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A Neurodegenerative Disorder in a 10 Year Old Boy

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Clinical Summary

This 10 year old Portuguese boy had a long history of mental retardation and quadriparesis.

The father and mother of the patient were unrelated and were in good health. There was no significant family history. A second son, now 9 years old, was normal. The pregnancy was full-term without complications with a birth weight of 3,000 gm. He achieved normal developmental milestones as a newborn and infant. At 16 months, he was furniture walking. The parents were away for a brief period; on their return, they noted that he had become withdrawn, did not speak as he did earlier and was immobile in his bed for up to 24 hours. Assessment at 18 months showed a normal general examination. He could not speak, smiled vacantly and lay in a frog-like position in bed with little spontaneous movement. There was pallor of both optic discs and internal strabismus. The hands were fisted with weak grips. The toes were extensor bilaterally and the deep tendon reflexes were 2+. An EEG showed slow background and multiple independent spikes. An isotope brain scan was normal. Serum and leukocyte acid hydrolases, urinary amino acids, arylsulfatase A and the mucopolysaccharidosis screen were normal. A pneumoencephalogram showed some enlargement of the lateral ventricles including the temporal horns and an enlarged cisterna magna and prepontine cistern. The CSF showed normal protein and glucose and the measles antibody titre was less than 1/8. The child's mental, physical and neurological problems were attributed to underdevelopment of posterior fossa structures.

Other normal investigations over the years included a karyotype, serum lead, porphyrins, TORCH (toxoplasmosis; other; rubella; cytomegalovirus; herpes) screen, and skull x-ray. A computerized tomographic scan done at age 5 showed mild generalized cerebral atrophy.

An assessment at 7 years of age showed a blind child with bilateral optic atrophy and nystagmus. The head circumference was 52 cm (fiftieth percentile). He would turn to noises; there was marked hypotonia. An early contracture was present at the left elbow. Reflexes were hyperactive in the upper extremities and absent in the lower extremities. The toes were extensor. No scoliosis was noted. One observer reported left hemihypertrophy. No history of seizures was elicited from the parents.

At age 9, the patient developed "drop attacks" lasting 10 seconds. They were preceeded by a fixed stare. He was treated with valproic acid. Assessment at this time showed him to be unresponsive to voice. He was able to withdraw his limbs weakly to pain. His pupils reacted sluggishly to light and at times were constricted tonically for several minutes. He was blind. There was spontaneous conjugate eye movements to the right and a fine right beating jerk nystagmus on forward gaze. No facial movements were apparent. He made snorting sounds; there was no head control, the trunk was flaccid and there was scoliosis. Muscle tone in the limbs was increased and flexion contractures of the extremities were observed. Sensation (pinprick; pinching) was perceived in all extremities. The reflexes remained hyperactive in the upper extremities and absent in the lower extremities. Palmomental reflexes were elicited bilaterally. Repeat biochemical investigations — serum and leukocyte acid hydrolases (mannosidase, fucosidase, B-glucoronidase, B-galactosidase, B-N-Acetylhexosaminidase, hexosaminidase A) and urine arylsulfatase-A were normal. An EEG was unchanged from the EEG at age 6.

At age 9 11/12, the patient was admitted to hospital with pneumonia and bouts of syncope. The latter consisted of profuse sweating, bradycardia (60/min) and apparent apnea lasting about one minute. With stimulation, the child would recover and breathe spontaneously. A cardiac monitor showed episodes of bradycardia and sinus tachycardia likely of central origin. Multiple calcifications of the vertebral bodies were noted.

At age 10, he was transferred from an outside hospital to be assessed for a special chair. On the day of admission, he developed fever, became cyanotic and unresponsive following breakfast. Previous bouts of choking had occurred; he was severely ill, drowsy and breathing at 7/min. Clinical, laboratory and radiological data supported a diagnosis of respiratory failure due to aspiration. Despite antibiotics and supportive therapy, he died the next day.

