) including oculopharyngeal dystrophy (Matsunaga et al 1973; Probst et al 1982), Kearns-Sayre syndrome (Berenberg et al 1977) and mitochondrial encephalomyopathies (Morgan-Hughes et al 1982). A small proportion of these may show evidence of peripheral nerve involvement (Drachman 1968; Croft et al 1977; Probst et al 1982) and even ataxia (Stephens et al 1958).

All the three ocular motor nerves (third, fourth and sixth)

together with the first division of the fifth cranial nerve traverse the cavernous sinus. These structures may be damaged there by an intravenous aneurysm of the carotid artery and in this situation the internal and external ophthalmoplegia is usually accompanied by pain and sometimes sensory loss and paraesthesia along the distribution of the first division of the trigeminal nerve. Hunt et al (1961) described painful ophthalmoplegia arising from cavernous sinus inflammation and pointed out that the condition does not show any systemic reaction. Angiography and (even surgical exploration) usually fail to show an abnormality. The disorder might show spontaneous remission, sometimes with mild neurological deficit and the attack may recur. Pain usually precedes the opthalmoplegia and the first division of the fifth cranial nerve, periarterial sympathetic fibres and the optic nerve may be involved. In the superior orbital fissure syndrome caused for example by a tumour invading the fissure, the total ophthalmoplegia is again accompanied by pain and sensory loss in the distribution of the first division of the trigeminal nerve. The manifestation is unilateral and the eye is often proptosed as a result of obstruction of the ophthalmic vein. Within the orbit, the third, fourth and sixth nerves may be affected by conditions such as tumours and granulomas. Again this is unilateral, the eye is proptosed and is easy to differentiate from the MFS. These three extraocular nerves may also be affected singly or in combination as a part of other conditions causing cranial neuropathy. This may occur as a feature of systemic disorders like sarcoidosis, diabetes mellitus or connective tissue disease or in basal meningitis. These do not usually constitute

a problem and they are easily differentiated by the presence of the systemic disorder and other features.

CHAPTER 8

CONCLUSION

The essential features of the syndrome described by Miller Fisher in 1956 comprise an acute bilateral, usually symmetrical external ophthalmoplegia (or ophthalmoparesis) with variable degrees of involvement of pupillary or levator palpebrae superioris muscles associated with severe ataxia which mainly involves the gait and the trunk, and a generalised areflexia. Clinical motor and/or sensory deficit is usually absent or minimal but other cranial nerves may be affected. No mental changes or disturbance of consciousness are present. The illness has a benign course with rapid and usually complete recovery occurring within weeks to months after onset. As in the Guillain-Barré syndrome, a mild to moderate increase in the CSF proteins unassociated with increase in the cell count is usually present and an antecedent illness, usually in the form of an upper respiratory tract infection, commonly precedes the syndrome by about 1 - 3 weeks.

Since the report of this triad by Fisher (1956) the nature and aetiology and in particular the localisation of the pathological changes in the syndrome have been a subject of controversy. Speculations have been based mainly on clinical observations unsupported by pathological findings in typical cases due to the benign nature of the disorder. Some authors have, therefore, considered the syndrome to be part of the spectrum of acute inflammatory demyelinating polyradiculoneuropathy of which the Guillain-Barré syndrome is the most familiar example and have held that the pathological

changes are localised to the peripheral nerves. Others have implicated a brainstem inflammatory lesion or encephalitis. A third group has maintained that the syndrome is due to a combination of both peripheral and central brainstem lesions.

A review of the literature revealed that more than 80 cases have been described often in considerable detail but without permitting conclusion on the question of the localisation of the underlying pathological process. Detailed and comprehensive neurophysiological investigation of cases of the Miller Fisher syndrome (MFS) is lacking. The latter has been mostly confined to the application of conventional electromyography and nerve conduction studies in the extremities to a few patients usually only once during the course of their illness. These conventional studies test the distal segments of the nerves of the extremities and are insensitive to changes in the proximal segments or abnormalities in the cranial nerves.

