THE MORBID ANATOMY OF A CASE OF HEREDITARY ATAXY.

(No. VI. of *Dr. Sanger Brown's Series of Cases*).

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WITH AN INTRODUCTION BY DR. SANGER BROWN.

BY way of introduction to Dr. Adolf Meyer's Anatomical Report, and with the purpose of rendering the same more easily understood by those who have not read, or who do not distinctly remember, my clinical report of the series published in 1892, in *BRAIN*, and in the *North American Practitioner*, I now reproduce my original diagram, showing how the disease was transmitted, and the ages at which the respective subjects of it were attacked, with other data calculated to give a fairly good general idea of the nature of the symptoms, and a more particular clinical report of the case which furnished the material for Dr. Meyer's report.

For the purpose of giving a general idea of the symptoms in my series, perhaps I cannot do better than to quote from my original paper :—

“Taking these cases alone for a text, and assuming them to be cases of hereditary ataxy, the following diagnostic criteria might be fairly deduced :—

“Hereditary ataxy is a disease which may be traced through several—at least four—generations, increasing in extent and intensity as it descends, tending to occur earlier in life, and advance more rapidly. It usually attacks several members of the same family. It occurs most frequently between the ages of 16 and 35, but it may begin as early as 11 and as late as 45. It shows no marked preference for sex, but it descends through females four times as frequently

as through males. The influence of an exciting cause can rarely be demonstrated, but in some instances a fall or injury has appeared to determine the onset; and any cause like child-bearing or lactation, which very much depresses the vital forces, may produce a rapid advance of all the symptoms. There is always considerable incoördination of all the voluntary muscles, and a sluggishness of the movements, which they produce when the disease is well established. This is usually noticed first in the muscles of the legs, but in a few months or years extends to the arms, face, eyes, head, and organs of speech. Sometimes it occurs first in the upper extremities, and sometimes in the organs of speech.

"The ataxy is often extreme, and the gait devious, the patient deviating several feet on either side of the intended line of progression, before he loses the power of walking. The ataxy is not markedly increased by closure of the eyes. The sense of posture is perfect.

"Some weakness of the muscles of the legs, without atrophy, is frequently an advanced symptom, and occasionally there is permanent spastic contraction of the legs. In developed cases there are usually choreiform movements of the head, and often of the arms, accompanying all voluntary movements. These irregular movements occur in the hands, legs, or head whenever it is attempted to maintain either of these parts in a fixed position by a voluntary muscular effort.

"There is usually some degree of static ptosis, with overaction of the levator on looking upward. In rare cases there may be temporary diplopia in the early stages, due to weakness of the external rectus. There is no nystagmus of any kind.

"Atrophy of the optic nerve is a constant and early symptom, and usually progresses slowly with the other symptoms. Rarely it begins earlier in one eye than the other.

"The response of the iris to light and accommodation is sluggish, and diminishes with the advance of optic nerve atrophy. When this latter is complete, as may happen in

advanced cases, there may be complete internal and external ophthalmoplegia.

"There is always marked disturbance of the articulation, probably due to incoördination of the muscles concerned, for weakness cannot be demonstrated. In some cases there is a troublesome tendency to strangulation in swallowing liquids, due to their getting into the larynx, but otherwise swallowing is in no way difficult.

"Occasionally the sphincters are slightly, but positively, affected, this symptom only appearing in those cases where spontaneous pains in the legs co-existed, having some of the characteristics of those occurring in locomotor ataxy. Excepting the spontaneous pains already mentioned, there is no disturbance of sensibility. There are no vaso-motor or trophic symptoms, but there is a marked tendency to emaciation; there is no hypertrophy or valvular lesion of the heart.

"The knee-jerk is always exaggerated, and there is frequently ankle-clonus, and the cutaneous reflexes are also always exaggerated, but to a less degree. The exaggeration of the reflexes is an early symptom, and they often decline considerably when the disease is far advanced.

"There is never paralytic club-foot, nor any other deformity, excepting rarely permanent spastic contractions of the legs in advanced cases. In none of these cases have the patients ever suffered from rheumatism, so far as I can learn.

"I wish to repeat that the above summary of symptomatology of hereditary ataxy is only intended to apply to this particular series of cases; and I have only presented it in this way so that it might be the more easily compared with other series."

