Occasional review

Ataxia and other data reviewed in Charcot-Marie-Tooth and Refsum's disease

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SUMMARY The author reports his experience on Refsum's disease and that gained after personally examining in detail 64 patients with Charcot-Marie-Tooth disease over the past ten years. The "cerebellar" inco-ordination in Charcot-Marie-Tooth disease (with or without distal wasting) and in Refsum's disease is analysed. Some variations in the motor and sensory neuropathy of Charcot-Marie-Tooth disease and Refsum's disease are discussed. The adequacy of motor conduction velocity in genetically distinguishing types of the abovementioned familial peripheral neuropathies is reviewed. Data on the neuropathy assessed by modern techniques of three original patients of Roussy and Levy (1926) are given. The possibility of extensor plantar responses in patients with Charcot-Marie-Tooth and Refsum's disease without structural lesion of the pyramidal tract is pointed out. The existence of the association between Friedreich's ataxia and Charcot-Marie-Tooth disease is criticised. It is emphasised that spinocerebellar degeneration (other than Friedreich's ataxia) presenting with distal limb weakness and wasting and sensory impairment may mimic Charcot-Marie-Tooth disease.

Charcot-Marie-Tooth disease^{1,2} usually is a dominantly inherited disease and is relatively common in clinical practice. Although there is occasional central nervous system involvement (spinocerebellar tracts and optic nerve tracts), Charcot-Marie-Tooth disease is considered to be a familial peripheral neuropathy with impairment of motor and sensory nerves. There are various degrees of weakness and wasting. Some patients with Charcot-Marie-Tooth disease show a disorder of movement similar to that seen in patients with essential (familiar) tremor.^{3,4} Although motor conduction velocity (MCV) in the upper limbs is substantially reduced in the majority of cases some patients show normal or only slightly reduced MCV. Neurologists with the most experience with this condition use the MCV as a means to differentiate this disorder into two subgroups because there may be concordance of MCV in the upper limbs within each family.⁵ There are families, however, with widely different MCV in affected members.⁶ Some

modern writers have preferred to discard the eponymous title and designate Charcot-Marie-Tooth disease as hereditary motor and sensory neuropathy. Charcot-Marie-Tooth disease is diagnosed generally without difficulty; however, when unusual features are present, this may not be so. This may happen when added to the obvious peripheral neuropathy there is inco-ordination mimicking cerebellar disease.³ This problem may become more accentuated when there is such inco-ordination without distal wasting.⁷

Refsum's disease is a recessively inherited familial disorder. Its clinical manifestations are a chronic peripheral neuropathy, pigmentary retinal degeneration and sometimes a combination of the following abnormalities: pupillary changes, neurogenic impairment of hearing, skin anomalies, cardiac manifestations and skeletal abnormalities. Age of onset has varied from early childhood to the third decade. Phytanic acid accumulation is an essential finding for its diagnosis.⁸

The purpose of this paper is to report the author's experience on Charcot-Marie-Tooth disease and Refsum's disease and to summarise new findings on these diseases. Recent observations are widely scattered in the literature and there are several features encountered in such patients which deserve further discussion.

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Case material

Sixty-four cases of Charcot-Marie-Tooth disease were studied from 1972 to date. Diagnosis was made according to the criteria set by Charcot and Marie¹ and by Tooth² and were concordant with those set by modern authors with the most experience in this disorder.^{9,10} Forty-two were males and there were 34 families. Forty-one of these patients (14 families) involved a family history suggesting dominant inheritance. In 22 cases (19 families) type of inheritance could not be determined with certainty. One case was probably recessively inherited, was severely affected and has been reported in detail previously (Case I Ref 3). Fifty-eight patients had MCV measured in the upper limbs and some of them also in the lower extremities. Ages ranged from 9 to 75 yr for the males and from 8 to 62 yr for the females. Fifteen patients had normal or slightly reduced MCV and 43 had substantially reduced values. The dividing line was taken at 38 m/s in the upper limb as proposed by Thomas and Calne in 1974,¹¹ in spite of the fact that wherever this line was placed there were kinships with affected members above and below.⁶ In one family with a dominantly inherited form four affected members had considerably thickened nerves (MCV studies were refused) and Argyll-Robertson pupils, whereas another affected member had similar pupillary changes and normal motor conduction (Case I of Salisachs and Lapresle,¹²). One patient with the dominantly inherited form of the disease was found to have plantar ulcers. MCV was not measured but post mortem examination showed abundant onion bulbs.¹³ Four patients had extensor responses of whom only one had substantially reduced MCV but their affected relatives had absent or normal plantar responses. The clinical notes of experienced colleagues who examined some patients sometimes many years previously to the present author, mentioned extensor plantar responses in four other instances. All four had substantially reduced MCV in the upper limbs and when examined by the present author had either normal and/or absent plantar responses.

