Degenerative diseases of the central nervous system have until recently been considered as being rather fixed in type, and most cases could be readily classified. The outstanding degenerative diseases are: Amyotrophic Lateral Sclerosis, Spinal Muscular Atrophy, and Friedreich's Tabes in the spinal cord. In the encephalon they are: Atrophy of either basal ganglia or the cerebellum, together with a number of nuclei and fiber systems related to them. While in some cases a whole system is changed, in others only parts of a certain system are involved. Transitional cases in which parts of more than one of the systems are affected apparently were rarely seen, and for a long time degenerative diseases restricted to one system only have been considered the rule. These types of diseases were in most instances familiar and hereditary, and it was assumed that the cause was a defective anlage of the system involved. However, in the course of the last 25 years a number of transitional cases have been described, and it becomes more and more obvious that the “typical” forms have too soon been assumed to be invariable.

Cases of combined systemic diseases described in the literature are: Five cases of olivo-ponto-cerebellar atrophy with atrophy of the substantia nigra and the striatum (Scherer (14)); Friedreich's tabes with 1. degeneration of the lenticular nucleus (Josephy, (9)); 2. with degeneration of the globus pallidus and the substantia nigra (Greenfield, (8)); and 3. with degeneration of the pyramidal tract, the basal pontine and dentate nuclei (Gerstmann, Sträussler and Scheinker, (7)). Other combinations are: Degeneration of the basal pontine nuclei, the posterior funiculi, Clarke's columns, the cerebellar cortex, the dentate nucleus and of the substantia nigra (Waggoner, Löwenberg and Speicher (19)). Verhaart (15) reported the combined degeneration of spinal and brain stem muscular atrophy, Clarke's columns and Gower's tract, of the globus pallidus, the subthalamic body, the basal pontine nuclei, the superior colliculus, the dentate nucleus, and of the brain stem tegmentum. Van Bogaert (4) described the following combinations: pallido-nigral, combined either with olivo-pontine degeneration and degeneration of Goll's funiculus or with degeneration of the cerebellar cortex, the dentate and olivary nuclei, Goll's funiculus, the ventral spinocerebellar tract and the papillo-macular bundle, or with a general cerebellar atrophy. Olivo-ponto-cerebellar atrophy was combined with degeneration of the substantia nigra (Lambie, Latham and McDonald (11)). Van Bogaert (6) reported a combination of Hallervorden-Spatz disease with cerebello-dentate

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Table 1

Review of Literature on Heterogeneous System Degeneration, indicating Parts of Central Nervous System Involved (+)

<table>
<thead>
<tr>
<th>Basal Ganglia</th>
<th>Cerebellum</th>
<th>Brain Stem</th>
<th>Spinal Cord</th>
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</thead>
<tbody>
<tr>
<td>Scherer '33</td>
<td>5+</td>
<td>5+</td>
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<tr>
<td>Josephy '33</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Josephy '34</td>
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<td>+</td>
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<td>Greenfield</td>
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<tr>
<td>Gerstmann et al. '36</td>
<td>+</td>
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<tr>
<td>Waggoner et al. '38</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>Verhaart '40</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>v. Bogaert '46</td>
<td>+</td>
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</tr>
<tr>
<td>Lambie et al. '47</td>
<td>+</td>
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</tr>
<tr>
<td>v. Bogaert '47</td>
<td>+</td>
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</tr>
<tr>
<td>Idem '47</td>
<td>+</td>
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<tr>
<td>v. Leeuwen '49</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>Bénard et al. '52</td>
<td>+</td>
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<tr>
<td>Biemond et al. '55</td>
<td>+</td>
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<tr>
<td>Idem '55</td>
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<td>Neuemann et al. '55</td>
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<tr>
<td>Verhaart '56</td>
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</table>

