Striatal degeneration in childhood

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SUMMARY The clinical features, and the radiological and neuropathological findings of 3 unrelated children with striatal degeneration are presented. In one case the father had recently developed choreiform movements while in the other two the family history was negative for neurological disorders. Two patients had juvenile onset of psychiatric symptoms, seizures, and rigidity. The 3rd child presented with focal seizures at 9 weeks of age. The neuropathological findings are virtually identical in all 3 cases. The classification of striatal degeneration in childhood is discussed.

Isolated degeneration of the striate body in childhood is rare and constitutes a diagnostic problem. Patients with juvenile Huntington's disease demonstrate striatal degeneration but the lesion is not usually restricted to that structure. Cases with striatal necrosis have also been described. Three unrelated children with progressive degeneration of the striate body are reported.

Case reports

Case 1. This girl was the first child of unrelated healthy white parents. She was born at term after a normal pregnancy, labour, and delivery and weighed 3.02 kg at birth. There was no family history of neurological disorder, but the father had been adopted and details of his family's medical history are not known. The father remained in good health until about one year after his daughter's death when, at 30 years, he gradually developed choreiform movements. The patient's younger sister, now aged 11, remains in good health. Up to age 5 years, the only abnormalities noted in the patient were a mild dysarthria and a tendency to walk on her toes. At age 5 years she was seen by a psychiatrist because of occasional incontinence and the development of disturbed behaviour characterised by sudden outbursts of crying without obvious reason. Physical examination at that time showed left internal strabismus, slight increase in muscle tone in all extremities, and mild incoordination. Her full scale IQ by the Stanford-Binet test was 92. At age 7½ years she had her first generalised convulsion but no more

occurred until a year later. Meanwhile, a slow deterioration in her mental capacity became evident and at age 8 years her IQ had dropped to 54.

She was first seen at The Hospital for Sick Children at age 9 years. During the previous year she had had increasingly severe generalised, akinetic, and myoclonic seizures which responded poorly to a variety of anticonvulsant medications. On examination she was alert, co-operative, but obviously mentally retarded. Her head circumference (49 cm) and her height were at the 3rd centile. She had an impassive facies and mild ptosis of the left eyelid. There was difficulty in initiating movements and postural control was poor. She had a fine resting tremor and an unsteady tip-toe gait. Generalised rigidity was noted and the tendon jerks were brisk. The plantar responses were flexor.

An electroencephalogram demonstrated multifocal spike discharges, particularly on the left. Electroretinography and visual evoked responses were normal. Nerve conduction studies were normal. Although an electromyogram was suggestive of myopathy, a muscle biopsy was within normal limits. Computerised tomography of the head demonstrated enlargement of the lateral ventricles, particularly anteriorly (Fig. 1). Routine investigations of blood and urine were normal as were serum electrolytes and liver function studies. Serum copper and caeruloplasmin levels were normal. There was no increase in blood pyruvate or lactate. Assays for white blood cell β -galactosidase, arylsulphatase A, and hexosaminidase A and B activity were within the normal range. CSF examination showed no abnormality.

After discharge from hospital, our patient's seizures were better controlled but the tremor and rigidity were increasing. She was admitted to the local

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Fig. 1 Computerised tomogram of the head, demonstrating lateral ventricular enlargement particularly anteriorly in the area of the head of the caudate nucleus.

hospital at age 9½ years because she had become too difficult to manage at home. She died 3 months later after further neurological deterioration.

Necropsy (Dr R. Salm)

The body was rather thin. No lesions were found except in the CNS.

The brain was reduced in size, the total weight being 1070 g; the cerebellum and brain stem accounted for 154 g. (The average weight of normal brain is 1290 g for this age.) No morphological abnormality was noted externally but coronal sectioning showed enlargement of the lateral ventricles which was more pronounced anteriorly at the level of the striate body. The caudate nucleus and the putamen were shrunken on both sides (Fig. 2). The shrinkage of the caudate nucleus was severe along its entire length, while that of the putamen appeared less marked more posteriorly. There was slight shrinkage of the thalamus and the third ventricle was enlarged (Fig. 3).

Both the caudate nucleus and the putamen showed great loss of neurons, the small neurons being mainly affected. The lesion was increasingly severe caudally. The loss of neurons was accompanied by moderate astrocytic proliferation (Fig. 4). The glial fibre formation was sparse (Fig. 5). Sudanophil or PAS-positive material was not demonstrated in the

Fig. 2 Coronal slice of the brain. Note marked shrinkage of the striate body and large lateral ventricles.

Fig. 3 Coronal slice of the brain at level of mid-thalamus. Note marked shrinkage of caudate nucleus and slight shrinkage of thalamus.

caudate nucleus or putamen. In sections stained for myelin and axons it was obvious that there was marked loss of the caudato-putaminal and putamino-pallidal fibres (Fig. 6). The globus pallidus and the thalamus showed no neuronal loss or gliosis but the myelin sheaths were weakly staining and there was some loss of axons. Patchy loss of nerve fibres accompanied by demyelination was also present in

Fig. 4 Microphotograph of putamen showing a single neuron (arrow) in a field of proliferating astrocytes. H & E $\times 400$.