Males tended to be more affected and females showed more "formes-frustes" as noted by Harding and Thomas.⁵ The major clinical features including duration of symptoms, pes cavus, kyphoscoliosis, motor and sensory impairment, essential tremor, did not differ from the findings reported in the largest series so far reported⁵ in that patients with substantially reduced MCV in general were more affected clinically. Seven patients (in three families) had Argyll-Robertson pupils. MCV was only measured in three and was found to be normal in some nerves whereas it was slightly diminished in others.¹² Two patients (one male with substantially reduced MCV) with an undetermined type of inheritance had optic atrophy. One patient with moderate ataxia, bilateral extensor plantar responses and substantially reduced MCV had been said to have Friedreich's ataxia. Other affected members of his family had a dominantly inherited form of Charcot-Marie-Tooth disease with substantially reduced MCV. This kinship had been wrongly considered to be one of these rare families in which Friedreich's ataxia alternates with Charcot-Marie-Tooth disease.¹⁴ In three other kinships three patients with Charcot-Marie-Tooth disease with "cerebellar" ataxia and normal or absent plantar responses had also been

misdiagnosed as spinocerebellar degeneration (other than Friedreich's ataxia). The findings of seven nerve biopsies (six patients with substantially reduced MCV) did not differ from those reported by others.^{9,15,16} All patients in this review were under the personal care of the author. Affected members of kinships of the abovementioned patients who, although examined by the author, were not under his direct care were not included in this series. Patients seen briefly for "opinion only" were also excluded.

The present author has had under his direct care one case with Refsum's disease (with moderate "cerebellar" ataxia and substantially reduced MCV in the upper limbs¹⁷) and has examined clinically another.¹⁸ In addition he has had access to three necropsy cases (Ref 18 and through the kindness of Professor LW Duchon has examined Case III of Gordon and Hudson,¹⁹ and Case 15/65 unpublished, National Hospital, Queen Square).

Discussion

VARIATION IN THE MOTOR AND SENSORY NEUROPATHY IN CHARCOT-MARIE-TOOTH DISEASE

Some members of a family with Charcot-Marie-Tooth disease without muscle wasting can be detected easily because the MCV is substantially reduced, despite the absence of clinically detectable atrophy.⁹ However, in the cases in which the MCV is normal or slightly reduced and there is no muscle wasting, Charcot-Marie-Tooth disease may remain undiagnosed or mistaken for distal spinal muscular atrophy unless there is distal sensory impairment or sensory conduction studies are carried out. This confusion in diagnosis may result in unusual genetic patterns and also in the association in the same family of spinal muscular atrophy and Charcot-Marie-Tooth disease. It is worth noting that slight degrees of muscular wasting in the legs of females may be masked by the distribution of body fat.

Functional recovery of sensory nerves after local anaesthesia shows that the normal threshold for touch and two point discrimination is attained when the sensory potentials have not yet reached 50% of their pre-anaesthetic amplitude.²⁰ Hence it is not surprising that in Charcot-Marie-Tooth disease weakness and wasting have been reported to be more marked than sensory disturbances. In Charcot-Marie-Tooth disease motor and sensory impairment are known to occur in various degrees and combinations. However, until recently, marked afferent denervation in the absence of significant motor impairment has received little attention.⁷

Davidenkow²¹ and Ricker *et al*²² stressed that in Charcot-Marie-Tooth disease the scapuloperoneal and the distal distribution had no real relationship and would never occur in the same family. Harding and Thomas,²³ however, recently reported a kinship with both distributions and showed that the

scapuloperoneal weakness and wasting may occur as a phenotypical variation of classical Charcot-Marie-Tooth disease.

