HEREDO-FAMILIAL TENDINOUS AREFLEXIA
WITHOUT PUPILLARY CHANGES*

BY

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In 1926, in conjunction with Dr. A. Klaus, I observed a family in which on routine clinical examination a generalized tendinous areflexia was found in a man of 39 years and in two of his sisters. This constitutional abnormality was not associated with any symptomatology. This observation was placed on one side in the expectation of other similar cases appearing. Adie's (1932) description of tendinous areflexia with tonic pupils and of hereditary dystastic areflexia (Roussy and Lévy, 1932) have aroused fresh interest in the subject of essential tendinous areflexia.

Early in 1938 another family with similar areflexia came under our observation. As one of the patients died from an intercurrent affection we are able to present the first pathological report dealing with this peculiarity.

Clinical observations

The L . . . family (1926). (Fig. 1.)

Father A. L. 61 years old. Suffered from coronary sclerosis. The blood

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Wassermann was negative and there was no evidence of syphilis. The pupillary reflexes and the ocular fundi were normal. There was a fine tremor of the upper limbs.

Mother L., 58 years old. She was in excellent health and had seven children living. She had had a left ovariectomy performed at the age of 43 years.

Jean L. (II/1). 30 years old. He suffered from jaundice at the age of 30 years and had a tendency to biliary congestion, headache, and indigestion. A friend was diagnosed as a case of cerebral tumor; L., very worried, went to Dr. Klaus and demanded a complete examination with lumbar puncture to make sure this diagnosis could be ruled out in his case. On examination in 1926 we noted the absence of the ankle, knee, biceps, triceps, cubital-pronator, and radial jerks on both sides and also the jaw jerks. The abdominal reflexes were obtainable and the plantar responses were flexor. There was no cerebellar or sensory disturbance, no abnormality of the cranial nerves. Pupils reacted normally and the ocular fundi were normal. Examination of the cerebro-spinal fluid (21st August, 1926) showed clear fluid; 1·7 cells; albumin 20 mgm. per 100 c.c.; Wassermann negative; colloidal benzoin negative. The blood Wassermann was negative.

Anne L. (II/2). 28 years old. Married at the age of 21 years and has two children alive and well with normal tendon jerks. Neurological examination (10th March, 1927) revealed the absence of ankle, knee, biceps, triceps, cubito-pronator, radial, and jaw jerks. The abdominal reflexes and plantar responses were present and ocular fundi were normal. Blood Wassermann was negative.

Hélène L. (II/3). 26 years old. Married at the age of 23 years; has one child alive and well with normal reflexes and pupils. Neurological examination revealed the absence of ankle, knee, biceps, and triceps jerks. The jaw jerk and the radial and cubito-pronator jerks were present. The pupils and ocular fundi were normal. The blood Wassermann was negative.

Four younger children, ranging in age from 24 to 17 years, showed no neurological abnormalities in 1927.

Out of seven children of one family the three eldest showed tendinous areflexia. It was impossible to establish the date of onset of this abnormality. According to Jean (II/1) it had always existed in his case and he was certain that at the age of 17 he and his sisters had discovered the absence of the reflexes by comparison with the brisk tendon jerks of their younger brothers and sisters.

In these three cases it was not possible to elicit these reflexes even with the aid of the well-known methods of reinforcement: the techniques of Jendrassik, of Justmann, of Monteinezzo, of Brun, of electric current, of the cold bath as advised by Beevor, and in one patient (Jean) an injection of adrenalin, as advocated by Schmidt, all gave negative responses. On re-examination in 1938 the abnormality was still present and had not progressed, the same reflexes being absent as in 1926–7. In the case of Hélène (II/3) the cubito-pronator, radial, and jaw reflexes were still present.

This type of tendinous areflexia appears not to progress. All or only some of the tendon jerks may be affected. The pupillary reactions remain normal, as do the cutaneous reflexes. There are no trophic, muscular, cerebellar, or sensory disturbances to suggest that the areflexia be part of a more complex clinical syndrome. The areflexia is not present in the parents. The negative serological examinations in the parents and their children, the absence of any clinical sign to suggest syphilis, and the negative cerebrospinal fluid in one of the children rule out the possibility of the condition being hereditary tabes.
The P... family (1938). (Fig. 2.)

Mother P. (1/1) died aged 59 years of carcinoma of the uterus.
Father P. (1/2), aged 71 years, is still living. Diffuse senile cataract; tendon jerks present; pupil reactions normal; Wassermann negative; no mental trouble.

This man and woman had 11 children, of whom 9 are still alive and 8 could be examined.

