

A Case of Charcot-Marie-Tooth Disease Mimicking Friedreich's Ataxia: is there any association between Friedreich's ataxia and Charcot-Marie-Tooth disease?

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SUMMARY: *The authors report a case of Charcot-Marie-Tooth disease that mimicked Friedreich's ataxia and featured impaired tendon reflexes in the limbs, inco-ordination mimicking cerebellar disease in the extremities, extensor plantar responses on both sides, bilateral foot deformity, impaired position sense in the toes, absent vibratory sense in the distal parts of the legs and minimal distal weakness with wasting. Motor conduction velocity in the upper limbs was substantially reduced.*

Other cases similar in nature reported in the literature resemble spino-cerebellar degeneration in general, and Friedreich's ataxia, in particular. It is emphasized that the natural history, EMG, motor conduction velocity studies and examination of

other affected members of the family permit the correct diagnosis to be made in such cases. It is also emphasized that patients similar to the one reported here may also resemble, and should be differentiated from, cases of familial dorsal column ataxia (Biemond type). Stress is put upon the fact that when Charcot-Marie-Tooth disease mimicks spino-cerebellar degeneration, substantial slowing of motor conduction in the upper limbs is generally sufficient to establish the diagnosis.

The relation between Friedreich's ataxia and Charcot-Marie-Tooth disease is reviewed and it is concluded that these two disorders are distinct clinical and pathological entities.

RÉSUMÉ: *Les auteurs rapportent un cas de maladie de Charcot-Marie-Tooth imitant une maladie de Friedreich avec abolition des réflexes ostéotendineux des membres, incoordination d'allure cérébelleuse aux extrémités, signe de Babinski bilatéral, déformation des pieds, perturbation du sens de position des orteils, abolition de la sensibilité vibratoire à la partie distale des jambes et une minime faiblesse sans atrophie. La vitesse de conduction motrice était notablement réduite aux membres supérieurs.*

D'autres cas de la même nature ont été rapportés dans la littérature, ressemblant aux dégénérescences spino-cérébelleuses en général et à la maladie de Friedreich en particulier. Les auteurs soulignent que l'histoire naturelle, l'EMG, la mesure des

vitesse de conduction motrice et l'examen des autres membres atteints de la famille permettent dans de tels cas d'aboutir au diagnostic correct. Ils soulignent également que des cas analogues au leur doivent être différenciés de l'ataxie familiale de type Biemond à laquelle ils peuvent aussi ressembler. Ils insistent sur le fait que le ralentissement de la conduction motrice aux membres supérieurs suffit généralement à établir le diagnostic de maladie de Charcot-Marie-Tooth lorsque celle-ci imite une dégénérescence spino-cérébelleuse.

La relation entre la maladie de Friedreich et la maladie de Charcot-Marie-Tooth est discutée, aboutissant à la conclusion qu'il s'agit de deux entités cliniques et pathologiques distinctes.

INTRODUCTION

Charcot-Marie-Tooth disease (CMTD) is usually a dominantly inherited peripheral neuropathy and is relatively common in clinical practice. Although there is occasional central nervous system involvement (spino-cerebellar tracts and optic nerves and tracts) CMTD 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 CMTD show a disorder of movement similar to that seen in patients with essential (familial) tremor (ET) (Salisachs, 1976; Salisachs et al, 1979). 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 values.

Friedreich's ataxia (FA) is a recessively inherited disease with pathological changes localised mainly to the posterior columns, spino-cerebellar and cortico-spinal tracts in the spinal cord, and dentate nucleus in the cerebellum (Oppenheimer, 1976). There is a significant drop out of the large diameter fibre population in sensory nerves of the lower limbs (Hughes et al, 1968; Dyck et al, 1968; McLeod, 1970). The neurological manifestations usually become apparent during the first or second decade of life, are progressive and are characterised by inco-ordination usually starting in the lower limbs and affecting later the arms. The tendon reflexes are absent in the legs (Salisachs, 1974; Barbeau, 1976; Harding, 1981) and usually in the arms also, but in a small percentage of patients, with optimum reinforcement, a minor reflex response may be obtained in the arms (Salisachs, 1974; Harding, 1981). The

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jaw jerk is brisk (Salisachs, 1979). There are extensor plantar responses, foot deformities, loss of proprioceptive sensation in the extremities and, in many cases, cardiomyopathy and kyphoscoliosis.