DATA ON THE NEUROPATHY ASSESSED BY MODERN TECHNIQUES OF THREE ORIGINAL PATIENTS OF ROUSSY AND LEVY (1926)

The original Case IV of Roussy and Levy²⁴ had mild distal weakness and wasting consistent with Charcot-Marie-Tooth disease, substantially reduced MCV in the ulnar nerve (15 m/s), onion bulbs in the distal part of the sural nerve and chronic partial denervation on EMG.²⁵ Case III, a nephew of Case IV, had the typical picture of Charcot-Marie-Tooth disease with stork legs, substantially reduced MCV in the ulnar nerve (14 m/s), chronic partial denervation on EMG, onion bulbs and prominent segmental demyelination in teased fibre preparations.²⁶ Case I, the mother of Case III, had a similar picture as her son but with no onion bulbs in the sural nerve though with prominent segmental demyelination and a MCV of 15 m/s in her ulnar nerve. Therefore, one can probably categorise this family as having an entity that corresponds with what some authors call the hypertrophic variety of Charcot-Marie-Tooth disease. In some members of this kinship there was essential tremor since 1926 (Cases I, II, VI and VII of Roussy and Levy, 1926²⁴) whereas in at least one other patient (Case IV) essential tremor developed later in life.²⁵ It is to be stressed that the difficulties in standing and walking described in the seven patients of Roussy and Levy²⁴ have sometimes been misinterpreted as ataxia. The abovementioned three patients had difficulty in standing and walking ("clumsy gait"), but not ataxia (as measured by the finger-to-nose and heel-to-shin tests) when the present author examined them clinically in the early seventies. Thus, ataxia was not present in 1956 when Lapresle²⁷ examined some of them or in 1926. The use of the eponym Roussy-Levy has been strongly criticised because it seems to be historically misleading and unhelpful, and it may perpetuate conceptual inaccuracies concerning some hereditary degenerative disorders.²⁸

DATA ON THE NEUROPATHY OF REFSUM'S DISEASE

Reports on Refsum's disease show that motor and sensory impairment occur in many degrees and combinations.⁸ MCV in the majority of cases is substantially reduced, a fact that is directly related to prominent segmental demyelination. However, Ulrich *et al*²⁹ found that MCV in the ulnar nerve of their patient was 45 m/s but few details were given. In a further case studied in detail by Sahgal and Olsen,³⁰ MCV was 40 and 45 m/s in the ulnar and median nerves respectively. Barolin *et al*³¹ reported in detail the clinical features of two sisters with Refsum's

disease. MCV in Case I were 45 and 50 m/s in the median nerves, whereas Case II had values of 23 and 27 m/s in the same nerves. It is worth noting that MCV values in Case II point to an underlying prominent segmental demyelination in the nerves of this patient. However, the MCV values in the cases of Ulrich *et al*,²⁹ Sahgal and Olsen,³⁰ and in Case I of Barolin *et al*,³¹ would imply that axonal degeneration was the main trait of the peripheral neuropathy. Consequently in Refsum's disease one may find (even in affected individuals of the same family) a neuropathy that shows axonal degeneration and wide variations in the degree of segmental demyelination.

It is interesting to point out some details of the case reported by Flament-Durand *et al*.³² MCV in the median nerve (wrist-elbow) was 45 m/s. However, post mortem studies showed large numbers of onion bulbs in paraffin embedded material on proximal parts of the peripheral nervous system (roots of the cauda equina, fig 7 of their paper). These findings would imply that whereas axonal degeneration seems to be the main trait in the distal part of some nerves demyelination prevails in the proximal segments of other nerves.