Fig. 5 Microphotograph of putamen showing astrocytic nuclei with sparse glial fibre formation. Holzer $\times 400$.

the internal capsule. The claustrum, substantia nigra, subthalamic nucleus, red nucleus, and amygdaloid nucleus were intact.

The cerebral cortex showed good preservation in all regions except in the Ammon's horn where there was some neuronal loss and gliosis in the Sommer's sector and endplate. The centrum semiovale and corpus callosum were normally myelinated. The only changes in the brain stem were in the inferior olives. The spinal cord was not available for examination.

The cerebellar cortex showed severe diffuse loss of Purkinje and granule cells with prominent gliosis in all parts. Patchy neuronal loss was observed in the dentate nucleus and the white matter was somewhat pale on myelin staining. The inferior olives showed slight loss of neurons.

Case 2. This baby girl was the 2nd child of non-consanguineous white parents. There is an elder sister, one year older, who remains well. The father died at age 28 years of carcinoma of the stomach. There is no family history of degenerative neurological disease. The patient weighed 3.6 kg at birth

and was 2 weeks postmature. Pregnancy, labour, and delivery were otherwise normal. Growth and developmental milestones were normal until 3½ years when she was noted to have a fine tremor of the hands. During the next 2 years she developed increasing clumsiness of gait and slurring of speech. At age 5½ years behavioural problems became evident. She had violent swings of mood with screaming at night and outbursts of violence towards her sister followed by withdrawal and apathy. She was admitted to The Hospital for Sick Children for evaluation.

On examination she was distractible and generally behaved in an immature manner. Her head circumference approximated the 50th centile (50 cm). She had a fine action tremor and was clumsy in manipulating small objects. Her gait was clumsy and awkward. The deep tendon reflexes were brisk. The plantar responses were extensor. Her verbal IQ score was 85 and her performance IQ score was 70 on the Wechsler scale. The neurological examination was otherwise normal. An electroencephalogram demonstrated multifocal spike discharges with variable localisation. During the next year she

Fig. 6 Microphotograph of putamino-pallidal bundles showing partial demyelination. Luxol fast blue and cresyl violet. $\times 240$.

continued to deteriorate. She began to have brief drop attacks and her educational progress ceased. By 6½ years she had developed cogwheel rigidity of all extremities. She was readmitted to hospital. Her head circumference was 52 cm. An air encephalogram was normal. Examination of the CSF showed no abnormality. Blood and urinary amino-acid pattern was normal. Serum copper and copper oxidase levels were normal. At this time she had her first generalised convulsion. Thereafter she had frequent seizures which were generalised, akinetic, or myoclonic in type. Anticonvulsants only partially controlled the convulsions and a course of ACTH did not result in clinical improvement. A trial of benzhexol (Artane) did not alter the rigidity. During the next 18 months repeated admissions were necessary to control her seizures. When admitted at 8 years, she was severely demented and could say only a few intelligible words. She seemed to suffer from terrifying hallucinations and declared she saw insects in her bedclothes and hair. Her head circumference was 51 cm. She was rigid and lay in a 'catatonic' posture with a face lacking any expression. Any voluntary movement of the upper extremities

was hampered by severe action tremor. She had difficulty in swallowing which necessitated feeding through a nasogastric tube. All reflexes were brisk. Sustained ankle clonus was present. The plantar responses were extensor. The fundi were normal and there was no abnormality of eye movements. She died of bronchopneumonia at age 8½ years.

Necropsy

The body was thin with slight flexion contractures of the elbows and knees. The lungs showed bronchopneumonia. No other abnormalities were found except in the CNS.

The brain was reduced in size, the total weight being 1120 g; the cerebellum and brain stem accounted for 133 g. (The average normal brain weight for this age is 1273 g.) No morphological abnormality was noted externally but coronal sectioning showed enlarged lateral ventricles. The enlargement was more pronounced anteriorly owing to the shrinkage of the striate bodies (Fig. 7).

The caudate nucleus and putamen showed moderate loss of nerve cells, the small neurons being mainly affected. The neuronal loss was accompanied by marked astrocytic proliferation and slight fibrous gliosis. The caudate nucleus was fairly uniformly affected at every level while in the putamen the damage was greater in the lateral than in the medial portions. The caudato-putaminal and putamino-pallidal bundles showed severe loss of nerve fibres and the myelin sheaths were poorly stained. The globus pallidus showed slight pallor of myelin. No changes were present in the hypothalamus, thalamus, claustrum, substantia nigra, or amygdaloid nucleus.

Fig. 7 Coronal slice of the brain. Note marked shrinkage of the striate body.

No abnormality was detected in the cerebral cortex or centrum semiovale.