I shall again quote from my original paper the description contained of case vi., upon which Dr. Meyer's report is based.

"*Case VI.*—Female, age 63. First symptoms at 45, consisting of ataxy of legs. The course of the disease has been slow. She can still walk on an even surface without assistance, but has to go very slowly and sways about considerably, usually steady-

FAMILY TREE OF HEREDITARY ATAXY.

reported by

Dr. Sanger Brown

ing herself by holding on to furniture. The hands are certainly involved, but not greatly, as she can still do needlework and pour tea. Vision is considerably affected, but she can read coarse print in dim light. Cannot read in a bright light. Speech has become very slow, but is quite distinct. General health fairly good. Other symptoms negative. History given by a relative, himself affected, who has seen her almost daily for years."

This person died at the age of 67, of tubercular diarrhoea, from which she suffered for several months. About four months prior to her death, the neck of the femur was fractured by a fall, after which she was unable to leave her bed. Dr. R. L. James had been her medical attendant for over a year prior to her death, and noted very carefully the symptoms pertaining to her nervous disease, which he was particularly well qualified to do, inasmuch as he had in the past four years been medical attendant to, and seen almost daily, socially or professionally, two nephews and a niece of the patient who suffered from the same disease. He states that the knee-jerks were greatly exaggerated, but that there were no sensory symptoms of any kind; that there had been marked failure of vision two years at least before death, so that the patient was unable to read, but could see sufficiently well to play cards. She had lost the power of walking alone for at least two years before breaking her thigh, and for the last year she had been unable to do needlework or pour tea, though she could still manipulate cards fairly well. The facial expression for the last eight or ten years of life was highly characteristic, that is to say, the partial ptosis and relaxation of the facial muscles, being suggestive of somnolence when in repose, but when in animated conversation there was over-action of some of the muscles of expression and under-action of others, giving the face a very peculiar appearance. There was never any evidence of mental disorder.

The autopsy was performed under great difficulties, and the brain reached me in a rather lacerated condition, in Müller's fluid. Unfortunately there are no data on hand on the autopsy, the fresh appearance of the tissues, the weight of the brain, and especially the cerebellum. The

latter was centrally softened, as far as could be ascertained, owing to the slow action of Müller's fluid in the very warm weather. The spinal cord was well preserved. Of the brain, the medulla oblongata, cerebellar cortex, and the optic nerves and tracts were taken for examination. In absence of macroscopic description we proceed at once to the study of the sections.

Spinal Cord.—Sections from the lumbar, lower and upper thoracic and cervical cord were made. For the study of the corpora amylacea a short fixation in Müller's fluid, and subsequent alcohol hardening proved satisfactory for a stain with Bohmer's hæmatoxylin. The other specimens were completely hardened in Müller's fluid, and, with or without a total stain in a 1 per cent. carminate of sodium solution, dehydrated and embedded in the usual manner. The stain for the medullated fibres, was Wolter's modification of Weigert's method, with or without counter-stain by 0.5 per cent. acid fuchsine.

The cross-section of the cord is not thinner than might be expected in a woman of 67. The diameters are as follows:—

		Transverse.	Antero-posterior.
Cervical enlargement	...	10.8 mm.	8.5 mm.
Mid-dorsal region	...	7.0	7.0
Lumbar enlargement	...	9.5	8.0

The specimens stained with Böhmer's hæmatoxylin after a short fixation in Müller's fluid, show a remarkable number of corpora amylacea throughout the spinal cord, the bodies are distributed very much as Redlich represents them in his drawing.¹

They are most numerous in the dorsal half of the cord, especially in the entrance zone of the posterior roots, where they are arranged in strings of several layers; further along the posterior septum, in the subpial neuroglia layer, along blood vessel septa, and all through the posterior columns. In the lateral columns they keep near the surface; they are

¹ E. Redlich, Die Amyloidkörperchen des Nervensystems. *Jahrbücher f. Psychiatrie.*, vol. x., 1892, p. 23.

relatively rare in the anterior columns and anterior horns and practically absent in the rest of the gray matter and in the ground bundles. In one posterior root zone over two hundred can be counted readily. They vary in size, and are easily distinguished from the much smaller nuclei. As Redlich, Koller and others have shown, they occur frequently in old people, but I have not been able to obtain such an excessive number in any of my cords, nor could any one show me similar specimens. We must say though that in the ordinary staining methods the granules do not present themselves as clearly as in a specimen which was not very long in Muller's fluid. The material of comparison is therefore not quite fair.