Atrophy; family cerebellar degeneration with partial pallidal atrophy (5), and together with v. Leeuwen hereditary ataxia with pallido-subthalamic degeneration. A rather widespread degeneration was described by Bénard, Grossiord, Gruner and Hoppler (1): Pallido-nigral degeneration with Friedreich's ataxia, atrophy of the anterior horns of the spinal cord, of the tegmentum of the brain stem, of the fasciculus solitarius, the pyramidal tract, the dentate nucleus, the Purkinje cells, and of the sensory and vestibular nuclei. A combination of
Friedreich's tabes with degeneration of the substantia nigra was seen by Biemond and Sinnege (2), and of neural muscular atrophy with degeneration of the substantia nigra by Biemond and Beck (3). Finally, Neumann and Cohn (13) published the case of 2 brothers with neural muscular atrophy, degeneration of Clark's columns, some olivo-ponto-cerebellar atrophy, and atrophy of the reticular formation of the brain stem.

The aim of this paper is to describe a complicated case of combined systemic degeneration in which especially the brain stem reticular formation was involved, and to compare it with a few similar cases described in the literature and to discuss the nature of such cases.

CASE REPORT

History: The patient was a man born July 1905, who in 1946 began to show changes of character with paranoid delusions and loss of interest. In 1949 he was in a mental hospital for a short time, and received electro-shock treatment. In September 1950 he was admitted at the St. Joris Mental Hospital at Delft, where he stayed until his death, June 6, 1955.

In September 1953, he became bedridden, demented, spastic-paretic on all 4 extremities, and severely dysarthric. In May 1955 he developed a mask-like face, total dysarthria, hyper-salivation, and severe spasticity of all 4 extremities. Dr. C. J. Kamp, who supplied me with this information, sent me the brain for examination.

Post Mortem Findings: The brain was fixed in formalin; it was rather small, the pons was narrow, the ventricles were not distended. At transverse sections the tegmentum pontis was very atrophic and brownish, and the pes was of normal dimensions. The medulla similarly showed atrophy of its tegmentum, whereas the olivary complex and the pyramid were of about normal size.

Microscopical examination was carried out on sections of the medulla, the pons, the mid-brain, the thalamus, the basal ganglia, the cerebellum and the cerebral cortex stained either with hematoxylin and eosin or with Lugol fast blue and cresyl violet (Klüver and Barrera (10)). Transverse serial slides stained with Haggqvist's method were made of the greater part of the medulla, the pons and the midbrain with the thalamus and the basal ganglia.

In the brain no striking changes were found. Both the caudate nucleus and the putamen were normal; the bundles of very small fibers also were present in large quantities. The globus pallidus was somewhat reduced in size, its neurons were reduced in numbers, its own fiber system was very scanty, as were those of the ansa and Forel's fasciculus lenticularis H2. There were a few pallidal fibers traversing the internal capsule, but they could not be followed into the subthalamus. The subthalamic body was greatly reduced in size and its neurons in number. The substantia nigra everywhere showed small groups of pigmented neurons, decreased in numbers, especially in more caudal levels, and pigment was found within the glia cells. The very small striatal fibers were numerous within the globus pallidus, the cerebral peduncle, and the rostral parts of the substantia nigra.

The thalamus was well developed, it contained everywhere large numbers of ganglion cells, and the CM nucleus was fairly normal.

In the mesencephalon the superior colliculi were totally degenerated; no ganglion cells being found in them, the inferior colliculi showed a severe reduction both in size and ganglion cell content in their rostral half only. The posterior commissure consisted of a few myelinated fibers only, its nuclei were gliotic and contained a small number of neurons. The central gray matter around the aqueduct was atrophic; it contained ganglion cells in its ventral aspects at the transition to the pons, otherwise it was totally devoid of them (fig. 1). The reticular formation was decreased in size, a few stray ganglion cells were found in it, but the typical heterogeneous fiber bundles were entirely absent. The red nucleus was small, both because of the atrophy of the superior cerebellar peduncle and the disappearance of a
number of its small neurons. In its most rostral levels these neurons were rather numerous, but caudally they were diminished in numbers. The large cells were found in clusters of 4 to 10 along the latero-dorsal aspect of the superior cerebellar peduncle, closely caudal to its entrance in the parvicellular part of the red nucleus. The tecto-spinal tract and the predorsal fascicle proved to be totally degenerated. The central tegmental tract stood out very conspicuously because of the disappearance of the reticular formation bundles and the severe atrophy of the superior cerebellar peduncle. Probably it was somewhat smaller than normally, its fiber contingent from the annulus aquaductus being much less than normal. In a middle mesencephalic level its fibers could be seen to curve medially and ventrally around the red nucleus to the nuclear formation along the medial line. Fibers passing between the bundles of the medial longitudinal fascicle into the central gray matter were much less numerous than normally (Verhaart (18)).