MCV VS SENSORY CONDUCTION VELOCITY IN CHARCOT-MARIE-TOOTH DISEASE AND REFSUM'S DISEASE: UPPER LIMBS VS LOWER EXTREMITIES
Buchthal and Behse³³ have divided patients with Charcot-Marie-Tooth disease into two categories using sensory conduction velocity studies. In their report motor and sensory nerves showed similar values. However in common with Thomas,^{5,11} we prefer studying MCV because sensory action potentials may sometimes not yield the information required to measure conduction velocity. The same may be true in Refsum's disease (see the case reported by Flament-Durand *et al*³²). In Charcot-Marie-Tooth disease it might seem preferable to study MCV in the lower limbs instead of in the upper. However the denervation in the lower limbs is sometimes so great that either no motor response can be obtained or the MCV is slowed to a degree out of proportion to that seen in the upper extremities. Therefore, many authors today disregard MCV in the lower limbs when categorising patients or discussing differential diagnosis.^{3,4,5,34}

INCO-ORDINATION IN CHARCOT-MARIE-TOOTH DISEASE AND REFSUM'S DISEASE

In Charcot-Marie-Tooth disease when proprioceptive deafferentation is sufficiently severe inco-ordination may occur. In other patients however inco-ordination with^{3,4} or without^{7,14} wasting, mimics cerebellar disease. This latter type of inco-ordination has been said to be due to various degrees of proprioceptive

deafferentation associated with essential tremor.³⁷ Post mortem studies of patients with typical Charcot-Marie-Tooth disease showed that the cerebellum was normal.³⁵ Also in three cases with inco-ordination, categorised as cerebellar that came to post mortem, the cerebellar systems were intact. In some patients with essential tremor Rondot *et al*³⁶ and Adams and Victor³⁷ found a cerebellar type of ataxia, and Harding and Thomas⁵ when studying the clinical features of Charcot-Marie-Tooth disease assessed ataxia and tremor together because distinguishing between these two features separately was often difficult. Inco-ordination due to essential tremor affects more often the upper extremities alone and less frequently the upper and lower limbs together.

Refsum⁸ noted in his view that inco-ordination was not present in some patients having the disease that bears his name. When it was present it could be reminiscent of that seen in cerebellar disorders and it was evident either in the upper limbs only or in both upper and lower extremities. Other patients with the disease have a disorder of movement similar to essential tremor (see among others Refsum's summary⁸ on the patients reported by Rake and Sanders and Frier *et al*). In the experience of the author in patients with Charcot-Marie-Tooth disease associated with essential tremor a cerebellar type of inco-ordination may be absent,^{3,4} present in the upper limbs only,^{3,4} or present in all four limbs.^{3,4,7,14} Thus, there seems to be a striking similarity both in the manifestations and distribution of the "cerebellar" inco-ordination seen in patients with essential tremor, Charcot-Marie-Tooth disease associated with essential tremor and Refsum's disease. Indeed, all of them may exhibit either normal co-ordination, "cerebellar" inco-ordination in the upper extremities or in all four limbs.

The site of the cerebellum as the cause of the cerebellar inco-ordination in Refsum's disease may be seriously questioned because (1) except in some cases of cerebellar cortical atrophy where inco-ordination may be more marked or limited only to the lower extremities and/or ataxia of gait, in the spinocerebellar degeneration ataxia is equally conspicuous in the lower limbs as it is in the upper extremities. Refsum⁸ mentioned that in Refsum's disease the "cerebellar" inco-ordination may be limited at least at one stage of the disease to the upper limbs (see among others the patient reported by Gordon and Hudson¹⁹). (2) In the spinocerebellar degenerations presenting with cerebellar inco-ordination there is damage to the cerebellum that is generally more marked pathologically than suspected clinically and is usually visible to the naked eye. In contrast, as reported by Cammermeyer³⁸ and Refsum⁸ only five necropsy cases of Refsum's disease

have shown "some" microscopical changes in the cerebellum. In this respect it is to be stressed that large parts of the cerebellum can be destroyed without there being any clinical measurable effect.³⁹ In addition many cases with Refsum's disease show severe "cerebellar" inco-ordination in all four limbs without any pathological lesion in the cerebellum (see among others Case III of Refsum reported by Cammermeyer,⁴⁰ Case II of Gordon and Hudson,¹⁹ and the case of Reese and Bareta⁴¹). It is to be remembered that in essential tremor no pathological changes have been found so far.