Discussion

Dr. G. Hinton (Pediatric Neurologist)

During the past week I have seen one new patient every day with one of the degenerative diseases of childhood. The present-

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ing problem is fairly common in that approximately 28% of childhood admissions to a pediatric neurological service are for the investigation and treatment of suspected degenerative neurological disease.[1] There are many causes of degenerative disease and the investigation may be prolonged and expensive. There are also ethical problems of investigating a child with advanced neurological disease and severe multiple handicaps who is unresponsive and blind with seizures and contractures. Does the family want further study? Will the diagnosis benefit the patient? Is genetic counselling important to the family?

Dyken[1] states there are over 600 possible diagnoses in a child such as we are discussing today. In this recent review, he lists 307 and he has determined about 100 different diagnoses in his own experience. One useful approach is to localize the disease from the signs and symptoms and to decide whether the illness represents primarily a gray or white matter disease.

This child had normal developmental milestones until 16 months when he was still furniture cruising. The parents were absent for a period of time and when they returned the child was not speaking and was less mobile.

This history suggests an early onset of cortical degeneration, but pale optic discs with blindness without retinal change may be a gray or white matter disease. Initial hypotonia and then early contracture, increased reflexes and extensor plantars all suggest widespread central nervous system involvement of white matter tracts. This is further confirmed by an air study suggesting atrophy of posterior fossa structures, though we cannot assume the main burden of the disease relates to this anatomical area in the early stages.

At 7 years of age there was optic atrophy and nystagmus, but he was still able to hear and turn to noises. The lower extremity reflexes had disappeared, which may indicate peripheral nerve involvement and the plantars remained extensor. The suggestion of left hemihypertrophy presents a peculiar problem with regards to diagnosis. It is seen with tuberous sclerosis or neurofibromatosis. There may have been more wasting or atrophy on the right rather than hypertrophy. At any rate, the observation of hemihypertrophy was not confirmed or repeated. We shall leave it unexplained.

At age 10 years, just 4 months prior to his death, this boy developed drop seizures, conjugate eye movements to the right and jerking nystagmus to the same side which suggested brain stem disease. Eventually, he began to have apneic episodes and slow respirations; unusual findings which resulted in pneumonia. Death was probably due to a combination of bronchopneumonia with central loss of respiratory drive.

The disease appears to be widespread in the nervous system involving both grey and white matter, thus the possible causes of this 9 year history of progressive illness may be narrowed considerably.

A congenital or inherited abnormality such as, absence of the corpus callosum with hindbrain malformation, tuberous sclerosis or neurofibromatosis may all be associated with seizures and progression of motor handicap, but in the absence of skin lesions or hydrocephalus, these conditions are unlikely to produce widespread involvement. Similarly, a primary or secondary neoplasm would not usually progress so slowly without focal signs and vascular abnormalities such as Moya Moya disease are rare and associated with localized ischemic events.

One fairly common infectious disease producing dementia, seizures and blindness is subacute sclerosing panencephalitis. The EEG is characteristically periodic but the definitive test is the measles antibody level in the CSF, which was normal. Rubella may produce a similar deterioration. Perhaps we could see the EEG now.

Dr. B. Young

The EEGs taken from age 6 to 10 years are essentially alike, with a lack of normal background rhythms for age. There are generalized spike and wave, polyspike and waves and so-called slow spike and waves at 2 cps throughout the entire record. The child seems to have very active epileptiform activity as well as multiple independent spikes in both hemispheres. I believe the appearance is not suggestive of SSPE in which the complexes are usually broader, are separated by a larger distance and a larger amount of time, eg. several seconds.

Dr. G. Hinton

Virus antibody levels and TORCH screen of serum were done twice without indicating rising antibody titers. Alper's and Lafora's disease both may present with seizures, but usually show gray matter disease alone without the widespread involvement of the optic nerves or long tract signs. The cerebral retinal diseases or gangliosidoses may begin at a few months of age, but the absence of hyperacusis, macular change, hepatosplenomegaly and normal biochemical studies of hexosaminidase A and B, galactosidase virtually eliminate Tay Sachs, Sandhoff's, Gauchers or Neimann-Pick disease.[1]

Batten-Jansky-Bielchowsky disease or its early variant described by Santavuori[2] may begin with optic atrophy and seizures resistant to therapy. These are now grouped under the term, neuronal ceroid lipofuscinoses, but these diseases are not entirely neuronal because peripheral lymphocytes are vacuolated and single cell electron microscopy of cultured fibroblasts may show typical curvilinear bodies. The course is shorter than the ten year history in this case. Presumably, in our patient, the blood smear was normal, but the dolichol levels in urine or tissues were not measured.