Hélène P. (II/1). 59 years old. Amenorrhea; no children; pupillary reflexes and ocular fundi normal; X-ray of dorsal and lumbar spines revealed nothing unusual; Wassermann negative.

Pierre P. (II/2) died aged 6 years of pulmonary tuberculosis.

Marie P. (II/3) died under our care 1st February, 1938, and was the subject of a histo-pathological examination. At the age of 18 years she suffered from rheumatic fever with involvement of the heart. Married at the age of 21 years, she had four children. She suffered from metrorrhagia at the age of 52 years. She has never complained of any nervous symptoms. For two years previous to admission on 25th January, 1938, she suffered from palpitations and from pain in the left breast extending into the back. Òedema of the lower limbs came on two days previously. She had menorrhagia and hypertrophic metritis of the cervix. She had tachycardia with some irregularity and on auscultation a mitral systolic murmur was heard. The urine was scanty. The liver was slightly enlarged and there was Òedema round the ankles. No albumen or sugar were reported in the urine. Blood urea was 31 mgm. per cent.; the blood Wassermann was negative. Neurological examination showed absence of all tendon jerks except the right ankle jerk, which was at times obtainable, but very much diminished. No method of reinforcement (Jendrassik, Justmann, Monteinezzo, Brun) evoked the tendon reflexes. All the cutaneous reflexes were intact. The jaw jerk was absent. The pupils reacted to light and on accommodation. The ocular fundi were normal. An adrenalin test was carried out on 26th January, 1938; no return of reflexes was noted. Cerebrospinal fluid examination was as follows: albumin 25; cells 0.3 mgm. per 100 c.c.; Wassermann negative; benzoin normal. X-ray of the lumbar and sacral spines showed no abnormality. She was again admitted to hospital on 31st May, with severe cardiac failure, and died the next day.

Marie P. (II/3) has four children. The eldest, a daughter (III/1), is 18 years old and quite healthy; pupil reactions are present and tendon jerks are normal. No abnormalities of the vertebral column are to be seen. The second child (III/2) a tall, thin boy, shows an absence of all the tendon jerks, including the jaw jerk. Pupil reactions are normal. Ocular fundi are normal. In the third and fourth children (III/3) and (III/4) the jaw, pupillary, and tendon reflexes are present and they are psychologically normal.

Louis P. (II/4) died at the age of 39 years of "depression," leaving two children: a son (III/5), who has been examined and shows no abnormality; he is married and
has a son aged 2 years (IV/1) alive and well with reflexes present. A daughter (III/6) is unmarried; she is well and her pupil and tendon reflexes are present. X-ray of her lumbo-sacral spine is normal.

Gregoire P. (II/5) is alive and well, as are also his two children (III/7 and III/8). He has been examined and his nervous system found to be normal. The two sons have spasmodic rhinorrhœa.

Jeanne P. (II/6) is 46 years old and shows various tics. The tendon jerks are abolished in the lower limbs with preservation of the abdominal responses. No pupillary troubles are present. Ocular fundi are normal. She has no clinical signs to suggest a spina bifida. The blood Wassermann is negative. Adrenalin test has not been carried out. Cerebrospinal fluid examination—2 cells; albumin 20; Wassermann negative.

Émile P. (II/7) is 43 years old and unmarried. Examination is completely negative except for signs of hypertrophic rhinorrhœa and emphysema. No spinal abnormalities are present. Wassermann is negative.

Rosa P. (II/8) is aged 41 years and single, with normal intelligence, absence of knee and ankle jerks and of the biceps, cubital, and radial reflexes. The cutaneous reflexes are present. No pupillary abnormalities are to be found. The blood Wassermann is positive. X-ray of the dorsal and lumbar columns is normal.

Of eleven children three females show tendinous areflexia. The areflexia is not accompanied by any other neurological signs and the subjects themselves have been unaware of their peculiarities. This areflexia is limited to the lower limbs only in one case (II/6). The pupil reactions and the abdominal reflexes are obtainable in all cases. The serological reactions have been negative. Examination of the cerebrospinal fluid in all cases in which it has been carried out has been negative. Generalized tendinous areflexia has been found in one child out of the four children of one patient with areflexia (II/3). Of the other areflexic patients (II/6 and II/8) one is married but without children and the other is single.

After the histological examination of case II/3 with the discovery of "peripheral neural angiomatosis" we reviewed the condition of the patients in this family. Dr. Bauwens, ophthalmologist of the Bunge Institute, was kind enough to examine the retinæ of all the subjects and evidence of other malformations was sought for by us. These investigations proved completely negative.