The neuroglia and the blood vessels were examined with a stain of Ehrlich's hæmatoxylin and subsequent counter-stain with picric-acid fuchsine solution. This stain gives a very satisfactory bright colour to the mesoblastic connective tissue, while the neuroglia proper remains a duller red.

The pia is somewhat thickened, from 0.1—0.15 mm. over the lateral columns, but only about 0.025—0.04 over the dorsal columns, and 0.04—0.05 over the anterior. The blood vessels are normal in number, and there is very little if any hyaline degeneration of the muscularis of the larger ones.

The neuroglia is somewhat increased in the whole extent of the subpial neuroglia layer. The latter measures about 50μ over the dorsal columns, about 25μ over the ventral half, and over the dorsal part of the lateral columns and the posterior root zone it varies between 40 and 100μ . Fromann¹ says the diameter of the neuroglia margin varies between 0.01 and 0.06 mm., according to Goll from 0.02 to 0.03 mm. Kölliker² states that the layer varies from 0.022 to 0.045 mm. There is no doubt, therefore, that the increase is fairly well marked in our case. In the region of the pyramidal decussation this is quite plain, since the thickening is limited to the extent of the cerebellar tract.

¹ Fromann, Untersuchungen über die normale und pathologische Anatomie des Rückenmarkes. I. Theil, 1864, p. 28, quoted by Weigert, Beiträge zur Kenntniss der normalen menschlichen Neuroglia, Frankfurt, 1895, p. 146.

² Kölliker, Handbuch der Gewebelehre des Menschen, 6. Aufl. Vol. II. 1896, p. 151.

The neuroglia of the rest of the cord will be spoken of in the analysis of the various tracts.

Lumbar Cord.—The roots are quite normal. *The posterior columns* have a normal proportion of thick and thin fibres. It is hardly possible to detect anything abnormal; perhaps the neuroglia septa are slightly broad in the central portions of the posterior columns. But it is impossible to make out anything but a faint similarity with Flechsig's¹ or Marinesco's² figures since the roots, and especially the lateral part of the middle root zone are quite normal; only the mesial part of Flechsig's middle root zone may have a slight increase of neuroglia.

The amount of fibres and collaterals is quite normal in the gray matter; the motor cells, though pigmented, show mostly a well defined nucleus near the centre of the cell body.

The antero-lateral columns are densest close to the gray matter (ground bundles). The region of the pyramidal tracts shows very few thick fibres, but no striking increase of neuroglia.

In the *Thoracic* region nothing deserves special notice besides the condition of Clark's columns. The number of their cells is decidedly small. The cells that remain are partly normal, partly show a change which I noticed often in general paralysis and elsewhere, and which Marinesco³ has lately described in cases of locomotor ataxia.

The normal cells, very few in number, have the nucleus round, and in the centre or near it. The granulations, of course, are not visible, since the hardening with Müller's fluid rarely preserves them. The larger number of the cells are more vesicular; the nucleus is pressed to the periphery and is crescent shaped. There are further a few cells which are quite shrunken and have no differentiation. There can

¹ Flechsig, Ist die Tabes dorsalis eine "System-Erkrankung." *Neurolog. Cbl.* Vol. IX. 1890, p. 73, fig. 6.

² Marinesco, "Lésions de cordons postérieurs d'origine exogène." Part V. of "Babes' Atlas," plate VII.

³ Sur une particularité de structure des cellules de la colonne de Clarke, et sur l'état de ces cellules dans le tabès simple et dans le tabès associé à la paralysie générale, par G. Marinesco. *Revue Neurologique*, 4e Année, Nov. 15, 1896, p. 633.

be no doubt that these findings stand in some connection with the condition of the cerebellar tract mentioned below.

The posterior and antero-lateral columns show no deep lesion. Their condition stands about midway between that found in the cervical and the lumbar regions with regard to the increase of neuroglia and the proportion of thick to thin fibres.