Other metabolic errors such as phenylketonuria and maple syrup urine disease begin very early, but this boy was dark complexioned and of Portuguese extraction with no characteristic odor. There is no comment on the presence of coarse facial features which may be seen in the mucopolysaccharide group of diseases or the mucolipidoses.

The leukodystrophies may follow the clinical course as described with maximal involvement of subcortical white matter. Early dementia and seizures are less common. Metachromatic leukodystrophy (MLD) is a fairly common degenerative disease with a wide spectrum, but aryl sulfatase tests were negative on two occasions. Our group have described MLD with an activator protein deficiency which impairs sulfatide hydrolysis despite intact aryl sulfatase activity in vitro.[3,4] The absence of reflexes in the lower limbs and the late occurrence of seizures certainly make this diagnosis possible. Adrenoleukodystrophy (ADL) is relatively common, but usually begins at ages 4 to 12 with behaviour problems, awkward gait and visual disturbance. Hyperpigmentation may not be obvious in a Portuguese boy, but the absence of Addison's disease and family history of X-linked diseases reduces the likelihood of ADL.

Canavan's disease is associated with hypotonia, optic atrophy and seizures, but survival is short. Pelizaeus-Merzbacher disease begins with more involuntary movement. Optic atro-

phy is common, but is frequently associated with nystagmus. Long survival is possible. Krabbe's disease begins at 3 to 4 months of age, but the children do not survive 10 years. These children may have optic atrophy, nystagmus and the reflexes are often absent because the peripheral nerves may be involved. Our routine screening does not include the enzyme galactocerebrosidase so Krabbe's globoid leukodystrophy may be overlooked unless the enzyme is specifically requested.

Disease entities in the spinocerebellar group of atrophies such as Friedreich's Ataxia may begin before 8 years of age, and occasionally may be associated with the clinical features seen in this child. Friedreich's Ataxia usually progresses over 1 to 2 years with increasing dysarthria and ataxia. Olivopontocerebellar atrophies may occur in childhood. Ataxia telangiectasia may occur in the very young, but the conjunctiva or skin lesions are seldom missed. Hallervorden-Spatz disease begins at an older age and presents with dystonia and speech involvement.

Finally, there are three remaining possibilities. If this Portuguese boy came from the Azores, we should consider one of the several forms of cerebellar degeneration which occur specifically in Portuguese families. These degenerations begin at adolescence with nystagmus, gaze paresis, depressed reflexes and upgoing toes, but to my knowledge, no children have been described.[5]

The second diagnosis is Leigh's disease or subacute necrotizing encephalitis. These children usually have breathing difficulty, they are weak, ataxic, with ophthalmoplegia, decreased vision and optic atrophy. Seizures occur and an associated peripheral neuropathy may account for absent reflexes. The disorder is said to be due to a pyruvate enzyme inhibitor and can be partially treated with thiamine. It has interesting pathology with neuronal degeneration, gliosis and capillary proliferation in the brain stem, ragged red fibres in the muscle and optic atrophy.

Finally, the disease I believe is present here, infantile neuroaxonal dystrophy (INAD). This disorder related to Hallervorden-Spatz disease is an autosomal recessive degenerative disease. It begins in the first year of life, is associated with slowly progressive motor and mental retardation. There may be hypotonia and areflexia or generalized spasticity and rigidity with muscular atrophy. There is associated visual disturbance, nystagmus, optic atrophy. Extrapyramidal and cerebellar symptoms are less common. Seizures are a late feature and multifocal spike waves appear on the EEG. There is no organomegaly and a paucity of specific laboratory findings. All these features were present in our child and we were able to exclude most of the metabolic/storage disorders. Other disorders as enumerated above are less likely due to the elements of, time of onset, progression and associated findings. The pathology of INAD is the widespread presence of axonal spheroids throughout the central nervous system. Other types of neuroaxonal dystrophy are labelled by the age of onset, the tempo of evolution, neurological signs and the occurrence of abnormal pigment deposits in the basal ganglia. Often the clinical diagnosis is speculative.

