FRIEDREICH'S ATAXIA

A Neurophysiological Study
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Many important studies have thrown doubt on the validity of the orthodox classifications of the hereditary ataxias. Nevertheless, the name Friedreich's Ataxia has persisted.

The disease, to quote Greenfield (1958), 'has come to be recognised as one of the most common hereditary disorders of the nervous system'. It has been studied extensively from the clinical and pathological points of view but one important feature of the condition remains unexplained - the early loss of the ankle jerks.

Most writers on the subject are elaborately vague about this. For example one well-known textbook (Russell Brain, 1955), after describing the pathology as consisting of degeneration of the corticospinal, spinocerebellar tracts and posterior columns, says, 'the tendon jerks are lost because of interruption of the reflex arc on the afferent side'. The reflex arc does not, of course, involve any of the structures named. There are in fact some changes in the dorsal roots but these appear to be minor and no writer has laid much stress upon them. I do not think that they can wholly explain the profound and early areflexia so characteristic of the condition.
METHOD

In order to study this problem I have used the method first described by Hoffmann (1918 and 1934) and recently studied by Magladery et al (Magladery: 1950a, 1950b, 1950c, 1951a, 1951b, 1952, 1955, 1958; Teasdall: 1951, 1952a, 1952b; Park: 1951; Languth: 1952) and Paillard (1953a, 1953b, 1953c, 1954, 1955a, 1955b, 1959a, 1959b) amongst others.

It is based on the fact that provided certain precautions are taken, it is possible to stimulate the afferent fibres in the medial popliteal nerve and to obtain a reflex contraction of the calf muscles, that is, a sort of ankle jerk which by-passes the muscle stretch receptors.

The patient lies prone on a couch. Small silver electrodes are applied to the skin over the soleus muscle and led through a standard Ediswan portable electro-encephalograph amplifier to a cathode ray oscilloscope.

The soleus muscle was used rather than the gastrocnemius because, although there is no clear differentiation between red and pale muscle in man, the soleus appears to play a greater part in reflex contraction. There is considerable evidence that this is true in animals which show a clear differentiation between red (soleus) and white

Stimulating electrodes are applied to the medial popliteal nerve behind the knee. A constant current stimulator is used. This puts out square pulses of 1 m.sec. duration up to a maximum of about 15 m. amps. Paillard (1955a) has stressed the importance of using wide pulses of the order of 1 m.sec. and this is in keeping with the well-known physiological fact (Erlanger and Blair: 1938; Skoglund: 1942; Kugelberg: 1944) that sensory fibres have a lower threshold for wide pulses than motor fibres and vice versa.

It is important to use a constant current stimulator rather than the constant voltage one favoured by the Medical Research Council subcommittee on stimulators (1958). This arises from a point briefly mentioned in the report of this subcommittee and is that when a constant voltage stimulator is used the current flowing through the skin is distorted so that the effective stimulus consists of two brief spikes of opposite polarity separated by an interval during which the current is only a small fraction of the nominal one (fig. 1a). When the nominal pulse length is increased the two spike components move apart but the length of the effective stimulus is not necessarily increased (fig. 1b). This effect is not seen with a constant current stimulator (fig. 2a and b).
Fig. 1: Showing the form of the current flowing through the skin as monitored by a sampling resistance when a constant voltage stimulator is used. Nominal pulse length 250 u.sec. (a) and 1 m.sec. (b)
Fig. 2: Same as Fig. 1 with a constant current stimulator. Nominal pulse length 250 u.sec. (a) and 1 m.sec. (b)
Fig 3:  

a) Electromyographic record from a normal subject obtained as described in the text following medial popliteal stimulation. Showing the 'H' wave. Time 500 c/s.

b) Current increased to show both 'M' and 'H' waves.
The sort of record obtained in normal subjects is shown in figure 3. The base line is displaced at approximately 30 m.secs. by a wave (known as the 'H' wave). As the current is increased a second wave appears preceding the 'H' wave. This second wave is known as the 'M' wave. These waves have been so named by Magladery et al (1950a, ) who have shown that the 'M' wave is caused by impulses set up in the muscle by direct stimulation of the motor fibres in the nerve and the 'H' wave by reflex contraction of the muscle set off by stimulation of the afferent fibres. These workers have produced good evidence to suggest that the impulses involved are carried by group I afferents and that the reflex is a monosynaptic one with a synaptic delay of the order of 1 m.sec. (Magladery et al 1951a).

Under the conditions I have described I have never failed to obtain an 'H' wave in 50 normal subjects.

RESULTS

This method was used in studying 8 cases of Friedreich's ataxia all showing absent ankle jerks. Only uncomplicated cases of Friedreich's ataxia have been included in this series. Mixed forms with signs of peripheral nerve involvement such as those that go under the name of the Roussy-Lévy syndrome (Roussy and Lévy: 1926, 1934) have been deliberately excluded.
In every case tested, 'H' waves were obtained from the calf muscles of both legs (fig. 4a and b).