The Cervical Cord.—Here we find a number of very pronounced alterations.

The *posterior columns* show a field of degeneration along the middle of the septum; the superficial part of Goll's column is also affected, though less markedly, and, on either side, the transition area between Burdach's and Goll's tracts

is somewhat rarefied. In the normal cord most of the fibres in these regions are of moderate thickness, forming plain rings with the Weigert stain; thin fibres, with almost no lumen, are rare. In our sections many of the thick fibres are gone, and also the thin fibres are scarcer. The neuroglia is correspondingly increased, the blood vessels are a little wider and surrounded by thick neuroglia masses. The changes are somewhat more diffuse and less marked than in tabes.

The *lateral columns* of the *normal* cord show a layer of thick fibres plainly limited all along the surface of the pyramidal tract, but less distinctly outlined in the region of Gowers' antero-lateral tract. The distinction is formed by the fact that the fibres of the direct cerebellar tract have very few collaterals, while these are abundant in the pyramidal area and also in the ground-bundles and a little less in the antero-lateral columns. The collaterals show with the Weigert stain under a low power (Reichert or Leitz 3) as points without lumen; under a higher power (Reichert 7) they show a small lumen, except the smaller ones, which are point shaped.

In our case, we notice at once the diminution in size of the direct cerebellar tracts. Only relatively few large fibres are left, and they are separated by neuroglia. In the normal cord, this area, so free from neuroglia and collaterals, is about 0·4—0·5 mm. broad; in our sections, the atrophic area measures 0·15 mm. at the most on the side where the proliferation of neuroglia is less marked; on the other side it is of normal breadth (0·4—0·5 mm.), but containing much interstitial neuroglia, fewer fibres, and broader blood vessels. Farther ventrally beyond about the middle of the lateral columns the area loses its demarcation rather suddenly, and all we can see is a general deficiency of thick fibres along the surface. On the one side the bundle is rarefied *en bloc* for 2·2 mm. from the posterior root and superficially only with a little less demarcation for further 2·4 mm. (fig. 1).

The fibres which remain are very large, averaging a diameter of 10·15. Throughout the rest of the anterior and lateral columns there are only few fibres of this size in our

specimens, while they are fairly numerous in the normal throughout the pyramidal tracts and the antero-lateral tract area. The direct pyramidal tracts show a slight increase of neuroglia, the lateral pyramids lesser. It is hardly possible to make out Gowers' tract; all we can say is that the ground-bundles are denser and richer in collaterals than the more superficial layers.

The gray matter shows no evident alteration.

Transition into the Medulla.—All we have to note is the extension of the changes described; hardly any change in the pyramids, slight degeneration in the posterior columns, and especially degeneration of the direct cerebellar tract on both sides, not complete, but leaving a triangular area with scanty large fibres, broad neuroglia septa, and especially a well-limited thickening of the marginal neuroglia layer. The field is decidedly smaller than normal (it is easy to see it in the normal canine specimens and also in Weigert sections). The thick fibres of the antero-lateral tract (ventral cerebellar) are also rare, but not kept apart by neuroglia.

Medulla Oblongata.—The medulla had been torn off from the pons at the autopsy and was not satisfactory for a careful examination of the topography. All we can say from the sections is that the area of the direct cerebellar tract continues as described and then disappears in the restiform body, where at best a slight rarefaction of fibres can be made out. The ventral cerebellar tract has few large fibres and is somewhat pale. The olives have a normal amount of fibres and cells. The pyramids are slightly less dense than normal.

Cerebellum.—Only pieces of the cortex of the hemispheres are examined. The folia are hardly atrophic as a whole. Nothing can be made out but, perhaps, a slight reduction of then umber of Purkinje cells in a few parts. This also occurs in normal specimens, although perhaps less than here. Other folia have a very large number of perfect Purkinje cells.

The *optic nerves* are free from degeneration, and also from neuroglia-overgrowth.

In the monograph of Londe,¹ the autopsies of Fraser,

¹ Londe, "Maladies familiales du système nerveux. Hérédotaxie cérébelleuse." Paris, 1895.—See BRAIN, 1895, p. 421.

