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PROGRESSIVE ATROPHY OF THE GLOBUS PALLIDUS

A SYSTEM DISEASE OF THE "PARALYSIS AGITANS TYPE" BEGINNING IN EARLY LIFE AND ASSOCIATED WITH ATROPHY OF THE MOTOR CELLS OF THE GLOBUS PALLIDUS MECHANISM

THE SYNDROME OF THE GLOBUS PALLIDUS

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It is almost a century since James Parkinson wrote his celebrated "Essay on the Shaking Palsy" (1817) and clearly outlined the chief clinical features of the disease which now justly bears his name. Since his time there have been many important contributions to the symptomatology and a vast amount of pathological research in the effort to find and identify the essential lesion of this disease. The more recent monographs show a great diversity in the supposed pathological lesions, and an absence of any well defined conception as to the underlying pathological condition. The theories, even of to-day, include such widely different structures as the cerebral cortex, cerebellum, basal ganglia, the brain stem and spinal cord. Even the glandular and myogenic conceptions are still upheld by some.

Clinically, three types of the disease are recognized, viz.: the *presenile*, the *symptomatic*, and a rare *juvenile* type. There are also subdivisions corresponding to variations in the symptomatology, *e. g.*, *formes frustes*, paralysis agitans without tremor, and more rarely paralysis agitans without rigidity.

It is most unlikely that an affection which is so diverse in its manifestations should represent a single disease, corresponding always to one uniform pathological condition. It is rather a *syndrome*, including more than one affection, differing pathologically and even clinically, and yet bearing a general resemblance to one another as do cases of spastic paralysis.

Paralysis agitans undoubtedly includes a variety of types which are related clinically, as they present the chief symptoms of *Parkinson's syndrome* (rigidity and tremor), but which must present differences in the localization and character of the underlying pathological lesions. In brief, our position toward paralysis agitans to-day is much what it would be toward spastic paralysis (paralysis with its associated spastic phenomena) if the function and course of the pyramidal tracts were unknown.

In the present study an effort is made to isolate a special group of paralysis agitans cases (viz., the juvenile types) from the larger syndrome, on the basis of certain definite pathological changes in the motor cells of the

corpus striatum; also to indicate the probable extent and nature of the tract system which underlies the affection; and to outline a syndrome for the globus pallidus which is the essential structure involved.

ABSTRACT OF CASES

Case I.—No hereditary or familial history of any similar affection. Onset of the disease at age of fifteen with tremor of left foot and later of left arm with rigidity. Gradual extension of tremor and rigidity to the right arm and leg. Four years after onset difficulty in articulation and deglutition. Gradual progression of all the symptoms; typical attitude and gait with Parkinsonian mask; propulsion—slowness of movement and delay in initiating movement; infrequent winking. Tendon reflexes present and active; at times pseudoclonus; abdominal reflexes present. No Babinski. Sensation normal. Pupils equal and react; optic nerves normal; tremor-like nystagmus. For twenty years patient was under observation in the Montefiore Home. In last years of the disease was almost totally rigid and immobile, with marked tremors of the face, tongue, arms and legs, of the paralysis agitans type; also dysphagic and almost anarthric. Abdominal reflexes were usually elicitable up to the last. No Babinski; no plantar flexion of the toes. No spasmodic or athetoid movements. No special intelligence defect. General visceral examination negative. Urine normal. Wassermann negative. Exitus at the age of forty from exhaustion, cardiac failure and edema of lungs.

Diagnosis: Paralysis agitans (juvenile type).

Duration of the disease: Twenty-five years. Autopsy twenty hours after death.

Case II.—(Abstract of History.) A woman aged thirty-three has been under observation at the Montefiore Home for past four years. No hereditary or familial history of any similar trouble. Onset of the disease at the age of thirteen with tremor of the right arm; one year later it appeared in left arm. At age of fifteen left leg became weak and tremulous and a year after this right leg similarly affected. Gradual progression of weakness, stiffness and tremor. At age of twenty-three difficulty in swallowing liquids and articulation became slow and difficult. There is the typical facies, posture, gait, rigidity and tremor of paralysis agitans. Propulsion—slowness of movement and of motor initiative; infrequent winking. Tremors of the extremities are coarse but diminish on intention; there is also some tremor of tongue and face, and a nystagmus-like tremor of the eyes. Speech is slow, low pitched and dysarthric. Tendon reflexes are present and moderately active; no clonus; no Babinski; abdominal reflexes are present. Pupils equal and normal; eye grounds negative; sensation normal. Urine normal and Wassermann test of blood and cerebrospinal fluid is normal. General visceral examination is negative.