The best clinical diagnosis in this case is INAD.

Dr. C.F. Bolton

We reported a case of neuroaxonal dystrophy some years ago.[6] In reviewing the literature at that time, optic atrophy was not a usual manifestation, but it was a prominent feature in that case. The pathology was similar to the infantile cases, but clinically the disease began at the age of 10 years with optic atrophy and the patient died at the age of 20. A worthwhile point, is that the time of onset and course can be variable.

Dr. B. Gordon

We looked for the variety of storage diseases that Dr. Hinton has mentioned, but all our investigations were negative.

Pathological Findings

Drs. M.J. Shkrum and J.J. Gilbert

At post mortem, there was marked limb contracture of all extremities and marked scoliosis of the thoracic spine. The lungs showed gross and microscopic evidence of pneumonia. Foreign material was present indicating aspiration.

The brain showed no gross external abnormalities and in the fresh state weighed 1075 gm (N-1290 gm). After fixation, on coronal section, there was mild dilatation of the lateral ventricles; moderate dilatation of the third ventricle; loss of tissue in the corpus callosum and diminution of the subcortical white matter (Figure 1). A small incidental cavernous angioma was seen in the right frontal white matter. The optic nerves, chiasm and tracts were small and had a gray appearance. There was tan-brown discolouration of the medial portion of the globus pallidus. The midbrain was small and showed considerable loss of tissue in the cerebral peduncles. The pons was small and had a gray appearance. The dentate nuclei of the cerebellum were not discrete. In a myelin stained whole mount section of the pons, the crossing fibres were present, but there was virtual absence of any long tracts in the basis pontis (Figure 2). In the medulla, the inferior olives were normal, but the pyramids showed marked atrophy.

All areas of the cerebral cortex including the hippocampi show diffuse dropout of neurons with a vacular or spongiform change. Many of the remaining neurons are shrunken and slightly eosinophilic indicating a terminal ischemic insult. There are round homogenous, sometimes granular, eosinophilic structures, axonal spheroids, scattered throughout all areas and all layers of the cerebral cortex. Spheroids (best demonstrated with Bodian's stain) (Figure 3) are occasionally present in the white matter. There is mild demyelination throughout the white matter and this is associated with mild gliosis.

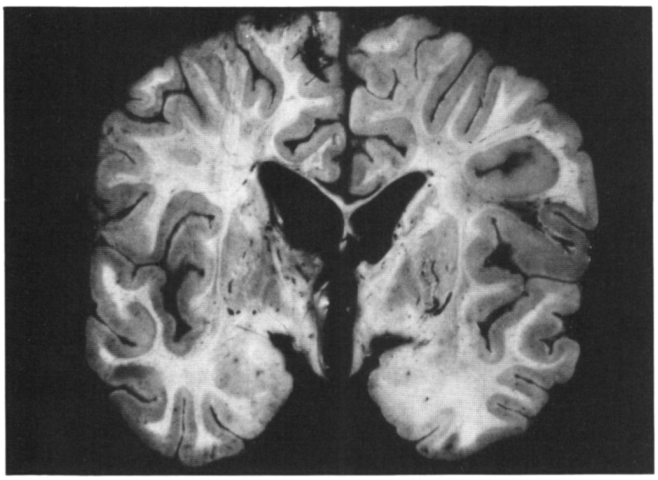

Figure 1 — Coronal section of the brain at a level just rostral to the mammillary bodies.