The medial longitudinal fascicle was poorly provided with myelinated nerve fibers, the oculomotor nuclear complex likewise had lost many of its elements, the roots of the third nerve, however, were not atrophic. The trigeminal nerve mesencephalic root and its large neurons of origin were entirely absent, the superior cerebellar peduncle was severely degenerated, especially its thick fibers proved to be very rare. Cranially it decreased in size still more, and only a few small fiber bundles could be followed into the thalamus. The fasciculus retroflexus presented a fairly normal appearance. The medial lemniscus and the cerebral peduncle were of normal size and appearance.

In the pons the most conspicuous change was the enormous atrophy of the tegmentum, between the medial lemniscus and the floor of the fourth ventricle only a narrow strip of tissue being present (fig. 2). It showed a striking absence of the typical heterogeneous reticular formation bundles (Verhaart (18)), which normally abound in the medial half of
the pontine tegmentum, especially caudal to the trigeminal nerve level of entrance. Reticular formation neurons were found in relatively large numbers in the raphe and along the medial quarter of the medial lemniscus, otherwise only a few stray large ones could be seen. The nucleus pigmentosus was much smaller than normally, its neurons reduced in numbers, and the central gray matter contained ganglion cells in the neighborhood of the medial longitudinal fascicle only. The medial longitudinal fascicle was atrophic, the central teg-

Fig. 2. Middle pontine level. The tegmentum is very atrophic, within it only the central tegmental tract is distinguishable.

Fig. 3. Transitional level between pons and medulla. The tegmentum is atrophic, the central tegmental tract can be seen dorsolateral to the medial lemniscus.
ment of its myelinated fiber bundles.

The reticular formation dorsal to the olive has lost most of its myelinated fiber bundles.

The superior cerebellar peduncle proved to be very atrophic, and deprived of myelinated fibers, especially in its dorsal half. The fourth nerve root and its nucleus were normal, the trigeminal nerve, its motor and its main sensory nucleus, as well as its descending branch were normal; its mesencephalic root, however, was absent.

The basal pontine nuclei, the middle cerebellar and the cerebral peduncles showed no appreciable alterations.

In the medulla, similar changes were found as in the pons, severe scarcity of neurons and fiber bundles was very conspicuous in all the reticular formation. The medial longitudinal fascicle caudal to the level of the vestibular nuclei alike was tiny and contained relatively small numbers of fibers. The medial lemniscus, the pyramid, the olivary complex with the restiform body as well as the superior olive with the trapezoid body were about normal. The vestibular nuclei were very atrophic; they were represented by a small number of large neurons only, widely scattered over the dorso-lateral aspect of the tegmentum. The lateral reticular and the arcuate nuclei were unaffected. Deiters' lateral vestibulo-spinal tract was restricted to a few thick fibers (figs. 3 and 4). Only the first cervical segment of the cord was available for examination. The pyramidal decussation was very asymmetric, and the lateral pyramidal tracts were not atrophic; small fibers, however, seemed to be rather rare. Everywhere within the anterior and the lateral funiculi small fibers, normally very abundant, proved to be relatively rare, the few thick fibers of the medial longitudinal fascicle and Deiters' vestibulo-spinal tract, therefore, being more conspicuous than normally. The spino-cerebellar tracts were distinguishable, and they contained a fair number of thick fibers. The posterior funiculi were normal and much more densely packed with myelinated fibers than the other funiculi of the white matter. Anterior horn neurons were rare, the lateral horns were replaced by glia and contained almost no ganglion cells.
The cerebellar cortex was nearly normal; there was a paucity of Purkinje cells, and the granular layer was too narrow. The central nuclei were very atrophic and almost totally deprived of ganglion cells. The hilus of the dentate nucleus was severely demyelinated and replaced by glia.