A study of these two families permits the following observations to be made.

A. The absence of tendon reflexes seen in these two families is quite independent of any obvious somatic abnormalities or trophic changes and is not the result of hereditary syphilis.

B. The jaw jerk may remain in these families. It seems difficult to infer from its absence if the areflexia is congenital or acquired in nature.

C. The cutaneous reflexes are always present.

D. It has not been possible to obtain the tendon reflexes in these patients by any of the usual methods, not even by an injection of adrenalin.

**Post-mortem Findings**

Patient number II/3 of the P. family died from heart failure due to rheumatic carditis. Complete autopsy was kindly carried out by Dr. H. J. Scherer. Special interest is attached to the findings in the nervous system.
The left sciatic nerve was of normal thickness and showed no external abnormality. On a longitudinal section of this nerve it was observed that the centre was made up of a dark yellow tissue with grossly dilated veins. Unfortunately no other nerves were examined. The brain was of normal size and configuration and weighed 1,425 gm. The vessels of the base and meninges showed no abnormality. Section through the frontal lobes revealed no enlargement of the ventricles and the boundaries of the white and grey matter were everywhere distinct. The brain stem, the cerebellum, and the spinal cord appeared normal to the naked eye. Microscopic study of the central nervous system failed to reveal any pathological alteration whatever. The angioma on the sciatic nerve constituted the sole abnormality.

Sections of the nerve stained with Van Gieson's stain showed very few myelinated fibres (Fig. 3). The centre of the nerve was occupied by a series of cavities visible to the naked eye, which, in sections stained with hematoxylin-eosin, were seen to be made up of venous channels (Fig. 4). There was an endothelial inner layer, variable in thickness. Immediately outside it was a thick muscular coat replacing the middle tunic. This middle layer varied in thickness according to the level of section. Directly outside the muscular coat there was a layer of adventitial connective tissue of normal appearance (Fig. 5). The vessel wall showed neither hyaline degeneration nor calcification. Nowhere was any evidence found of true tumour formation, despite the appearance of infolding of the walls. In no place was there true localized
hyperplasia of the muscular coat. Elastic stains showed that at certain points the walls had elastic fibres present in the middle tunic; this did not form a continuous elastic coat.

We are of the opinion that the histological picture is essentially a malformation of the venous system. This appearance closely resembles that seen in venous angiomata situated in the brain. On comparing the pictures of our case with those of Buckley's case (reproduced in Cushing and Bailey's book (1928)) the resemblance is very striking. In the case described in this paper apparent infoldings of the vessel walls may be seen and in the same blood vessel the thickness of the walls may vary. Also the composition of the vessel wall itself varies from section to section. In some places there are two layers of fine muscle fibres running in different directions with but little connective tissue, whereas in other places there is little muscular tissue but much thick connective tissue. This apparent proliferation of the fine muscular fibres is at times so
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dense as to suggest in longitudinal section an artery. Similar vascular malformations in cerebral venous angiomata have been described by Bergstrand (1936).

Discussion

We have searched in vain for analogous cases in the literature at our disposal. In a case of Bergstrand's, with a tumour of the finger, a racemose angioma, malformed vessels of large aperture were observed within the actual large nerve trunks. Through Dr. Bergstrand's kindness we have been able to study the original sections of his case; the appearance of the lesion, however, differed from those observed in our own cases.

Apart from the rarity of the case, the great interest of this histological observation is that it shows areflexia does not depend on demonstrable alterations in the cerebrum, cord, or roots, but that it is associated with anomaly in the nerve trunks—an angiomatous malformation. Since all the nerve trunks were not examined this view must be put forward with reserve.

An embryological basis for this condition is worthy of consideration, and we owe to Professor Dalcq the following information. In the early stages in the development of the posterior limb the principal arterial and venous channels follow the fibres of the great sciatic. Following the formation of the ventral derivative, which is made up of the femoral arteries and vein, the crural part of the sciatic vessels shrinks. Of the latter artery there remains the nutritive branch to the sciatic nerve. The vein disappears in the crural region but persists lower down as the small or external saphenous nerve. The crural part of the sciatic vessels occupies in our case the whole thickness of the sciatic nerve,

Fig. 5.—The endothelial layer is recognizable lined by a first layer of transverse connective fibres. This corresponds to a thicker muscular wall (middle tunic).
the nerve fibres of which are scarcely detectable, and the appearance of this angiomatous formation argues in favour of its embryonic character. Such a malformation would correspond therefore with an anomaly in the development of the primitive vascular plexuses of the nerve sheath, in the same way as one associates the occipital angiomata with dysplasias of the posterior plexus of the primitive vascular anlage and of the dura mater.

