Poliodystrophia Cerebri Progressiva
(Diffuse Degeneration of Grey Matter)

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Degenerative diseases affecting the central nervous system of children present many perplexing clinical and pathological problems despite numerous investigations in this field. There have been descriptions of a great many different varieties of such conditions resulting in further confusion and problems in terms of classification and understanding. Owing to the expanding knowledge in the field of neuropathology and neurochemistry, refinements in the diagnosis of many of these cases have made it possible for us to classify many of them into several broad categories.

The first category includes the so-called storage disease group. Amaurotic familial idiocy, Gaucher's disease, Nieman-Pick's disease and Gargoyleism are in this group.

Belonging to the second category are many different types of degenerative diseases affecting primarily the white matter of the central nervous system (Schilder; 1912, 1924, Krabbe; 1916, Scholz; 1928, Meerabacher; 1928, Bielschowsky; 1927).

Differing from the first group of storage diseases, there is another type of degenerative condition affecting primarily the grey matter of the nervous system. Clinically this condition is almost indistinguishable from the primary white matter diseases, but pathologically the findings are entirely opposite. Prominent degenerative processes are identified in the grey matter, whereas the white matter remains relatively intact.

Contrary to the extensive investigations and descriptions of the primary white matter diseases, there have been very few descriptions of this last group of diseases, and no more than a dozen cases have so far been recorded in the world literature. Recently we had an opportunity to examine a case that we feel belongs to this group, and we have noted interesting new features which have not been recorded in previous reports.

REPORT OF A CASE

Clinical Summary

H.I. was a 9 year old white boy who was born after an uneventful, full term pregnancy, weighing 7 pounds and 6 ounces. There was no evidence of birth injury. He had some feeding difficulty in the neonatal period and an intussusception was reduced by barium enema at the age of six months. He was able to speak in short phrases at the age of two years and was toilet-trained between the ages of 2 and 3. He did not walk alone until the age of two years. At the age of 16 months, he was admitted for an evaluation of poor weight gain. At that time he was unable to walk or to sit and showed a psychometre of 19%. He received a triple arthropodesis of his right ankle 4 years after his first admission. At the age of 6 years and 8 months, he fell without losing consciousness. He was taken to a hospital where he had two episodes of convulsions. The convulsions were of the grand mal
variety, corroborated by a fast spike and third-second generalized seizure patterns on the E.E.G. He remained in the hospital for 2 weeks for the treatment of bronchopneumonia. He was given Dilantin, which improved his seizures a great deal. However, his ataxia was noted to be more marked than it had been previously.

Six months later, the patient began to have some visual difficulties. His visual loss and ataxia became progressively worse over the ensuing 6 months period.

There was no past history of other serious illnesses or of significant injuries. No family history of neurological or muscular diseases was elicited.

On physical examination, he was alert, cooperative, well-nourished and moderately well-developed. A moderate wide-based ataxic gait with mild titubation of the trunk and head were noted. The speech was slow and slurred. Gross finger-to-nose and heel-to-knee ataxia were noted. There was generalized hypotonia of extremities, and no deep tendon reflexes could be elicited. A left Babinski sign and pes cavus was noted in the left foot with a flexion deformity of the left great toe. There was loss of vibratory and position senses in both lower extremities. Marked paling of both optic nerves was seen with only occasional ability to count fingers at one foot. The remaining cranial nerve functions were not remarkable. There was no scoliosis.

Laboratory Findings: X-rays of the skull with special views of the optic foramina were normal. A chest film was normal. Electroencephalograph showed markedly and diffusely slow readings with paroxysmal features. No focus was demonstrated on repeated E.E.G.s. Routine urine and blood studies were normal except for white counts of 3,800, 4,200 and 3,700 with 69% and 51% lymphocytes on 2 occasions. The fasting blood sugar was 55.5 mg per 100 cc Blood serology was negative. A lumbar puncture revealed no evidence of increased pressure, but showed 3 mononuclear cells, 43 mg of sugar per 100 cc, a 4-plus Pandy reaction and 432 mg of protein per 100 cc. Repeated serological examinations of the spinal fluid were negative. Pneumoencephalogram showed only mild enlargement of the lateral ventricles. A retrograde right brachial arteriogram was done which filled both the vertebral and basilar systems, and the carotid circulations were quite satisfactory. The patient was eventually discharged and later died with signs of bronchopneumonia.