DISCUSSION

In this case a chronic degenerative disease was found, starting at the age of 41 years, which, in the course of 9 years, caused severe atrophy of different parts of the central nervous system. Almost totally degenerated were: The globus pallidus, the superior colliculus, the mesencephalic trigeminal branch, the brain stem reticular formation, the central cerebellar nuclei, the posterior commissure and its nuclei, and the vestibular nuclei. Less severely affected were the inferior colliculus, the red nucleus, the substantia nigra, the subthalamic body, the oculomotor system, the annulus aquaeductus, and the spinal gray matter.

The present case obviously belongs to the non-classical forms, in which not only one system is more or less totally affected, but parts of different systems partake in the degeneration. It is evident that such cases offer great diagnostic difficulties during life, since symptoms may change during their course, and presumably never show features of affection of one system only. Reports of post mortem examinations are rather rare and are still much overshadowed by the impressive descriptions of those of the classical systemic degenerations. Probably many cases of multiple sclerosis not verified by autopsy belong to this category.

The case reported in 1940 (15) has much in common with the present one. In both the globus pallidus, the subthalamic body, the dentate nucleus, the reticular formation, the superior colliculus, and the motor nuclei of the cord were affected. In the former case the substantia nigra, the inferior colliculus, the mesencephalic root of the trigeminal nerve and the vestibular nuclei were intact, the spino-cerebellar system, the cranial nerves motor nuclei and the basal pontine nuclei were affected, the former two very severely. Quantitative differences consist in a much more severe degeneration of the subthalamic nucleus in the former and of the superior colliculus and especially the brain stem reticular formation in the present case. As the table shows, involvement of the superior colliculus, the brain stem motor nuclei and the reticular formation are rare among the cases described by other authors. Of the 21 cases summarized in this table only 2 more showed disease of the reticular formation and of one the superior colliculus and the brain stem motor nuclei. The same holds true for the degeneration of the vestibular nuclei which was reported in one other case only, whereas involvement of the inferior colliculus was reported in none but the present case. At the moment it seems entirely unfeasible to look for some definite system in the distribution of the atrophy in the cases under consideration. Most of the parts of the Central Nervous System affected belong to the systems of either the basal ganglia, the cerebellum or the non-cerebellar portions of the cord. Every part of one of the systems can be affected together with any part of the same and the other systems. Most frequently affected were the substantia nigra and the cerebellar cortex, 15 and 14 times respectively of which 10 times simultaneously. Next frequently affected were the globus pallidus, the basal pontine nuclei and the spino-cerebellar systems, 11, 11, and 10 times respectively. The former 2, however, were affected
simultaneously only in 2 cases, the first and the third as well as the second and the third in four. The putamen, although intimately related to the globus pallidus, was involved only in 5 cases, in all of which the globus pallidus was normal.

Probably in length of time, when larger numbers of these atypical cases will have been described, some correlation will appear to exist between the several parts affected.

Biemond and Beck (3) especially stressed the occurrence of variations in the same family in obviously hereditary diseases, causing extremely heterogeneous neurological disorders with only little clinical similarity in the different members affected. They stated that affection of the substantia nigra is not uncommon in both Friedreich's ataxia and spinal muscular atrophy and concluded that both diseases are related in some way or another. However, the table shows that the substantia nigra is the nucleus most frequently affected in the category of diseases under discussion and, therefore, their conclusion seems insufficiently substantiated.