This is in contrast with the findings in 8 cases of the Holmes-Adie syndrome (fig. 5a and b), 6 cases of tabes dorsalis and 7 cases of peripheral neuropathy also with no ankle jerks. In these cases 'M' waves were obtained but no 'H' waves.

Recently I have tested another patient. This was a 16 year old girl with an acute demyelinating condition and cranial nerve signs pointing to a lesion in the left side of the medulla. She had poor coordination in all limbs and depression of tendon reflexes. The ankle jerks were abolished and the right plantar was extensor. Sensation in the limbs was normal. The brain stem signs receded rapidly while she was being treated with prednisolone and the ankle jerks returned. During the period when she had lost her ankle jerks, the 'H' wave was present and its threshold remained unchanged throughout.

I have also seen this picture in three epileptic patients who lost their ankle jerks following a fit and in two patients with cerebrovascular accidents. These and other cases will form the basis of another paper.
Fig. 4: Records from a patient with Friedreich's ataxia.

a) Tension record following a blow on the tendo-Achilles demonstrating the absent ankle jerk. The spike marks the time of the stimulus. 
   Time signal: 100 c/s

b) 'H' wave obtained from such a patient by stimulation of the medial-popliteal nerve. 
   Time signal: 500 c/s.
Fig. 5: Records from a patient with Holmes-Adie syndrome

a) As in Fig. 4.

b) No 'H' wave obtained.
The second part of this study was concerned with an attempt to reproduce in normal subjects a situation analogous to that seen in these cases by the injection of dilute procaine around the medial popliteal nerve.

**METHOD**

The course of the medial popliteal nerve was plotted by electrical stimulation, monopolar cathodal stimulation being used in this case. The stimulating electrode was gradually moved from a position a few inches above the knee to as far as possible below the knee. At any one level, it was assumed that the nerve lay beneath that point which gave the greatest muscle response on stimulation. 5 mls. of 1% procaine were then injected around the lowest accessible part of the nerve. The ankle jerk and 'H' wave were tested every minute.

**RESULTS**

Three normal subjects with about 20 cms. of nerve accessible to stimulation were selected. This is important if the injection is to be carried out at a sufficient distance from the site of
stimulation. The requirement considerably limited the number of subjects available as in most cases only about 5 cms. of nerve was near enough to the surface to allow stimulation.

Within five minutes of injection the amplitude of the ankle jerk began to diminish and it was finally abolished at eight, nine and ten minutes. The amplitude of the 'H' wave and its threshold remained unchanged (fig. 6). When a similar quantity of saline was injected on the opposite side, no change was observed in the ankle jerk or 'H' wave.

The experiment was repeated on the next day when the highest part of the nerve was injected with procaine with the same results.

PART III

In order to exclude the possibility that the differential loss of ankle jerk with retention of the 'H' wave might be a quantitative effect, that is that the electrical stimulus might be a more 'powerful' one than the mechanical, I carried out a third experiment on five normal subjects. The ankle jerk and 'H' wave were recorded in the usual way. Then a sphymomanometer cuff was placed around the middle of the thigh and this was inflated to a pressure above the systolic. The ankle jerk and 'H' wave were
recorded at minute intervals in the first three cases and at half minute intervals in the others. Both the ankle jerk and 'H' wave showed a diminution in amplitude from about the sixth minute and disappeared simultaneously at about fifteen minutes, although the 'M' wave was still present (fig. 7). When the pressure was released both returned simultaneously at about ten minutes. At no time when the ankle jerk was absent, was the 'H' wave obtainable.
Fig. 6: Normal subject.

a) Before procaine infiltration. Tension record showing a normal ankle jerk and electromyograph showing 'H' and 'M' waves. Time 100 c/s and 500 c/s

b) Ten minutes after infiltration of 5 mls. of 1% procaine around the medial popliteal nerve. Ankle jerk abolished but 'M' and 'H' waves unchanged.
Fig. 7: Normal Subject.

a) As Fig. 6 Before inflation of cuff.

b) Fifteen minutes after cuff inflation. Abolition of both ankle jerk and 'H' wave.
These experiments seem to suggest that in Friedreich's ataxia and possibly in some other cases, the stretch receptors lose their sensitivity although the afferent pathway is still capable of conducting impulses to the spinal cord and evoking a reflex contraction of the muscles.

One possible explanation is that there may be some primary disturbance of the muscle spindles themselves. This, however, seems unlikely because as far as we know, skeletal muscle is not primarily affected in Friedreich's ataxia. I have not had the opportunity of obtaining a muscle biopsy from such patients but hope to be able to do so.

The notion that 'the general facilitatory and inhibitory systems of the brain stem are instrumental in determining the level of tonic discharge through the spindle loop as well as switching it on and off' (Granit: 1955) has received some support from the work of Granit and his colleagues. Granit's conception of the innervation of skeletal muscle is now well-known. It is summarised by the diagram shown in Fig. 8. It provides a plausible explanation for the situation in Friedreich's ataxia.
Fig. 8: Granit’s conception of the innervation of skeletal muscle. (After Granit, 1955).
It has been shown (Granit and Kaada: 1952) that in cats, at any rate, there is tonic firing in the gamma fibres and that this is to a large extent controlled by supraspinal influences. Is it possible that when these are permanently withdrawn by a lesion in the pathway, the gamma motoneurones cease to regulate the muscle spindles which ultimately become insensitive?