In considering similar cases one may classify the sporadic tendinous areflexia described in the literature into six groups:

1. The sporadic tendinous areflexias without any associated neurological or mental symptoms. Cases I and II of Goldflam (1911), of Nelki (1921), IV of Strohmayer (1919), I and II of Noica and Bistriceanu (1923), I, II, and III of Curveillé (1935), and I and II of Riser, Valatz, and Sol (1931) belong to this group.

2. The sporadic tendinous areflexias with mental symptoms. A good example is the case of Ducoté (1926), and those with a neuropathic heredity as described by Friedman (1930), von Hösslin and Gottberg, or with signs of mental degeneration—Sommer (1901) and Schmidt (1918).

3. The sporadic tendinous areflexia with vertebral or neural malformations. Such are the observations of Trömner (1919), Goldflam (1911), Babonneix and Debeayer. The coexistence of vasomotor and trophic disturbances has led Lewandowsky and Hirschfeld (1919) to interpret this partial areflexia as a sign of malformation of the reflex connections within the cord itself.

4. The sporadic tendinous areflexias suggestive of syphilis. The cases of Siebert (1916) are good examples. All those occurring before serological diagnosis should be accepted with reserve. Hereditary syphilis of the third and also of the fourth generation is well-established to-day (Brun, 1934).

5. The so-called congenital sporadic tendinous areflexia in which another toxic or infective cause can be evoked. Friedman’s (1930) patient was an alcoholic with depression.

6. The areflexias noted in the course of neurological disease which do not normally show these signs, such as epilepsy (Goldflam (1911)), Parkinsonism (Goldflam, Mendel and Graeffner), and essential tremor (Lewandowsky).

In such a classification, the necessity for following up patients with areflexia before admitting that the disorder comprises a constitutional abnormality is obvious. Nelki (1921) recalled that Westphal’s (1916) case was observed over a course of twenty-seven years, but that four years after publication of the case report—that is, thirty-one years after the areflexia had been noted for the first time—the clinical development of the case showed that it was one of true tabes dorsalis. We have been following our first family A. L. for twelve years and would not have published it had not the case examined histologically in the P. family allowed us to show that these areflexias may have no medullary or root lesions of syphilitic type as a substratum. We understand, therefore, why some neurologists, as Emil Redlich (1924), have refused to admit the existence of a constitutional tendinous areflexia. In one of his most recent works Redlich, before admitting the authenticity of a constitutional areflexia, says that four conditions must be fulfilled. First, the areflexias
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should be congenital, or at least not have appeared following an illness of which areflexia could have been a sign. Secondly, it should not be accompanied by any other neurological sign which would allow one to interpret it as part of another syndrome. Thirdly, a monosymptomatic areflexia is unlikely to be the result of a constitutional degeneration. Fourthly, the central and peripheral nervous system and the muscles of such a case should be recognized as "histologically" normal. Redlich justified his reserve by emphasizing that there does not exist any histological observations of such a malady. We agree entirely with Redlich’s reservations, though it should be recognized that the observations in the first family, recorded above, satisfy three of the conditions which he lays down.

Are such cases of areflexia common? Opinion differs considerably. Pelizaeus, quoted by Trömner (1919), puts the incidence in the general population as 0·04 per cent., while Sternberg, quoted by Curtius (1928), gives a figure of 0·016 per cent. Tromner found in 23,000 patients, whereas Curveillé (1935) discovered three during systematic examination of army officers. Nelki (1921) collected seven such cases. Kehrer (1937) believed the frequency to be comparatively high and stated that the presence of areflexia or of tendon hyporeflexia, with hypotonus in some cases, but always without ataxia, was not an exceptional finding in the course of a busy neurological practice. He himself collected five cases with associated stigmata of degeneration such as mental defect. It has been our own impression that these cases of pure and sporadic tendinous areflexia are rare. We have no valid evidence for believing that the cases of tendinous areflexia which we have observed belong to the group which Adie (1932) described. There is no reason either to associate the forms described here with an incomplete variety of hereditary areflexic dystasia (Roussy and Lévy, 1932).

Conclusion

A familial, sometimes hereditary, disorder, characterized by generalized or partial tendinous areflexia and unaccompanied by any neurological or psychical disorder, has been described. It has occurred in two families. Autopsy in one case showed no abnormality in the brain, spinal cord, or peripheral roots. The left sciatic nerve contained few myelinated fibres and a venous angioma.

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