For the reasons advanced above and the personal experiences of the author in Refsum's disease (see *Case material*) it is my opinion that when in Refsum's disease inco-ordination (as examined by the finger-nose-finger and heel-to-shin tests) has the clinical characteristics of cerebellar disease it is due to proprioceptive deafferentation associated with essential tremor. (See table 1 Salisachs,⁷ for details.) In Refsum's disease sudden exacerbations of the disease are known to occur.⁸ In patients with infectious polyneuritis (either in the acute phase or during the relapses that may occur) there is sometimes, and for a period of time only, tremor that though not necessarily identical to is clinically indistinguishable from essential tremor. The tremor generating factor of this neuropathy is not known. The present author believes that the relapses of the neuropathy in Refsum's disease may contribute to a temporary increase in the ataxia by adding an extra and presumably transient tremor generating factor to the pre-existing disorder of movement. It is suggested that ataxia in Refsum's disease can be improved by preventing the abovementioned sudden exacerbations (dietary restriction of phytol⁸) and by treating essential tremor. Patients with Charcot-Marie-Tooth disease associated with essential tremor may also be treated with drugs effective in essential tremor.

Table 1 *Features of some patients with Charcot-Marie-Tooth disease with little or no wasting which may suggest Friedreich's ataxia*

Club foot
Absent tendon jerks in the limbs
Romberg's sign positive
Errors in vibration sense
position sense
two-point discrimination
Inco-ordination (due to "essential tremor" and/or proprioceptive deafferentation)
Dysarthria (due to "essential tremor" affecting voice organs)
Kyphoscoliosis
Nystagmus

For discussion—see Salisachs, 1976.³

IS THERE ANY ASSOCIATION BETWEEN FRIEDREICH'S ATAXIA AND CHARCOT-MARIE-TOOTH DISEASE?

Reports on Friedreich's ataxia associated with Charcot-Marie-Tooth disease (either in the same individual or in different members of the same family) are based on clinical data (table 1) only, are not numerous and have been severely criticised.³ Those in which pathology is available were found to be misdiagnosed.⁷ For a detailed discussion see Salisachs *et al.*¹⁴ In addition it deserves to be emphasised that neither in the patients reported here nor in the largest ever series of patients with Charcot-Marie-Tooth disease⁵ or Friedreich's ataxia^{42,43} studied with modern criteria any patient or kinship was found to have both disorders, transition forms or any other degenerative disorder.

SPINOCEREBELLAR DEGENERATION (OTHER THAN FRIEDREICH'S ATAXIA) WITH DISTAL WEAKNESS AND WASTING VS CHARCOT-MARIE-TOOTH DISEASE

Patients with spinocerebellar degeneration (other than Friedreich's ataxia) with distal limb atrophy may have distal sensory deficit and may thus resemble Charcot-Marie-Tooth disease (table 2). These cases should not be considered as variants of Charcot-Marie-Tooth disease but illustrations of a dying back motor and sensory neuropathy in a complex system degeneration. Indeed, to the best of our knowledge there has never been a report in which a pathologically proven spinocerebellar degeneration coexisted with an anatomically verified case of Charcot-Marie-Tooth disease.

EXTENSOR PLANTAR RESPONSES IN CHARCOT-MARIE-TOOTH DISEASE AND REFSUM'S DISEASE

The Babinski sign has been reported in Charcot-Marie-Tooth disease^{3,5,10,14} and in Refsum's disease,³⁰ and this can occur in the absence of a structural lesion of the pyramidal tract or evidence of compression of the spinal cord, for instance, by hypertrophic roots.^{3,5} For a possible mechanism for this in some patients see Ref 3. It is commonly stated in clinical discussion that it is difficult to decide on the initial deflection of the toe when eliciting the plantar response in patients with foot deformity from familial peripheral neuropathies. It is my opinion that provided that the denervation is so severe that no movement occurs at all it is not difficult to decide on the direction of the movement but the significance of an extensor response in this situation does not necessarily imply a lesion of the pyramidal tract.