Many authors and text books suggest that there is an association between Friedreich's ataxia (FA) and CMTD because there are, in their view, many kinships where the two diseases co-exist and there are patients showing features of both disorders. The purpose of this paper is to report a patient with CMTD which mimicks FA and to put forward the view that FA and CMTD do not occur in combination nor do transition forms of the two disorders exist.

CASE HISTORY

The patient was a 16 year old boy who was the product of a normal pregnancy. His motor development was normal until the age of 6 years. He was then noted to be having progressive difficulty with running, jumping and to be developing 'high arches' of his feet. His mother attributed these symptoms to a 'family disease' that some members on her husband's side were known to have. When stressed or tense he had a tremor of both hands. On examination there were no abnormalities in the cardio-vascular, respiratory and alimentary systems. He was unsteady walking heel to toe and had bilateral pes cavus. He had a horizontal nystagmus on right and left gaze, the cranial nerves were otherwise normal, as were the appearances of the optic fundi. In the limbs there was a mild symmetrical distal weakness without wasting. The deep tendon reflexes were absent except for the left biceps jerk, which was present, though depressed. The plantar responses were bilaterally extensor. He had a fine postural tremor of the hands and arms and the right leg. There was moderate 'cerebellar' ataxia in the upper limbs on the finger/nose/finger test with a less marked inco-ordination of cerebellar appearance on the heel/shin test. Proprioception in the toes and vibration sense in the distal parts of the legs were impaired bilaterally. Laboratory investigations including full blood count, erythrocytes, sedimentation

rate, fasting blood glucose, serum lipoproteins, serum cholesterol, serological tests for syphilis, electrocardiogram and electro-encephalogram were all normal. There were no acanthocytes present in the blood film. This clinical picture did not change on repeat examinations by different examiners over a period of three years. Cerebro-spinal fluid examination by lumbar puncture was refused as was sural nerve biopsy. The patient was seen by many different physicians and a unanimous diagnosis of FA was reached and the poor prognosis that this disorder carries was given to the family.

Systematic examination of the family showed that two brothers, a sister and the father had typical CMTD and from the history, other members of the kinship, i.e. grandfather and some cousins, were similarly affected. One sister was clinically not affected. Thus it was concluded by many observers that this was one of those rare families in which FA co-exists with CMTD. The patient was subsequently examined by one of the authors (PS) who agreed with the observation of previous examiners but put a different interpretation on the findings and did not agree that the patient had FA. It was assumed that this patient showed the variable clinical expression of a single genetic disorder rather than a chance coincidence of an unrelated condition and the diagnosis of CMTD was made because:

1. FA is sporadically or recessively inherited, whereas the patient reported here had a dominantly inherited disorder.
2. In FA inco-ordination is as marked or more marked in the legs than in the arms whereas in CMTD, although inco-ordination mimicking cerebellar disease may have the same distribution as in FA, sometimes (as in the patient reported here) it is more evident in the arms than in the legs (see discussion below).
3. In FA when the Babinski sign is present bilaterally the jaw jerk is brisk (Salisachs, 1979), whereas this patient had a normal jaw jerk with bilateral extensor plantars which may suggest that such a sign was not

due to a structural lesion of the cortico-spinal tract but to a mechanical over-powering of the toe flexors (for detailed discussion on such signs in CMTD see Salisachs, 1976a).

4. The presence of nystagmus is not necessarily a "hard" feature against a diagnosis of CMTD because some otherwise typical cases will demonstrate this (Poursines et al, 1950; Salisachs, 1976a).

In spite of all these data against the diagnosis of FA some specialists still had doubts about the diagnosis, so electro-diagnostic support was sought using concentric needle EMG and nerve conduction studies in the four affected members of the kinship with typical CMTD and in the patient under discussion suspected of having FA from the same kinship. All five patients showed chronic partial denervation in the distal part of the upper extremities with a MCV in the upper limbs ranging from 33 msec to 16 msec. The patient with the original diagnosis of FA had an MCV of 17 msec. Although in FA the EMG may show changes in the distal part of the limbs compatible with denervation, the MCV in the upper limbs is normal or only slightly reduced (see Discussion), thus the diagnosis of FA in the patient was no longer tenable and the diagnosis of CMTD was agreed upon by all the specialists who had seen the patient. The parents of the patient were very satisfied because of the better prognosis of CMTD.