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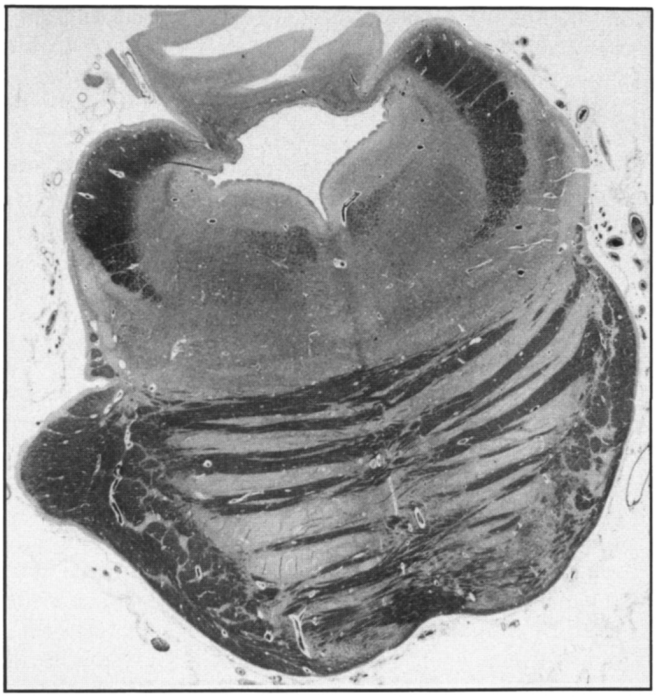

Figure 2 — Upper pons, horizontal section, myelin stain (Solochrome R).

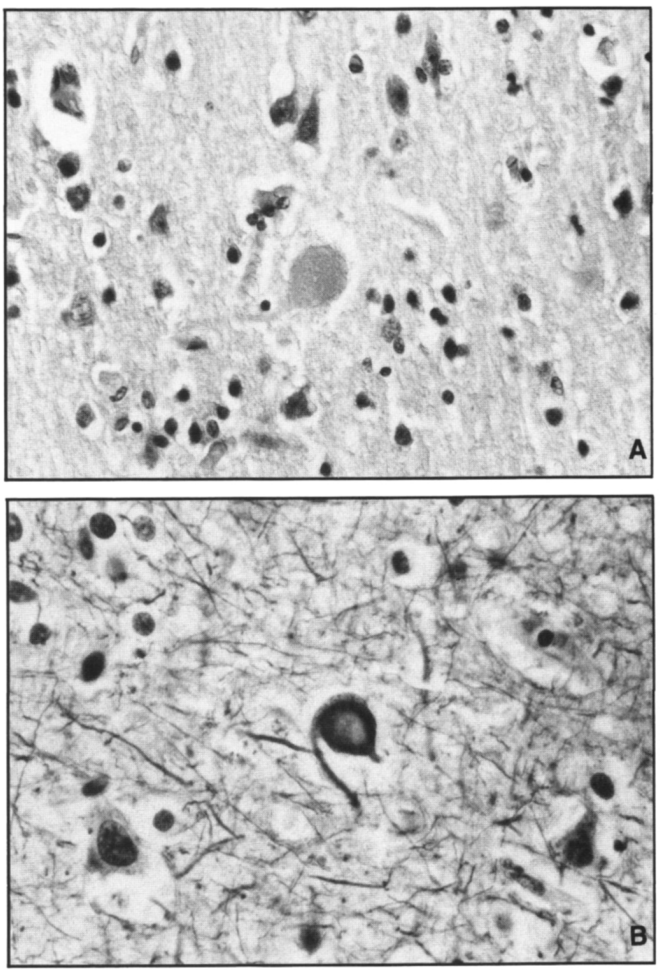

Figure 3 — A) Frontal cortex demonstrating an axonal spheroid (arrow). The neurons are shrunken and show perineural vacuolization. (X 600) - H&E. B) Bodian silver stain of similar area shows neuroaxonal spheroid with axon attached. (X 900)

The globus pallidus shows neuronal drop out with vacuolar change and the presence of axonal spheroids. The caudate and putaman show normal neurons, no spheroids but focal mild gliosis. The diencephalon shows a few spheroids. The thalamic nuclei are normal. In the substantia nigra, the neurons are not fully pigmented at this age, but there are spheroids present. The cranial nerve nuclei, the oculomotor, abducens and the trigeminal nuclei show normal neurons but many spheroids. There are spheroids in the tegmentum of midbrain and pons, in the brachium conjunctivum, and in the superior cerebellar peduncle. In the medulla the inferior olive is well preserved, but there is gliosis and many spheroids in the area postrema, nucleus cuneatus, nucleus gracilis, vestibular nuclei and tegmentum. In the cerebellum, there is replacement of the Purkinje cells by a diffuse band of astrocytes, the granular cell layer is diminished. The white matter is atrophic and there are spheroids in both the granular cell layer and the white matter. The dentate nuclei show loss of neurons with gliosis.