Diagnosis: Paralysis agitans (juvenile type).

Pathological Examination. *Case I.*—A general autopsy was performed twenty hours after death. There were no noteworthy lesions, macroscopic or microscopic, of the viscera or ductless gland system. The brain and cord were removed and placed in 10 per cent. formalin and later in Müller-formol solution. *Macroscopically* no pathological changes were noted in the meninges or central nerve structures. The cerebral vessels were practically free from arteriosclerotic changes.

Microscopic studies were made of various regions of the cerebral cortex (frontal, motor, occipital and temporal), the cerebellum including the dentate nucleus, the optic thalamus and corpus striatum, the crus cerebri, pons, me-

dulla and spinal cord. The methods and stains used were those of Nissl (toluidin-blue), van Gieson, hematoxylin-eosin, Sims, Weigert and Cajal glia stain, and the Weigert-Pal and Kulschitsky methods.

No pathological changes were noted except in the corpus striatum and these consisted of *atrophy and diminution in number of the large motor cells of the globus pallidus system*. The blood vessels were nowhere thrombosed nor occluded and only a very moderate degree of arteriosclerotic change was noted in certain of the vessels of the cerebrospinal axis. There were no evidences of inflammatory changes or gross lesions.

The Corpus Striatum, Thalamus and Hypothalamic Region.—A. Corpus striatum: In this region there is widespread atrophy and diminution in number of the large motor cells of the *globus pallidus system*. The large multipolar cells of the *globus pallidus* type which are scattered through the putamen and caudate nucleus also participate in the atrophy as well as the cells of the *nucleus Basale* of Meynert. These cells are similar in structure to those of the *globus pallidus* proper and are evidently similar in their function. Comparative cell counts with normal sections as a control show a reduction of from one quarter to three quarters, the greater number of the remaining cells showing various stages of chronic cellular atrophy. There is a moderate increase of glia nuclei in the regions involved, but no inflammatory reactions or noteworthy vascular changes. The *globus pallidus* contains an unusual number of highly refractive hyalin deposits of elongated or concentric configuration. These concentric calcareous-like bodies are also present in the normal controls, but are less numerous and are of frequent occurrence in this region. The smaller ganglion cells of the putamen and caudate nucleus are well preserved and present no evidence of atrophy or diminution in number.

B. The cell groups of the optic thalamus are well preserved and are not atrophic. The ganglion cells of the nucleus ruber, corpus Luysii and the substantia nigra are also normal in number and appearance. (The sympathetic vagus nucleus shows no evidences of atrophy.) The nerve tracts of the pons, medulla and cord show no evidences of atrophy. The corticospinal tracts (pyramidal tracts and internal capsule) are intact. There is some thinning of the ansa system (ansa lenticularis et peduncularis). There is no reduction of the medullary laminae of the *globus pallidus* or optic thalamus.

Résumé.—Histological examination of the central nervous system in this case reveals as the essential lesion: atrophy and disappearance of the large motor cells of the *globus pallidus system*. These cells are most numerous in the *globus pallidus*, but are found in considerable number in the caudate nucleus and putamen, also in the ansa radiations and in the Basal nucleus of Meynert. They constitute the essential motor nucleus of the corpus striatum and histologically are of the motor type. They may be regarded as the homologues of the cells of Betz in the motor cortex and the large multipolar cells of the anterior horns.

This lesion Dr. Hunt believes to be a primary atrophy (abiotrophy) of the motor or efferent *globus pallidus system*. It is a system disease and constitutes a pathological and clinical entity in the Parkinsonian clinical group. In a considerable number of the recorded cases of juvenile paralysis agitans a well-marked *familial tendency* has been observed which is corroborative of this pathological conception. It is not unlikely that the *presenile* and *symptomatic* forms of paralysis agitans are dependent upon senile degenerations and arteriosclerotic changes in various portions of this same mechanism.

The Syndrome of the Globus Pallidus.—A system degeneration limited to the motor cells of the *globus pallidus mechanism* is an ideal lesion for the construction of a *syndrome* of the *globus pallidus*. In recent years there

have been described two important syndromes of the corpus striatum, viz.: (I) the Vogt syndrome, characterized by spastic diplegia with double athetosis and pseudobulbar palsy. The lesion in this group of cases is a destructive one (*état marbré*) limited to the caudate nucleus and the putamen. (II) Wilson's syndrome based on the progressive lenticular degeneration, with rigidity and tremor of the Parkinson type, dysarthria and in some of the cases clonic and tonic spasms and athetoid movements. Among the first recorded cases of this affection were those of Gowers under the highly descriptive title of tetanoid chorea. Dr. Hunt attempts to explain and reconcile these two syndromes and their points of difference in the *syndrome* of the globus pallidus.