Pathological Examination

Gross Examination: The brain weighed 1270 grams after fixation. Externally, the brain appeared moderately pale, but was symmetrical and normal on palpation. The leptomeninges appeared slightly thickened. The ventricles were not remarkable. There was no evidence of cerebral edema. Serial coronal sections revealed normal ventricular configurations, and the gyral patterns were not remarkable. No focal lesions were demonstrable except that the post-Rolandic cortex appeared unusually thin. The white matter appeared normal. Sections of the brain stem and cerebellum were not remarkable.

Microscopic Examination

Multiple sections from the cerebral hemispheres, brain stem, cerebellum, spinal cord, roots and dorsal root ganglia, stained with haematoxylin and eosin, were examined. In addition, special areas were stained with the following: Bodian, PAS, ORO, thionine, toluidine blue, cresyl violet, and by the Grimbrin method for myelin.

The most important finding in this case was the presence of diffuse nerve cell degeneration in many regions of the nervous system. The greatest involvement was in the cerebral cortex and in the Purkinje cell layer of the cerebellum, but numerous other structures were involved, as described in greater detail below.

The changes in the cerebral cortex were characterized by a diffuse but uneven involvement of the cortex of both hemispheres. The changes varied all the way from slight nerve cell loss with slight astrocytic and microglial proliferation, to regions of severe depletion of nerve cells with involvement of all cortical layers. At the sites of most intense destruction, there was marked astrocytic proliferation and microglial activation,
most of the latter being of pleomorphic microglia, with only a few macrophages. There was a tendency for greatest involvement of the 3rd, 4th and 5th cortical layers.

It was further evident that the duration of involvement varied from area to area. For example, a section from the post-Rolandic (sensory) cortex revealed marked thinning with almost total loss of nerve cells; here the astrocytosis had the characteristics of a more remote gliosis, and fat stains revealed relatively few fat-containing microglia, whereas other areas showed numerous plump astrocytes indicative of more recent involvement, and fat stains disclosed numerous fat-containing microglial elements. With regard to the remaining nerve cells, many could be found which one might suspect were in early stages of degeneration, exhibiting early stages of pyknosis of nuclei, namely shrinkage and loss of nucleoli; in addition, there was loss of Nissl substance, and a granular appearance of the cytoplasm. At a more advanced stage of degeneration were numerous cells which were markedly shrunken; the cytoplasm was intensely basophilic, granular; in some cells very fine vacuoles could be seen, the cells had frayed marginal appearances, and nuclear pyknosis was marked. In some areas there were what appeared to be fragments of nerve cells remaining, with no nuclear structure whatsoever, probably representing the terminal stages of cell destruction. Although many of the nerve cell changes might be confused with the variations one might encounter in routine autopsy material, the changes in the majority of abnormal-appearing nerve cells seemed definitely to be valid pathologic alterations. However it should be emphasized that there were no specific nerve cell abnormalities which could be recognized; the fat stains did not disclose any nerve cells containing lipid material, and no inclusions were demonstrable.

The most important evidence bearing on the grey matter degeneration was not the changes in the nerve cells themselves, but the marked reactive response in the astrocytes and microglia.

A section taken from the region of the temporal cortex where a biopsy was taken several months before death disclosed a small cavity containing numerous macrophages, surrounded by an area of intense gliosis. The cortex from this area (away from the traumatic surgical lesion) disclosed only slight astrocytosis with no appreciable nerve cell alteration or depletion, indicating that this region had not been significantly affected by the disease.

It was noteworthy that there was seen, in sections available, a greater involvement of the occipital cortex than of any other portion of the cerebral hemispheres, the parietal being next, the frontal still less severely involved, and the temporal cortex least of all. However, there was marked evidence of degeneration of the hippocampus. There was no evidence of white matter involvement in any of the sections. A section of the optic chiasma revealed no degeneration.

Sections of the basal ganglia disclosed slight nerve cell loss with reactive astrocytosis in the caudate and putamen nuclei. There was a somewhat greater involvement of the globus pallidus, but the claustrum was markedly involved, showing severe depletion of nerve cells and reactive changes. In the thalamus there was only slight, spotty degeneration, except in the lateral nuclear mass, which was markedly involved.

In the brain stem there was minimal nerve cell degeneration in the substantia nigra. Severe degeneration was present in the red nucleus, with almost complete depletion of nerve cells and accompanying reactions. There was minimal involvement of the nuclei pontis. Otherwise the brain stem showed no significant changes.

It is noteworthy that although there was no evidence of inflammatory changes in the meninges or ventricles, there were a few ependymal granulations over the surface of the fourth ventricle and lateral ventricles.