This thesis reports the results of serial application of a comprehensive range of conventional and new neurophysiological techniques over a long period of time through the illness and recovery to a group of patients with classical MFS. It compares these results with those obtained from another group of patients with the Guillain-Barre´ syndrome investigated serially with the same tests at similar time intervals. The battery of neurophysiological tests employed was chosen to examine all the segments of the neural axis of various pathways and act as the physiological counterparts to morphological methods in neuropathology, information about which is largely unavailable in this syndrome. Tests were performed in parallel with serial

clinical examinations at identical intervals for easy comparison. The results of the neurophysiological tests in the patient groups were compared with the range of values derived from healthy control subjects.

The group of the MFS comprised seven patients seen over four years. The constellation of clinical features in these cases including the acute onset and the benign course makes them exemplary cases of the syndrome which displayed all the classical features of the disorder including CSF findings. In addition, some of them showed most of the additonal features found in the MFS including those which proponents of the central theory use to argue for an underlying central pathology.

Results of the application of the neurophysiological techniques to this group of patients with the MFS showed overwhelming evidence of peripheral nerve dysfunction. EMG showed no signs of limb denervation and there was evidence of only a mild but significant change in the shortest distal motor latencies (SDMLs) and fastest motor nerve conduction velocities (FMNCVs). Sensory nerve action potential (SNAP) studies in comparison showed more marked abnormalities. All these values progressively improved on serial studies. The main abnormalities in the peripheral nerves of the limbs were in the proximal segments, plexus or radicular portions. This was shown by the disproportionately abnormal late response (F-wave and H-reflex) studies and prolonged brachial plexus - cord transit time on SEP studies. The peripheral abnormalities in the extremity nerves were further supported by a drop in the motor unit number (MUN) estimated from the extensor digitorum brevis

muscle using a computerised technique. Computer assisted quantitative studies of somatic sensation revealed the presence of a significant abnormality of thermal and vibration sense in those patients without clinical evidence of such a disorder. This finding indicated the presence of dysfunction in both small and large fibre afferent pathways in these patients.

Evidence of involvement of the proximal and/or distal segments of the facial nerve peripherally was obtained through the combined application of facial nerve motor conduction and blink reflex studies in these patients. The abnormality was observed in those patients with clinical facial weakness.

Abnormalities of the pupils were quantified and the pupillary reflex pathway was studied by a quantitative photopupillometric method in combination with pupillopharmacological studies. These studies demonstrated evidence of postganglionic parasympathetic denervation.

All the neurophysiological parameters of peripheral nerve dysfunction improved progressively towards normality on serial studies. Their improvement followed or accompanied clinical recovery in all the patients.

Neither the neurophysiological, CT scan or NMR brain scan studies provided any evidence of dysfunction or abnormality in the CNS in any of the MFS patients in this series. The BAEP studies showed no abnormality in the auditory brainstem pathway traversing the entire length of the pons posteriorly. The SEP studies revealed normal central conduction time and thus provided no evidence of abnormality in the medial lemniscal pathway travelling through the brainstem caudo-rostrally. In addition,

no evidence of a brainstem involvement was seen in the blink reflex studies, the central pathway of which is situated in the pons and lateral medulla. EEG and pattern reversal VEP recordings were also normal in these patients. These studies, therefore, collectively provided evidence of integrity of brainstem and cortical function and their results were further supported by normal CT scan and NMR brain scan studies.