The corpus striatum is composed of the globus pallidus, the putamen and caudate nucleus. The globus pallidus and the putamen constitute the nucleus lentiformis of which the putamen forms the external segment. The globus pallidus, phylogenetically, is the older portion of the corpus striatum (the paleostriatum) and is found in the lower forms of fishes. The putamen and caudate nucleus on the other hand represent a later development of the corpus striatum which first appears in reptiles (neostriatum). The caudate and putamen are similar in structure and doubtless subserve a similar function. They become separated in the higher forms only by the development of the internal capsule.

The neostriatum (caudate and putamen) is composed of numerous small ganglion cells, through which are scattered the large multipolar cells of the globus pallidus type. These larger cells Dr. Hunt regards as part of the globus pallidus system and as subserving a similar function. There is, therefore, in the neostriatum a mixture of both types of cells, the large motor cell of the paleostriatum and the small cells of the neostriatum. These two types of cells have separate and distinct functions, viz.:

The large ganglia cells of the globus pallidus system are efferent or *motor*.

The small ganglia cells of the neostriatum (caudate and putamen) are *inhibitory* and *coördinating*.

The globus pallidus system is the motor centre proper, while the neostriatum forms an inhibitory and coördinating cortical mechanism which is controlled by pathways from other portions of the central nervous system.

The mechanism which is involved in this disease is the *motor or efferent system of the globus pallidus*, which acts upon subordinate nuclei in the hypothalamic region; the nucleus ruber, the corpus subthalamicum and substantia nigra, and through them exercises a controlling influence upon the extra-pyramidal tract system.

The globus pallidus cells occupy the same position in this automatic motor system as do the cells of Betz in the corticospinal system; the globus pallidus mechanism controls automatic and associated movements, whereas the higher cortical centers are concerned with complicated synergic and discriminative movements. Both of these motor mechanisms, in addition to the function of motor innervation, have also a controlling or inhibitory effect upon muscle tonus, and a destructive lesion in the case of the globus pallidus produces not only paralysis of certain automatic and associated movements, a slowness of movement and loss of motor initiative, but a great increase of muscular tonus as well (rigidity).

For many years it has been observed that chorea and athetosis frequently result from lesions in the region of the putamen. Recent investigations by Jellgersma, Alzheimer, Marie and L'hermitte and Dunlap have shown that hereditary chorea is associated with marked atrophy and disappearance of the ganglion cells in the caudate nucleus and putamen, with increase of the glia nuclei. So that the connection between the symptom, chorea and the

neostriatum is a very close one. Dr. Hunt has been able to study the specimens of a series of four cases of Huntington's chorea and finds that the large cells of the globus pallidus system are well preserved amid the wholesale destruction of the smaller ganglion cells of the neostriatum. The cell atrophy of the corpus striatum in Huntington's chorea appears to be limited to the smaller ganglion cells, and he regards these smaller ganglion cells with their short internuncial fibers, which terminate in the outer and inner segments of the globus pallidus, as exercising a coördinating and inhibitory control over the larger motor cells, and when this is lost the phenomena of chorea result. This small cell system stands in relation to chorea and the large cell system of the globus pallidus to the paralysis agitans syndrome. When there is a destructive lesion involving both types of cells in the caudate nucleus and the putamen, there results the Vogt syndrome of the corpus striatum, viz., double athetosis with spastic contractures and pseudobulbar palsy. In other words, athetosis and mobile spasm represent chorea plus a slight rigidity from involvement of the globus pallidus cells.

If the caudate nucleus and the lenticular nucleus are the seat of a massive destructive lesion, as in the progressive lenticular degeneration, there results the symptomatology of Wilson's disease, viz., the paralysis agitans syndrome with tremor and rigidity, but also associated with clonic and tonic spasms, and occasionally choreic and athetoid movements (Gowers' tetanoid chorea). Dr. Hunt therefore regards the corpus striatum as representing two important groups or systems of cells (paleostriatal and neostriatal) with totally different functions; one motor, the globus pallidus system, and the other coördinating and inhibitory, the small polygonal cells of the neostriatum. The globus pallidus occupies a position in the motor system somewhat analogous to the optic thalamus in the sensory system with which it is closely associated; and is engaged largely in the performance of functions which have to do with the association of movement and automatism. It has important independent functions but at the same time is closely associated with the cortical motor mechanism. A paralysis of either produces a characteristic and distinctive symptomatology. A lesion of the pyramidal tract system is followed by the phenomena of spastic paralysis; a lesion of the globus pallidus system by the phenomena of paralysis agitans.