IS MCV AN ADEQUATE MEANS TO GENETICALLY DISTINGUISH DIFFERENT SUBGROUPS IN CHARCOT-MARIE-TOOTH DISEASE AND REFSUM'S DISEASE?

The original division of two very different Charcot-Marie-Tooth diseases made by Dyck and Lambert and reported in two different papers⁹ has been restricted with the passage of time to a subgrouping of the Charcot-Marie-Tooth disease based on MCV in the upper limbs.⁶ Indeed in spite of severe criticism,^{6,44} it is still sometimes claimed that based on MCV in the upper limbs there are two different genetic subgroups of Charcot-Marie-Tooth disease (concordance of conduction velocity within families), the dividing line being now set at 38 m/s in the median nerve.⁵ However, the value of MCV as a tool to distinguish two genetically different groups is to be

Table 2 Differentiation of spinocerebellar degeneration (other than Friedreich's ataxia) from Charcot-Marie-Tooth disease with inco-ordination and absence or varying degrees of wasting

<i>Charcot-Marie-Tooth disease</i>	<i>Spinocerebellar degeneration other than Friedreich's ataxia</i>
(1) Inco-ordination is sometimes more marked in upper limbs.	Although inco-ordination is sometimes more marked in lower than upper extremities, it is generally as marked in the upper as in the lower limbs.
• Inco-ordination generally not so marked as in SCD of same duration.	Inco-ordination generally more marked than CMTD of same duration.
(2) When ataxia is present: the tendon reflexes in the limbs are generally absent, and Other members of the family may have more typical forms of the disease.	Ataxia and absent tendon reflexes in the limbs: rare, and
(3) Extensor plantar responses: rare.	Other affected members of the family may retain reflexes in the limbs; reflexes in the limbs may even be brisk.
(4) Natural history is different from that of SCD.	Extensor plantar responses: common.
(5) MCV in the upper limbs in the majority of cases is substantially reduced.	Natural history is different from that of CMTD.
(6) Sometimes distal deficit of pain and temperature.	MCV in the upper limbs is normal or only slightly reduced.
	Distal deficit of pain and temperature is rare.

CT scan may detect olivopontocerebellar atrophy which is the most common of the dominantly inherited SDC.
CMTD = Charcot-Marie-Tooth disease; SDC = Spinocerebellar degeneration; MCV = motor conduction velocity.

reconsidered because there are now many kinships with Charcot-Marie-Tooth disease with widely different MCV in the upper limbs in different affected members. Furthermore, in a patient with Charcot-Marie-Tooth disease studied by Ochoa⁴⁵ MCV in the upper limbs in one arm was slightly diminished whereas in the other it was substantially reduced.

Further doubts as to the usefulness of MCV has come from data on Refsum's disease. (See above *Data on the neuropathy of Refsum's disease* and particularly the comments on the two affected sisters reported by Barolin *et al*³¹ and the conflicting findings of the patient studied by Flament-Durand.³²) In recessively inherited disorders it is common to find that the expression of the disease is similar between and especially within families, but minor differences, which do not warrant different classifications are not uncommon. Therefore finding widely different MCV in the upper limbs in patients with Refsum's disease of different kinships (and especially in the same family) would make of such MCV differences a "minor variation" and would not only not warrant a different genetic classification of Refsum's disease on such bases but also would invalidate, in the view of the author, the genetical classification of Charcot-Marie-Tooth disease based on MCV. In consequence, the value of MCV as a tool to distinguish genetically different subgroups should be seriously reconsidered.

SUBGROUPING: THE FUTURE

Recently Guiloff *et al*⁴⁶ have described support for (at least) two genetically distinct forms of the dominantly inherited Charcot-Marie-Tooth disease. Type I was linked to the Duffy locus on chromosome I whereas type II was not. In Refsum's disease MCV may be normal or slightly diminished and affected individuals of the same family may have widely different MCV (see above). In this respect Thomas⁴⁷ pointed out that regarding Refsum's disease as a genetically homogenous disease may have to be reconsidered should future observations indicate clustering of MCV in the same family.

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