The neurophysiological methods were also applied to a group of 20 patients with the Guillain-Barre´ syndrome (GBS) all of whom fulfilled all the diagnostic criteria recommended for the diagnosis of this entity. Serial assessment of these patients was performed at similar time intervals to those of the MFS patients in the first 6 months and thereafter at 12 and 18 months from onset. The results of the neurophysiological studies in the 20 patients with GBS and others reviewed in the literature showed several patterns of abnormalities reflecting the pathological nature of the disease. It is clear that complete neurophysiological evaluation of patients with the GBS requires motor and sensory conduction, EMG and late response studies performed on multiple nerves in the upper and lower extremities. Somatosensory evoked potential (SEP) and direct facial and blink reflex studies provide additional information about proximal parts of the afferent peripheral fibres and proximal segments of the facial nerve. The proximal segments were found to be more frequently (and in some patients exclusively) involved than the distal segments. The sensitivity of these tests in detecting slight dysfunction was significantly enhanced when performed serially. Thus the neurophysiological results in these 20

patients were generally similar and in many of them identical to those found in the 7 cases with the MFS although changes in the former group were more pronounced and abnormalities took on average a longer time to improve.

Neurophysiological studies also appeared to be useful in assessing prognosis in cases of acute inflammatory demeylinating polyradiculoneuropathy so that evidence of extensive denervation, which indicates axonal degeneration, early in the course is associated with incomplete and/or prolonged recovery whilst those without evidence of denervation usually have a more complete and rapid improvement. For this reason absence of signs of denervation in the MFS patients accords very well with their usually complete and relatively rapid recovery. They are more or less comparable in this respect to those patients with the GBS without evidence of denervation.

From this series and those reviewed in the literature, it is evident that clinical presentation of the GBS like the neurophysiologal findings, is diverse. Many variants of the classical syndrome have been described in the literature. These include a type confined to cranial nerves, a type with prominent external and/or internal ophthalmoplegia, a type with prominent loss of deep sensation associated with severe sensory ataxia but only mild to moderate motor nerve involvement, a pure motor type, a type in which the weakness is confined to oropharyngeal, neck, shoulder and respiratory muscles with normal sensation, power and reflexes in the lower limbs and in contrast, a type totally confined to the legs in which the arms, face and cranial nerves are spared. Some of these variants have been reported to

progress to the classical GBS later in the course of the disease while others remain as abortive regional forms.

The diversity of clinical and neurophysiological findings is probably explained by the variation of the distribution and severity of the pathological findings. Nerve damage in the GBS is not a diffuse process but occurs in the form of discrete multiple foci of inflammatory demyelination, with or without axonal degeneration, scattered throughout the peripheral nervous system with variation in the site of maximal involvement especially early in the course of the illness. The presence of these variants suggests that the pathological process could be topographically and functionally selective and that certain groups of fibres may be selectively or maximally involved. This may in turn reflect the severity and duration of the underlying immunological process and their selectivity perhaps arising from differences in the nature of the antigen(s) involved and/or differences in the character of the nerve-blood barrier at various sites of the first order neurone.

Transitional cases between the GBS and MFS have been reported. These cases have clinical features common to both syndromes. In these patients total or severe external ophthalmoplegia and ataxia very similar to those observed in the MFS are found in patients who otherwise show classical changes of the GBS. These cases provide a link between the two entities and may reflect different points along the clinical spectrum of the same disorder and they suggest that a similar pathogenesis underlies both entities. In some of these patients with ataxia and ophthalmoplegia, autopsy studies revealed demyelination of

the oculomotor and other peripheral nerves similar to that observed in the GBS but no primary abnormality of the brainstem, cerebellum or other CNS structures was found.

There have also been instances in which patients with typical MFS went on, after some time, to develop the full picture of characteristic GBS when their ophthalmoplegia or ataxia were resolving. Patients have also been described where the two syndromes occurred sequentially.

These clinical observations and the presence of many clinical similarities between the classical forms of the two syndromes further support the evidence from neurophysiological and limited pathological studies that the GBS and MFS are related. They point to the presence of a graded continuum of neurological involvement in cases of acute inflammatory demyelinating polyradiculoneuropathy and permit the hypothesis that a similar pathogenesis underlies both disorders.