The syndrome of the globus pallidus may be summarized as follows: An affection of the efferent motor system of the globus pallidus mechanism has, as a result, the paralysis agitans syndrome pure, viz., paralysis of certain automatic and associated movements, rigidity and tremor.

An affection of the small cell system of the neostriatum releases the motor mechanism of the globus pallidus from control, and there results the phenomena of the chorea of Huntington.

A destructive lesion of both types of cells produces chorea, athetosis, spasms, rigidity and tremor in various combinations.

The presence of the Vogt syndrome and Wilson's syndrome will depend upon the localization and the extent of involvement of these two cellular systems.

Dr. Smith Ely Jelliffe agreed with Dr. Hunt that further analysis of the paralysis agitans syndrome is not only desirable but imperative. Neurological science is still too much burdened with entity concepts and it is advantageous to dismember the large paralysis agitans group. The method of doing it as just proposed is not so worthy of commendation. Disease in one synapse in a pathway does not describe a syndrome. Dr. Hunt's analysis is therefore far too fragmentary. Moreover, the functional relationships of the cell groups are not discussed nor even presented by Dr. Hunt. Malone's work on these groups is not considered. With reference to Dr. Hunt's remarks relative to Huntington's chorea, Dr. Jelliffe would state that Dr. Hunt

is not entitled to draw the deductions because the hereditary, biological data negatives the narrow interpretations Dr. Hunt has assumed.

Dr. B. Sachs was absolutely in sympathy with Dr. Hunt, to separate some of the groups of paralysis agitans. It was Dr. Hunt's first case mentioned that he had an opportunity to study. The case of this boy impressed Dr. Sachs at the time by the fact, and he thought he made the statement accordingly, that here was a case of paralysis agitans appearing in early life and with some of the symptoms that we ordinarily associated with disseminated sclerosis. In other words, when the disease occurs in early life it had some of the symptoms which we knew always occurred in early life, although the other disease appeared later in life. Dr. Sachs had no right, nor had he the desire, to deny that it may be due to changes in the globus pallidus and that there may be some explanation for the lesions in other cases of paralysis agitans. He thought there is one point we must consider thoroughly, that is, that in a disease lasting twenty years these changes in the globus pallidus are the only changes that Dr. Hunt is able to put his finger on. The danger of making that the seat of the chief pathological lesion is a very great one. The question arises are not they simple terminal changes. Have they any actual causative relation to the disease which has lasted twenty years? Dr. Sachs presumed the central nervous system has been gone over thoroughly. In a case of this sort it would be absolutely necessary to see the anterior pole of the brain and the very lowest part of the spinal cord in order to be sure that we had really got at the chief changes underlying the disease. The changes in the globus pallidus are undoubted, but whether that is the sole lesion in this form of disease we must reserve judgment until we find exactly the same changes in an entirely parallel case.

Dr. J. Ramsay Hunt said that while the pathological conclusions were based upon the study of one case, this case had been very carefully observed and thoroughly studied by modern histological methods. The large cells of the globus pallidus, as well as the cells of similar type which are scattered through the putamen and caudate nucleus, were definitely atrophic, so that Dr. Hunt regarded this as a system disease limited to the cells of the globus pallidus mechanism. The small ganglion cells of the neostriatum were not affected so that in this respect the atrophy was selective and definitely limited to a homologous cell type. That the cells showed a considerable diminution in number was shown by careful comparative cell counts of normal specimens at the same level and stained by the same histological methods. The reduction in the double number of cells varied from one sixth to three fourths in the different regions involved. Phylogenetically the globus pallidus mechanism is very old and is well developed as low in the animal scale as fishes; ontogenetically the tract system of the ansa lenticularis appears very early in the life of the fetus, so that this nucleus unquestionably has an important motor function. It is a motor controlling mechanism subsidiary to that of the cortical system and concerned largely with the control of automatic and associated movements.

INTRACRANIAL MURMUR OF LONG DURATION AND SPONTANEOUS CESSATION

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Female, 40, with cardio-renal disorder and of neurotic heredity; with a long series of recurring neuropathic manifestations, chiefly autonomic type; somatic and neurologic examinations being negative. Murmur: marked objective in the left occipital region, systolic bruit existing from childhood; at thirtieth year Dr. M. Allen Starr diagnosed case as hysteria with aneurysm