All levels of the spinal cord show a similar picture with demyelination of the dorsal columns and lateral columns including the lateral cortico-spinal tract and dorsal and ventral spinocerebellar tracts. In the cervical cord in the dorsal root entry zone, one can see spheroids which are also present in all the peripheral nerves sampled (superficial, deep, and common peroneal nerves and posterior tibial nerve). In the optic nerves, there are very few axons present, and there is demyelination and severe gliosis. The posterior pituitary shows many spheroids.

Both in the cerebral cortex of the frontal lobes and in the basal ganglia, and particularly in the globus pallidus there are iron deposits in the tissue in association with capillaries (Figure 4).

With the electron microscope, some spheroids appear to be surrounded by a thin myelin sheath. Within the swelling there are mitochondria, dense osmiophilic structures and numerous tubular/membranous structures (Figure 5). These "dystrophic" axonal spheroids may also demonstrate abnormal lamellar structures.[9]

Recently, there are some suggestions that the "spheroids" which are found in the cortex are dystrophic cortical boutons and not degenerated axons.[7,8] These may be under recognized because of technical problems in the preservation of the tissue.[7]

There are two types of axonal spheroids, reactive and

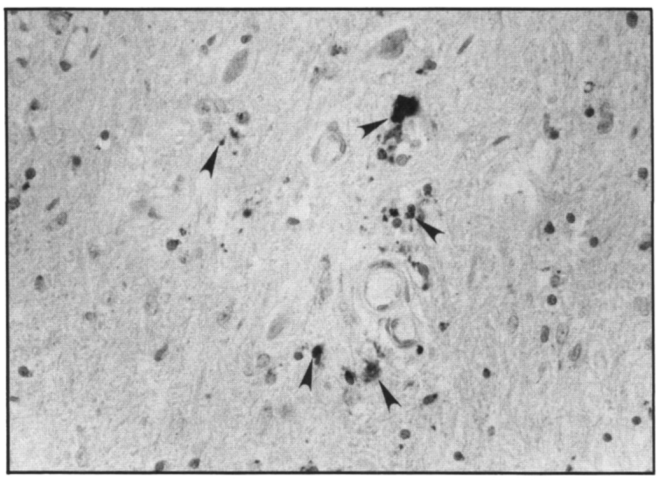

Figure 4 — Globus pallidus. Multiple small deposits of iron in the tissue and in a perivascular position (arrowheads). (X 600)

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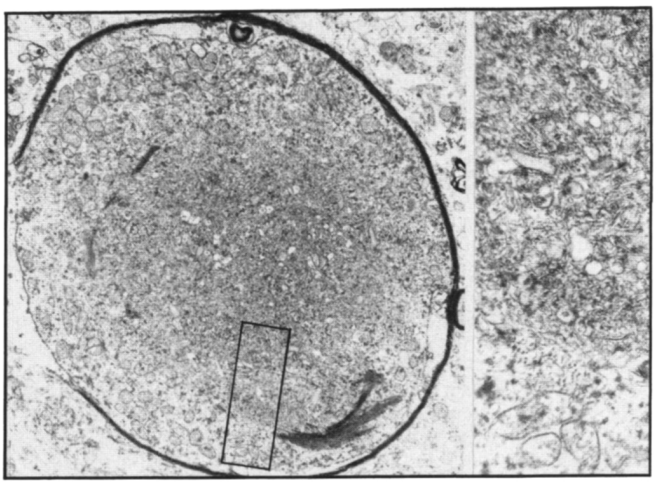