Most of the ocular signs alleged to arise from a brainstem disorder can be explained on the basis of peripheral nerve dysfunction. They have been observed to occur in patients with substantiated peripheral nerve lesions or in cases of classical GBS and, therefore, do not have an absolute localising value. Moreover, pathological studies in a case of MFS and in cases with classical GBS with similar eye signs have not been found to show histological evience of interruption of the supranuclear tracts in the brainstem. On the contrary, evidence of demyelination was found in the oculomotor and other cranial and peripheral nerves.

Due to the absence on clinical examination of sensory and/or

motor deficit of adequate severity to explain the profound ataxia in the MFS, it has been presumed that cerebellar or brainstem involvement is responsible for the ataxia. This thesis examined a theory proposing a peripheral disturbance as the underlying mechanism for this ataxia. Evidence for this is provided through the demonstration of a mismatch of input between afferent proprioceptives from muscle spindles and from Golgi tendon organs. This disparity disappeared when the ataxia recovered. Although disruption of central cerebellar connections is not as yet entirely excluded, it lacks pathological substantiation in a case of the MFS and in autopsy studies of those cases of the GBS who showed an identical type of ataxia. Furthermore, evidence of peripheral abnormality has been found in such cases. These findings would seem to make serious consideration of a central mechanism for the ataxia untenable.

Additional support for the peripheral theory in the MFS come from some pathological and immunological observations. Confirmation of peripheral abnormality similar to that of the GBS and absence of central disorder have been shown at autopsy in a case of the MFS. Sural nerve biopsy may not be suitable to show evidence of demyelination in the GBS and MFS patients as it has been shown that this nerve is relatively less frequently affected in the former, at least in the segment usually excised for these studies. A cell mediated immunity disturbance related to peripheral but not to central myelin in a patient with the MFS has been demonstrated. The findings were similar to those observed in cases of classical GBS using the same techniques.

In view of the findings in this study and those in the

literature this thesis proposes and provides evidence that the MFS is a variant of the GBS in which the main and primary manifestations occur in the oculomotor system with involvement of other parts of the peripheral nervous system some of which may be subclinical. The evidence does not support a significant central lesion. The existence of the latter is hardly defensible until pathological evidence counters the existing normal CNS autopsy findings and demonstrates the presence of a primary lesion in the CNS in typical cases of the MFS.

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APPENDIX

NORMAL VALUES

In all tests skin temperature = 34 ∓ 1°C

NERVE CONDUCTION

64, healthy subjects aged between 17 - 68 (m = 34.8, SD = 11.5) years

			mean	SD	95% CL
ULNAR	SDML	(ms)	2.9	0.44	3.78
	FMNCV	(m/s)	59.3	4.6	50.1
	SNAP	latency (ms)	2.76	0.24	3.24
	SNAP	amplitude (μV)	13	4.5	4
	SNAP	duration (ms)	1.2	0.27	1.74
MEDIAN	SDML	(ms)	3.5	0.45	4.4
	FMNCV	(m/s)	58.8	4.8	49.2
	SNAP	latency (ms)	2.92	0.23	3.38
	SNAP	amplitude (μV)	17.8	5.4	7
	SNAP	duration (ms)	1.28	0.26	1.8
COMMON PERONEAL					
	SDML	(ms)	4.2	0.67	6.14
	FMNCV	(m/s)	50.7	4.5	41.7
SURAL (Antidromic)	SNAP	latency (ms)	3.61	0.42	4.44
	SNAP	amplitude (μV)	8.8	2	4.8
	SNAP	duration (ms)	2.18	0.35	2.88

LATE RESPONSE STUDIES:

38 healthy subjects aged between 19 - 64 (m = 33.8, SD = 10.6) years.
Height ranged between 153 - 192 (m = 178.5, SD = 14) cm.

	mean	SD	ULN,95% CL	R-L difference 95% CL
H-Reflex				
latency (ms)	30.2	2.8	35.6	1.3
amplitdue (mv)	2.3	1.5	-	-

(Formula for theoretical H-latency = 2.74 + 0.14 height (cm) + 0.05 age (yr) ∓ 1.4 (95% CL, 2 S.E s).