DISCUSSION

Problems in Diagnosis - CMTD versus FA and posterior column hereditary ataxia (Biemond type):

The patient reported here was thought to have FA. Indeed, he had bilateral pes cavus, absent reflexes in the limbs except left biceps jerk, bilateral extensor plantar responses, impaired vibration sense distally in the legs and impaired position sense in the toes. There was nystagmus on lateral gaze, moderate inco-ordination in the arms and mild ataxia in the legs which was cerebellar in type. The diagnosis of CMTD was suspected when various members of his family were found to have classical CMTD with substantial-

ly reduced MCV's in the upper limbs and the diagnosis was confirmed when the MCV in the patient was also found to be substantially reduced. However, many specialists had diagnosed the kinship as one having a co-existence of CMTD and FA. The patient reported here was mis-diagnosed probably because ataxia mimicking cerebellar disease in CMTD is rare as is the presence of extensor plantar responses (Thomas et al, 1974; Salisachs, 1976a) and this patient demonstrated both of these features.

It has been suggested that, when in CMTD there is ataxia mimicking "cerebellar" disease, this is due to the association of proprioceptive deafferentation and ET and if the latter predominates the inco-ordination may sometimes be more obvious in the upper limbs (Salisachs, 1981). It is of note that his patient had episodes of tremulousness in his upper limbs. In this case the MCV and examination of the family settled the diagnosis. However, in 1970 one of us (PS) when working in La Salpêtrière under Professor P. Castaigne and Professor P. Rondot, had under his case a patient that had been diagnosed as a spinocerebellar degeneration. MCV was normal. It was only at post mortem that the diagnosis of CMTD was made (Case VI of Escourolle and Hauw). Thus, when MCV is normal or slightly diminished and/or there is no family history of CMTD and/or no other members of the family can be examined a mis-diagnosis is likely to be made. This differential diagnosis is of importance in that CMTD is a slowly progressive peripheral neuropathy which does not shorten life unless associated with cardio-myopathy (Legrand et al, 1950; Lascelles et al, 1970), and results in the long term in moderate physical disability only, whereas FA usually runs a crippling course with death occurring commonly between 40 - 50 years of age, though some patients have significantly earlier or later demise (Salisachs, 1974; Barbeau, 1976; Harding, 1981).

In addition, patients with CMTD demonstrating inco-ordination, with little or no wasting, may also be mis-diagnosed as familiar posterior column ataxia (Biernond type, 1954). Although

substantial reduction in MCV in the upper limbs should distinguish the two conditions, even when such data is available the diagnosis is sometimes incorrectly made (Singh et al, 1973).

Is there any association between CMTD and FA?

Many authors believe in an association between CMTD and FA. This association is supported by cases in which CMTD occurred associated with FA either in the same individual or in different individuals in the same family. The clinical cases to prove such association have come under severe criticism (Salisachs, 1976 a, b). We shall now comment on the cases where clinical and pathological data are available. Stephens et al (1958) reported a case which was said to have CMTD associated with FA. The patient showed considerable inco-ordination and distal weakness and wasting. All the tendon reflexes were absent. He also had a progressive ophthalmoplegia. Many other members of the family had CMTD which was inherited as a dominant trait. The changes in the spinal cord illustrated by these authors showed obvious degeneration of the columns of Goll and less marked impairment of the columns of Burdach - findings compatible with CMTD. In FA the dorsal and lateral columns of the cord show marked degeneration and gliosis, thus Stephens et al (1958) reported such a patient incorrectly as being a combination of FA and CMTD. Stucki and Luban (1953) reported a kinship with dominantly inherited CMTD; one member (Case 27/VI) was wrongly diagnosed as FA. The post-mortem examination showed changes in the posterior columns compatible with CMTD which are not changes of FA.

It may thus be concluded that in those cases in which FA and CMTD were said to be combined in the same individual (see comment of van Bogaert, 1948 on page 342 of paper by van Bogaert and Moreau, 1939; Stephens et al, 1958) the post-mortem examination showed that they were in fact cases of CMTD with marked inco-ordination and when FA was thought to co-exist with CMTD in different

members of the same family, the pathologic examination in the case thought to have FA showed only the changes of CMTD (Stucki and Luban, 1953).