Figure 5 — Electron micrograph of a neuroaxonal spheroid. Residual surrounding myelin sheath is present. A collection of organelles includes membranous material, mitochrondria and nonspecific organelles. (X 8230), insert (X 27480)

dystrophic. It is very difficult to separate these by light microscopy, but they may be distinguished on the basis of the ultrastructural characteristics. Dystrophic spheroids can show abnormal lamellar structures as opposed to the reactive spheroids where these are not found.[9] Reactive spheroids occur in transected axons. Dystrophic spheroids are thought to arise in two situations; secondary to normal physiological processes or primary (endogenous), related to some underlying disease. Axonal spheroids are very common in the nucleus gracilis in elderly people such that by the age of 40, 98% of people have dystrophic spheroids.[9] These are felt to be a consequence of the normal aging process. Spheroids of this type have also been described in cystic fibrosis, in the lipidoses, in the glycogenoses, in Wilson's disease and in congenital biliary atresia.

Under the so called "endogenous type" of dystrophic axonal spheroids are the group of disorders known as neuroaxonal dystrophies (NA). This involves a spectrum of about six different disorders;[9] including the infantile, late infantile, juvenile neuroaxonal dystrophy, neuroaxonal leukoencephalopathy, Hallervorden-Spatz disease (HSD) and presenile neuroaxonal dystrophy (with perhaps the recent addition of dermatoleukodystrophy).[10] In the late INAD the axonal spheroids are widespread in both the central and peripheral nervous systems. As the disease spectrum approaches HSD the spheroids become confined to the pallido-nigral system. There is little excess pigmentation in the disorders of INAD and late INAD; however, in HSD, there tends to be more abnormal pigment deposition, particularly in the pallidum.

The pathogenesis of a dystrophic spheroid is unknown. There are many theories; the most recent relates to injury to the neuron by lipid peroxidation, the generation of free radicals or unstable molecules due to injury and the complexing of these radicals to the membranes of the neuron.[9,11,12] The injury leads to decreased axonal maintenance and decreased axonal flow. The organelles which would ordinarily move in the axon collect at the terminal end resulting in the formation of a spheroid. Eventually, the spheroid will disappear, but so does the associated axon, neuron and myelin in the process known as the "dying-back" phenomenon. The formation of lipofuscin pigments in aging is also felt to arise from lipid peroxidation.[13] Perhaps the same type of process is going on in senescense to allow for the formation of spheroids in the brain stem sensory nuclei.[9] No one has related metabolic disorders with lipid peroxidation, but it is implied that there is some type of metabolic defect that is causing damage to the neurons. In Byler's disease[14,15] there is a deficiency of bile acid secretion. Patients do not absorb fat soluble vitamins including vitamin E which acts as an antiperoxidant. Some patients have been found with low serum vitamin E levels and pathologically show neuroaxonal spheroids in the central nervous system and dorsal root ganglia as well as neuronal loss in selected areas of the brainstem, basal ganglia and spinal cord. Vitamin E repletion may correct the neurologic dysfunction in children with chronic cholestasis.[11]

The endogenous spheroid type of disorder: INAD and HSD is even more mysterious. Some authors[9,12] suggest that the presence of iron particularly in HSD acts as an oxidant and is inducing lipid peroxidation. At this time this notion is not proven.

The diagnosis of infantile neuroaxonal dystrophy can be made in several ways. Post mortem examination is obviously unsatisfactory. A brain biopsy can be helpful, but this is drastic. Recently advocated is biopsy of peripheral nerve, conjunctiva, rectum or dental pulp[16,17,18] as the presence of spheroids can be demonstrated in nerve fibers at these sites.

To summarize, this is a case of neuroaxonal dystrophy with the presence of axonal spheroids involving all areas of the cerebral cortex, the subcortical white matter, basal ganglia, diencephalon, brain stem, cerebellum and spinal cord. There is siderocalcinosis involving the globus pallidus (moderate) and cerebral cortex (mild). Tract degeneration involves corticospinal tracts, dorsal columns of the spinal cord and dorsal and ventral spino-cerebellar tracts. There is severe optic atrophy and cerebellar atrophy.

Pathological Diagnosis

Neuroaxonal Dystrophy, late infantile type.
Aspiration pneumonia.
Ischemic encephalopathy, acute.
Venous angioma, right frontal lobe, incidental.

Acknowledgements

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