Sections of the cerebellum disclosed extremely severe involvement of Purkinje cells, with loss of almost all nerve cells of this type in the sections examined. There was no evidence of involvement of the granule cell layer. The dentate nucleus
revealed marked degeneration.

Involvement of the spinal cord was greatest in the posterior columns. Here there was severe degeneration of the fasciculus gracies bilaterally and symmetrically. Fat stains revealed very few fat containing microglia in these tracts, indicating a very remote process. In all probability this degeneration was secondary to nerve cell loss in the dorsal root ganglia. Marked demyelination was present in the dorsal roots. In the few sections of dorsal root ganglia available, many clusters of satellite cells could be found, with no remnant of nerve cells remaining, suggesting nerve cell death at these sites. Moderate numbers of apparently intact nerve cells were still present, however.

There was also bilateral degeneration of the ventral and dorsal spino-cerebellar tracts. The latter tract appeared to be related to a marked degeneration of the Column of Clarke bilaterally. It was difficult to find any remnant of this nucleus on either side in the thoracic and upper lumbar segments. There was slight demyelination in the lateral columns which might represent axonal degeneration secondary to cerebral cortex involvement. There was only minimal loss of nerve cells in the anterior horns. However, many of the remaining anterior horn cells appeared abnormal, and one had the impression that the best evidence regarding the early stages of degeneration of nerve cells in this disease could be found in the anterior horn cells. Many of the cells showed rounding, loss of Nissl substance, granularity of the cytoplasm (accompanied by a granular fragmentation of the neurofilaments with the Bodian stain), eccentric location and pyknosis of the nuclei, and in a few instances, large vacuoles present in the cytoplasm. Along with this there was slight paling of the ventral roots in the myelin stains.

Except for evidences of terminal bronchopneumonia, there was no significant pathological changes found in the rest of the body at autopsy.

COMMENTS

Alpers (1931) was the first to call attention to this unusual but interesting disease in his excellent and detailed article, “Diffuse Degeneration of Cerebral Grey Matter”, and since that time the disease is known as Alpers’ disease in American literatures.

His case was that of a month old infant who with repeated convulsions, hyperkinesis, and attacks of generalized rigidity of muscle and had widespread degeneration of grey matter. The neuronal degeneration was particularly marked in the entire cerebral cortex, showing degrees of involvement with spongy softening to simple histological evidence of neuronal degeneration. Astrocytic and microglial proliferation accompanied the areas of degeneration where there were also prominent proliferation of capillaries. There was also involvement of the striatum, pallidum and thalamus, but the cerebellum was spared.

Frederickson (1931) reported the case of a 19 year-old girl who had repeated convulsions and muscular twitching and had similar degenerative changes involving grey matter. The most prominent degeneration was seen in the occipital region and in the island of Reil. The striatum, pallidum, hypothalamus and dentate nuclei were also involved.

The anatomical findings in this disease are extremely difficult to distinguish from the changes seen in post-epileptic encephalopathy. Many had questioned the validity of this disease being a nosological entity because of this. Since almost all of these reported cases had had repeated episodes of convulsions in their past history. However, a report by Christensen and Krabbe (1949) describing a 2 1/2 year-old child who never had convulsions but showed a disease process identical to the disease in question certainly proved that somehow these changes can occur without any episodes of convulsions and that there must be other pathogenetic processes to produce this widespread degeneration of grey matter. Christensen and Krabbe also noted some evidence of a developmental defect in their case. No change was found in the brain stem, basal ganglia, cerebellum or white matter.

Ford and Livingston (1951) reporting four cases of this nature classified them into infantile and juvenile forms. In characterizing this disease, they
emphasized that the disease is a progressive degenerative disease affecting not only chiefly cerebral grey matter, but also the neurons of basal ganglia, thalamus and cerebellum as well. The clinical features were summarized as follows: convolution, myoclonus, spasticity, choreoathetosis, cerebellar ataxia, and dementia.