We have some information about the behaviour of de-efferented spindles. For instance Eldred, Granit and Merton (1953) in their work on single spindle afferents have noted that whereas the normal spindle shows tonic discharge at rest, the de-efferented one is silent at rest, has a higher threshold to stretch and adapts considerably - the rate of firing having been more than halved after half a minute of stretch at a constant tension.

As early as 1919 Liljestrand and Magnus had shown that the stretch reflex in cats could be abolished by intramuscular procaine and in 1947 Sarnoff and Arrowood produced a differential spinal block with procaine - that is, the abolition of reflexes with no change in motor power or proprioception.

Leksell (1945) suggested that the gamma fibres were more sensitive to procaine than the large alpha efferents. This was confirmed by Matthews and Rushworth (1957) who also showed that the stretch reflex and tendon jerk could be paralysed at a time when the motor response of the muscle was otherwise unchanged.
There is, therefore, reasonably good evidence from both human and animal experiments that blocking of the gamma efferents can abolish the tendon jerk by making the spindles insensitive to stretch without interfering with the afferent pathway proximal to them.

These were all acute experiments. It would be interesting to know something of the behaviour of spindles which have been de-efferentated for a long time. I have only been able to find one reference to this. Tower in 1932 described the histological changes in muscle spindles following section of the anterior root. At first atrophy occurred solely in the polar regions of the spindles but eventually the equatorial regions became affected.

There remains one possible alternative explanation that might fit the results. It may be argued that a partial lesion in the afferent loop of the reflex arc may allow the well-synchronised impulses produced by electrical stimulation to pass while interfering with the rather more dispersed ones produced by mechanical means. This is unlikely in view of the results of the cuff experiment. Ischaemia affects the large afferents first and produces an increasing block in these fibres. Here, both the ankle jerk and the 'H' wave disappeared and reappeared simultaneously.

So far, I have concentrated on what I might call the 'peripheral' part of the argument. I have presented evidence suggesting that spindles which have been de-efferentated eventually become insensitive
to stretch. The weakest part in my argument is the suggestion that
with the withdrawal of supraspinal excitatory influences the gamma-
mitoneurones cease to fire. The only evidence I have for this is
indirect - the case of the girl with the brain stem lesion who lost
her ankle jerks. It seems likely that this sort of disturbance
can occur. That it does occur in Friedreich's ataxia can only be
inferred.

Gilliatt (1961) has been studying this problem from a different
point of view. In his cases of Friedreich's ataxia he has found it
impossible to record nerve action potentials from the lateral popliteal
nerve with stimulation at the ankle. He suggests that there is
peripheral nerve involvement that is responsible for the loss of
ankle jerks. I do not think that his interpretation is valid
because:

1. His cases were not 'pure' cases of Friedreich's
ataxia. They showed muscle wasting and blunting
of superficial sensation. This type of case has
been excluded from my series because the loss of
tendon jerks does not constitute a problem.

2. The technique of recording sensory action potent-
ials from the lateral popliteal is an extremely
difficult one. The signals recorded from normal
subjects are of the order of a few microvolts and
failure to record them cannot be considered as
evidence of peripheral nerve involvement.
2. cont. Writing about nerve action potentials recorded from the ulnar nerve where the signal is usually about ten times that in the lateral popliteal, Gilliatt (1958) remarks that the action potentials 'were always small and in some obese but otherwise normal subjects they were altogether absent.' If this is true of the ulnar nerve is it not even more likely to be so of the lateral popliteal?

3. He used a constant current stimulator which may not have given wide enough pulses to stimulate the sensory fibres.

4. It is the medial, not the lateral popliteal nerve that is concerned with the ankle jerk. It does not necessarily follow that because the lateral popliteal is involved, the medial popliteal should be affected as well.

My results do not exclude the possibility that changes in the posterior root or peripheral nerves may contribute to the absence of tendon jerks in Friedreich's ataxia. I am only pointing to another important contributory factor, namely a withdrawal of excitatory influences which normally travel down the gamma-system.
SUMMARY

The basis behind the absence of ankle jerks in Friedreich's ataxia is obscure. The common explanation, that it is due to 'interruption of the reflex arc on the afferent side; is too vague.

If square pulses of the order of 1 m.sec. duration are used it is possible to stimulate the afferent fibres in the medial popliteal nerve and to obtain a reflex contraction of the calf muscles (the 'H' wave of Magladery). This wave is easily obtainable in patients with Friedreich's ataxia who have absent ankle jerks, as distinct from cases of tabes dorsalis, peripheral neuropathy and Holmes-Adie syndrome in which the 'H' wave is not obtainable.

The monosynaptic reflex arc is therefore intact proximal to the stretch receptors. It is suggested that spindle depression may result from absence of supraspinal facilitation.
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