Systemic degeneration comprises parts of the Central Nervous System, the different divisions of which are intimately connected. However, these connections cannot account for all of the features of classical systemic diseases, since the divisions may be affected to a very different degree. Even in the easily comprehensible olivo-ponto-cerebellar atrophy, variations are common, the degree of involvement of the olives varying from case to case. In other more or less classical degenerative diseases of the cerebellum variations are much more important, such as cortical atrophy with or without degeneration either of the olives or the central nuclei of both (Verhaart (15)). The same is seen in crossed cerebro-cerebellar atrophy, where many authors assume some topographical relationship between the cerebral lesion and the subsequent cerebellar atrophy. A survey of 38 cases from the literature (Verhaart and v. Wieringen-Rauws (16)), however, showed that such relationship is non-existent, since the location of the cerebellar atrophy in most of the cases proved to be identical, independent of the site and size of the cerebral lesion. It was pointed out, that atrophy can proceed from a part of the C. N. S. either by orthograde, retrograde or trans-synaptic degeneration. The orthograde Wallerian degeneration is the only one which never fails to develop, as far as we know, whereas the others are common in some, unusual in others, and exceptional in still other links of certain systems.

Probably susceptibility to some kind of unusual degeneration in parts of a certain system may increase following affection of other parts by some usual kind of degeneration, which upsets the interbalance of the different parts, thus making degeneration spread in different ways once it has entered a system. This suggestion with regard to cerebro-cerebellar degeneration was exemplified in the above mentioned paper (Verhaart and v. Wieringen-Rauws) by the fact that many pathways may be used when proceeding from the cerebrum to the cerebellum. Besides facilitation of some kind of degeneration following affection of parts of a system an individual susceptibility to degeneration of certain centers also may have to be taken in account in some of the atypical cases of degeneration in the C. N. S.

The factors mentioned tend to diminish the apparently large difference be-
between the typical and the atypical cases, the first ones showing irregularities only in the degree of involvement of the various parts of the system affected, the other ones also in the distribution over the parts of different systems of the C. N. S.

Which factors have to be taken to account in a special case will be hard to determine before much more is known both of interrelations between parts affected and facilitation of unusual forms of degeneration under the influence of affection of related centers.

Degeneration of the whole brain stem reticular formation is one of the most outstanding features in the present case, it has not been described as such till now. Among the cases reported atrophy of the tegmentum of the brain stem has been described in those of Bénard et al. (1), of Neumann and Cohn (13) and in my first case (1940). In neither, however, it has been recognized as a specific reticular formation atrophy. In the present study serial slides stained according to Håggqvist’s method it proved to be due to such an atrophy. Typical elements of the reticular formation are the stray ganglion cells of different sizes scattered in the brain stem tegmentum, which by some authors have been grouped in a number of vaguely circumscribed nuclei, and the small longitudinal fiber bundles, consisting of fibers of all sizes (Verhaart (18)). Outside the reticular formation a structure showing these elements is only very scantily found and therefore the formation can be readily recognized. In the present case both elements had disappeared almost entirely, whereas the lateral reticular nucleus of the medulla, though lying adjacent to the reticular formation nuclei, was normal. With regard to degeneration it reacted as a homogeneous nucleus or system being the only system totally affected in the present case over the whole brain stem.

This may mean that this formation in some way is an entity, comparable to that of other systems better known in detail anatomically. As far as could be established no differences in degree of degeneration could be found between parts serving different functions, as demonstrated by physiologists in the cat. However, about the function of such parts in man nothing is known and things may differ considerably from those in experimental animals. Probably more elaborate examination of the reticular formation in cases such as the present one may reveal regional differences within the brain stem reticular formation.

SUMMARY

In this paper a heterogeneous case of degeneration of the C. N. S. is described, outstanding because of severe general degeneration of the brain stem reticular formation. Besides parts of the cerebellar, the basal ganglia and the mesencephalic tectum and cranial nerves nuclear systems were affected in a rather unusual combination.

The case was compared to 21 other heterogeneous cases found in the literature. The importance of heterogenicity in apparently systematic degenerations of the C. N. S. as pointed out by Biemond et al. was reemphasized. It was stated that anatomical interrelations alone are insufficient to explain the atypical distribution and that facilitation of normally unusual types of degenerations has to be taken into account.
This facilitation can be brought about either by involvement of other parts of the system to which the part under consideration belongs, or to some special individual susceptibility to degeneration of such a nucleus. The unequal affection of the different parts of a system in typical cases was emphasized in order to exemplify variations in a typical case anatomically unaccounted for.

REFERENCES