Sporadic case reports have appeared in the world literature concerning this disease, though none have provided an answer to its exact pathogenesis. Kramer (1954) reported the case of a 4-year-old and 4-month-old girl who showed widespread degeneration of neurons in the cerebral hemisphere, cerebellum, stem ganglion, thalamus and the nuclei of the diencéphalon and brain stem. There was no demyelination of white matter and the axis cylinders were intact. He also noted evidences of developmental defects in that there were scattered embryonal cells and giant cells in the grey matter. Heterotopic Purkinje cells were also noted. Smulders (1956) described the case of a 13-year-old girl who was in good health until an episode of trauma. A few months afterward, she began to have convulsions and died in status epilepticus approximately 18 months later. The changes observed in the grey matter were more or less identical to Alpers' disease, but he stressed the point that the anatomical changes were indistinguishable from the changes produced by anoxia (Courville, 1932). Rangam and Pohowalla (1965) also reported a case in which grey matter degeneration of the cerebrum was pronounced. However, they pointed out the differences in clinical features between their case and the cases of Alpers and Freedom. De Jong and Pehin (1956) discussed a 27-month-old baby who showed diffuse ganglion cell degeneration of the cerebrum with prominent astrocytic proliferation. Steven and Dekaban (1958), reporting several cases of different degenerative diseases affecting the central nervous system of children, mentioned a case in which there was diffuse degeneration of grey matter as well as of white matter. A great diversity of opinion concerning the degenerative diseases can be found in several other papers (Crome; 1957, Greenfield; 1958, Lowenberg et al.; 1946).

It should be pointed out that the clinical features of this disease are by no means characteristic, though the above-mentioned features may be of help in making the diagnosis. Oftentimes a diagnosis of Schilder's disease had been made only to find an entirely opposite pathologic picture later. This is quite understandable if one reviews the anatomy of the central nervous system. It is generally held that this is a degenerative disease, although a possibility of some developmental defect has been cited frequently. There is no evidence to indicate a distinct hereditary aspect in reported cases. No one doubts the effects of repeated convulsions in bringing about the production of the final pathologic picture, which emphasizes a degenerative process involving diffusely and in varying degrees the neurons of the nervous system. What prompts degeneration in this manner is still an unsolved question. Perhaps atrophy, as suggested by others, may be the factor.

In our case, the question arises as to whether or not this case might be considered to be an acute form of Friedreich's ataxia. The anatomic distribution of severe involvement of cerebral cortex would be disproportionately greater than that characteristically seen in Friedreich's ataxia. There is also lacking a heredo-familial background. The question more properly would be, not whether this case should be classified as one of acute Friedreich's ataxia, but whether or not the whole category of so-called Alpers' disease actually may be related to the group of diseases to which Friedreich's ataxia belongs. The lack of a definite hereditary aspect again would be an argument against this. Although the emphasis in previously reported cases of Alpers' disease has been on the degeneration of the cerebral grey matter, examination of the spinal cord and dorsal root ganglia has not been reported in these. Our case distinctly showed that there was involvement of these structures also.

**SUMMARY**

A case of a peculiar degenerative disease affecting
the ganglion cells of the nervous system diffusely is presented with reports of detailed clinical and pathological examinations. For purposes of comparison, a brief review of the articles concerning cases of a similar nature is made. Although the exact nature and pathogenesis of this condition is not yet clearly known, the possibility that there might be some relationship between our case and some other forms of degenerative disease such as Friedreich’s ataxia has been considered. Certainly much more must be learned about the Alper’s group of cases before a more accurate classification and understanding can be achieved.

REFERENCES
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Krabbe, K.H.: Brain, 29 : 74, 1916
Schilder, P.: Arch. f. Psychiat., 71 : 327, 1926
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Fig. 1. Severe neuronal degeneration seen in occipital cortex. Intact neurones are practically not visible (100×).

Fig. 2. High power view of the same area as Figure 1. Note prominent plump astrocytes replacing the architecture almost completely (450×).
Fig. 3. Section from sensory cortex. The arrow indicates the entire thickness of grey matter which is extremely thinned out. Note scattered cystic changes within the grey matter (100×).

Fig. 4. Section from hippocampus. Note extreme degeneration of neurones with shrinkage, fragmentation and pyknosis of nuclei. Astrocytic proliferation is seen within the circular neuronal layer (100×).

Fig. 5. Grimming stain for myelin in the cerebral cortex. Note heavy staining of myelin on the right half of the picture indicating intact myelin structures (100×).

Fig. 6. Grimming stain of spinal cord. Note sharp demyelination of the funiculus gracilis as compared to the rest of the cord (100×).

Fig. 7. High power view of dorsal root ganglia. Note absence of intact neurones. Only satellite arrangement of cells are seen. One still contains fragmented portion of neurone (450×).

Fig. 8. Section of cerebellum. Note almost complete absence of Purkinje cells. Astrocytic proliferation is prominent in these areas. Granule cell layer is intact (100×).