Nonne and Menzel are discussed. Our case seems to be the first addition since Marie established the clinical picture of cerebellar heredo-ataxia. On account of the defective condition in which the brain reached the pathologist, several points cannot be as clearly decided as would be desirable; but the following statements are well founded.

1. There is no circumscribed cerebellar lesion, nor does the cortex show a marked decrease of the number of the Purkinje cells.

2. Parts of the spinal cord and medulla which are known to have relations with the cerebellum were found affected.

3. The spinal cord as a whole shows increase of the superficial neuroglia and a remarkably large number of corpora amylacea, similar to what is seen in very old people, in paralysis agitans, &c.

It would not be fair to build on this one observation a dogmatic theory of the disease of the family. We may, however, safely say this :

The separation of a *type cérébellaire* from the general picture of hereditary ataxia is clinically justified, but anatomically to less extent than Marie seemed to expect. In his case Nonne saw a simple hypoplasia of cerebellum and spinal cord and a peculiar preponderance of thin fibres in the anterior roots. Fraser found atrophy of the cerebellum, but no lesion of the cord (his case dates from a time when the Weigert hæmatoxylin stain did not exist). Menzel, however, had in his case even more varied lesions than we found : atrophy of the cerebellum with notable disappearance of Purkinje cells and changes of the dentate nucleus, changes in the spinal ganglia and posterior roots ; degeneration of Goll's and Burdach's tracts, the pyramidal tracts and cells of Clarke's column ; changes in the nuclei of the lateral and posterior columns, of several motor nuclei of the bulb, of the gray matter in the pons, the olives, corpus Luysii, and black substance of Sömmering.

The safest explanation is, that in our case we met with a diffuse deterioration of the afferent cerebellar system, with special involvement of the direct cerebellar tracts. Moreover, there is an affection of the peripheral sensory elements

in their course within the neuraxis, but apparently only of those collaterals which connect the lower level with the higher (cerebral and cerebellar) apparatus. We could not otherwise understand the persistence of an exaggerated knee-jerk in our case, and the absence of degeneration of the dorsal columns in the lumbar region; the reflex collaterals are intact; only the cervical cord shows plainly a degeneration of Goll's column. In a similar way we have found in general paralytics a degeneration of the crossed pyramidal tracts of the lower segments of the cord, where the crus cerebi and the oblongata did not manifest a degeneration of the pyramid. Whether the great number of amyloid bodies should be interpreted as an excessively senile phenomenon cannot be decided, since the patient died rather old, and we have not enough control specimens; it is, however, fair to admit, that even for a woman of 67, the number of these bodies and the general increase of neuroglia was at least indicative of marked retrogressive changes. The cerebellum manifests a slight decrease of Purkinje cells. The optic nerves are intact. There is no marked degeneration of the pyramids, but a slight diminution of the thick fibres.

My general attitude in explaining diffuse nervous affections has been put forth in a paper on Landry's paralysis, published with Dr. Diller, in the *American Journal of Medical Sciences*, April, 1895; this view is already taken for heredo-ataxia both by Nonne¹ and by Edinger.² The latter says: "I am inclined to accept Londe's opinion, according to which one would do better to keep the two diseases together under the name of hereditary ataxia; the one form Friedreich's disease proper, should be diagnosed where the disorder begins with spinal symptoms, while the name cerebellar heredo-ataxia should be reserved to the cases which start with cerebellar symptoms. Londe shows beautifully how Marie's type gradually associates itself with spinal symptoms, and Friedreich's with cerebellar ones. Moreover, cases are on record where both were attacked simultaneously. Schultze arrived apparently at similar conclusions. On the ground of the 'Ersatz

theorie,' I am of opinion that according to the varying localisation of the congenital weakness function will create various pictures."

That the character of the lesion is not identical in appearance with the typical gliosis of Friedreich's disease as described by Déjérine, must have its reasons in the difference in the age of onset, and the extent of the pathological process.

¹ Ueber einen in congenitaler beziehungsweise acquirirter Coordinations störung sich kennzeichnenden Symptomen-complex." *Arch. f. Psych.*, vol. xxvii., p. 497.

² (Art. "Friedreichsche Krankheit." "Real-Encyclop. d. ges. Heilkunde," 3 Aufl., 1895, vol. vii., p. 117).