It should be stressed that reports of FA associated with CMTD (either in the same individual or in different members of the family) are based only on clinical data (see detailed criticism by Salisachs, 1976b); and are not numerous. We have seen that those in which pathology was available had been mis-diagnosed. Further, textbooks quote the cases with clinical data alone but tend not to quote, or to misinterpret cases in which autopsy information was available. Authors wishing to establish a relationship between FA and CMTD quote papers based on clinical data only and these are in turn quoted in subsequent textbooks. The end result is a snowballing effect of misinterpreted cases. Other authors suggest a relationship between FA and CMTD by reporting patients with features common to both (Smith et al, 1978), however, because patients present signs common to two different diseases it cannot be assumed that they represent transition forms of these diseases.

To establish the diagnosis of FA one must use strict criteria including the type of inheritance (Salisachs, 1974; Barbeau, 1976; Harding, 1981), natural history (Salisachs, 1974; Barbeau, 1976; Harding, 1981), clinical features (Salisachs, 1974; Barbeau, 1976; Salisachs, 1979; Harding, 1981) electro-physiological findings (Dyck and Lambert, 1968b; McLeod, 1970; Salisachs et al, 1975; Peyronnard et al, 1976; Bouchard et al, 1979) and pathological data (Oppenheimer, 1976, 1979). It has been pointed out that FA and CMTD share many clinical features including club foot, absent tendon reflexes in the limbs, errors in vibration sense, two point discrimination and position sense, nystagmus, a positive Romberg's sign, kyphoscoliosis, dysarthria and inco-ordination (Salisachs, 1976a). Patients with CMTD in whom inco-ordination is moderate or marked are often mis-diagnosed and this is probably the reason that inco-ordination in CMTD is not discussed in textbooks. If wasting

is prominent, the patient with CMTD and inco-ordination is said to have CMTD plus FA; whereas the patient with CMTD with inco-ordination without wasting would be diagnosed as FA. The relationship between FA and CMTD is emphasized; however the important fact is that CMTD may occur with inco-ordination and is missed.

The mis-diagnosis of patients with CMTD should be less likely in the future because, as stated above, MCV in the upper limbs in the majority of cases of CMTD is substantially reduced whereas it is normal or only slightly reduced in FA. Thus if a patient with CMTD is mis-diagnosed on clinical grounds as FA or as FA plus CMTD, if the MCV in the upper limbs is found to be substantially diminished the correct diagnosis can then be made. However, if in patients with CMTD but resembling FA or FA plus CMTD, the MCV in the upper limbs is normal or only slightly diminished as happened in the family reported by Tilbery et al (1972), one would need to know and use the clinical criteria mentioned above to differentiate FA from CMTD.

Having argued against any relationship between FA and CMTD, we are aware that in FA there is damage to peripheral motor nerves. This has been established by the reduction of the amplitude of the compound action potentials and the slight diminution of MCV in the upper and lower limbs (Dyck and Lambert, 1968b; McLeod, 1970; Salisachs et al, 1975; Peyronnard et al, 1976; Bouchard et al, 1979). Peyronnard et al (1976) and Bouchard et al (1979) pointed out that in the distal muscles of the limbs of their patients there were changes compatible with denervation. Barbeau (1976) described these changes as "very slight". However, in FA we do not yet know the percentage of motor axons that must degenerate to result in (a) definite EMG evidence of denervation; and (b) clinically detectable atrophy. It must be remembered that most of the atrophy in the lower limbs has been said to be due to disease (Salisachs, 1974).

Compression of the nerves of the lower limbs in patients with FA who are bedridden or chair-bound may aggravate the slight slowing of MCV.

Hopf and Port (1968) reported slightly diminished MCV in the upper limbs of their patients with FA. The MCV in the lower limbs was very slow. Some authors would claim that these findings suggest FA in the upper limbs and CMTD in the lower extremities! Dyck and Lambert (1968b), McLeod (1970), Peyronnard et al (1976) and Bouchard et al (1979) found only slightly reduced MCV in the lower limbs of their patients with FA who were not bedridden or chair-bound.

In conclusion: FA may present with wasting of the distal muscles of the limbs but this does not imply that FA and CMTD occur either in combination or that there are transitional forms between these two conditions.

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