F-Wave*				
ULNAR, latency (ms) (ADM-wrist)	26.4	2.1	30.6	2.72
MEDIAN, latency (ms) (APB-wrist)	26.2	2	30.2	2.34
COMMON PERONEAL (EDB-ankle) latency (ms)	49.9	4.1	57.6	3.38
POSTERIOR TIBIAL (AH-ankle) latency (ms)	49.6	4.3	58.2	3.48

* The shortest latency of 10 responses was taken.

(Normal values are determined by using graphs or tables relating to arm length in cm. distance between radial styloid and C7 vertebra with arms abducted at 90°, for median and ulnar F-waves OR relating to subject's height in cm for common peroneal and tibial F-waves).

MUN ESTIMATION:

39 healthy subjects aged between 18-65 (m = 35, SD = 14) years

	mean	SD	LLN,95%CL	Sig.change*,95%CL
MUN	197	49	99	38

* Indicate significant change on repeated measurement in the same individual

FACIAL NERVE AND BLINK REFLEX:

The normal values of Kimura (1983a) are used as the technique used in this study is identical to that used by Kimura (1983a).
83 healthy subjects aged between 7-86 (m = 37) years.

	mean	SD	ULN,99%CL	R-L difference,99%CL
D-R latency (ms)	2.9	0.4	4.1	0.6
R_1 latency (ms)	10.5	0.8	12.9	1.2
R_2 (ipsilat) latency (ms)	30.5	3.4	40.7 (40*)	5
R_2 (contral) latency (ms)	30.5	4.4	43.7 (41*)	7

* Indicate figures taken by Kimura (1983a) as ULN

THERMAL THRESHOLDS:

106 healthy subjects aged between 6 - 73 (mean = 33, SD = 17) years

			mean	SD	ULN, 99% CL
WRIST	HT	(°C)	0.23	0.06	0.41
	CT	(°C)	0.15	0.05	0.3
ANKLE	HT	(°C)	1.35	0.73	3.54
	CT	(°C)	0.17	0.06	0.35

VIBRATION PERCEPTION THRESHOLD:

38 healthy subjects aged between 17 - 68 (mean = 35.6, SD = 15.4) years

CARPAL	(μm)	0.6	0.2	1.2
TARSAL	(μm)	1.58	0.3	2.48
TIBIAL	(μm)	0.8	0.26	1.58

SOMATOSENSORY EVOKED POTENTIALS:

47 healthy subjects aged between 20 - 63 (m = 32.8, SD = 11.3) years

		mean	SD	ULN,99%CL	R-L difference, 99%CL
EP latency	(ms)	9.78	0.7	11.88	1.132
N13 latency	(ms)	12.92	1.02	15.98	2.49
N20 latency	(ms)	18.62	0.88	21.26	1.143
EP - N13	(ms)	3.54	0.65	5.49	1.612
N13 - N20	(ms)	5.11	0.51	6.64	1.764

BRAINSTEM AUDITORY EVOKED POTENTIALS:

23 healthy subjects aged between 16 - 54 (mean 25.6, SD = 7.8) years

Wave I latency	(ms)	1.65	0.11	1.98	0.42
I-III difference	(ms)	2.2	0.13	2.6	0.44
I-V difference	(ms)	4.15	0.17	4.66	0.38
III-V difference	(ms)	1.9	0.14	2.3	0.54

PATTERN REVERSAL VISUAL EVOKED POTENTIALS:

62 healthy subjects aged between 19 - 61 (mean = 30, SD = 12) years

P2 latency	(ms)	103	5.6	118	8.76
P2 amplitude	(μV)	8.5	3.44	1.64 (LLN)	2.74