The cerebellar cortex showed moderate loss of Purkinje and granule cells. The inferior olives showed slight loss of nerve cells but otherwise the brain stem was normal. The spinal cord was normal at all levels.

Case 3. This boy was the second child of unrelated white parents. An older brother and a younger sister remain in good health. There is no family history of neurological disease. Pregnancy was complicated by bleeding at 4 months which necessitated hospital observation. Fetal movements may have been diminished. The delivery at term was uneventful. The birthweight was 3.8 kg. He was noted to smile and follow visually at 6 weeks, and he was sitting without support at 3½ months. However, at 9 weeks he had, on the same day, 5 left-sided seizures each lasting 10 min, unassociated with fever. He was admitted to a local hospital where an electroencephalogram suggested a right-sided abnormality with a background of generalised slowing. Approximately one month later, 4 similar attacks occurred. Phenobarbitone was administered but 24 hours later the child had a generalised seizure lasting 20 min. Diphenylhydantoin was added to the treatment but continued left-sided and generalised convulsions necessitated another hospital admission at 4 months of age. Examination at that time showed a rather pale, visually attentive infant who reached for objects without difficulty. His head circumference was at the 50th centile (42 cm). He had normal head control and vocalisation for his age. Hearing appeared intact. The other cranial nerves were also normal. The child preferred to use the right hand. The muscle tone was normal. The deep tendon reflexes were slightly brisker on the left. The plantar responses were equivocal. Laboratory investigations included a normal blood count, urine analysis, and serum electrolytes. Blood and urine amino and organic acid pattern was normal. Screening tests for congenital infections including rubella, toxoplasmosis, and cytomegalic inclusion disease were negative. The CSF was normal. An electroencephalogram demonstrated multifocal spike discharges, especially on the right. An air encephalogram was performed which suggested cerebral atrophy.

Continued seizures precipitated readmission at 7 months. His head circumference was 44 cm. The neurological findings were unchanged except that his response to auditory stimuli was less acute than at the previous examination at 4 months. His course continued to be marked by periods of poor control of the seizures.

During the next year he developed complex choreoathetotic movements of all extremities. There was marked hypotonia although the tendon jerks were brisk. The child was developmentally retarded at the 4 months level. His condition remained static until he died at age 2½ years.

Necropsy

The body was well covered and there was fine hair over the neck, back, arms, and thighs. The head was small, head circumference 45 cm. There was terminal bronchopneumonia. No abnormality was detected in any organ except the CNS.

The brain was reduced in size, the total weight being 810 g, the cerebellum and brain stem accounting for 90 g. (The average weight of normal brain is 1140 g for this age.) No morphological abnormality was noted externally but coronal sectioning showed enlargement of the lateral ventricles which was most pronounced anteriorly. The caudate nucleus was shrunken along its entire length while the putamen appeared to be of normal size (Fig. 8).

Marked loss of neurons was observed in the caudate nucleus, the small nerve cells being affected more than the large ones. The degeneration was accompanied by prominent astrocytic gliosis but only little fibrillary reaction. The process was

Fig. 8 Coronal slice of left hemisphere. Note marked shrinkage of the caudate nucleus.

increasingly severe more caudally. There were also a few microscopical foci of spongy appearance. The putamen on either side showed less marked loss of neurons, but there was obvious proliferation of astrocytes in the dorsal regions. Loss of nerve fibres was noted in the caudato-putaminal bundles. No changes were seen in the thalamus, subthalamic nucleus, globus pallidus, substantia nigra, or mammillary body. The Ammon's horn showed marked neuronal loss and gliosis throughout. The remainder of the cerebral cortex was well preserved. The centrum semiovale was normally myelinated.

There was severe loss of Purkinje and granule cells in the cerebellar cortex with prominent gliosis. The white matter of the folia showed pallor on myelin staining. Slight loss of nerve cells was apparent in the inferior olives. The pons showed a few microscopical foci of recent haemorrhage. There was no abnormality in the spinal cord.

Discussion

The outstanding pathological feature of the 3 cases presented is bilateral striatal degeneration. The histological picture bears the hallmarks of a chronic process—i.e. total absence of a mesodermal reaction and breakdown material in spite of the obvious neuronal loss and astrocytic proliferation.

Degeneration of the striatum is the characteristic lesion in Huntington's disease (Campbell *et al.*, 1961; Jervis, 1963; Markham and Knox, 1965; Byers and Dodge, 1967; Byers *et al.*, 1973). However, Byers *et al.* (1973) reviewing the neuropathological findings in 14 children with Huntington's disease, noted that in addition to the striatal lesion, virtually all reported cases also showed degeneration of the globus pallidus and the cerebral cortex albeit to a less severe degree than that of the striate body. In their own 4 cases which were extensively studied similar damage was detected in the thalamus, pontine tegmentum, vestibular nuclei, and the cerebellum.

Roessmann and Schwartz (1973) described 2 brothers with a subacute progressive neurological syndrome that was characterised by onset in infancy, psychomotor retardation, and rigidity. Pathological examination showed marked neuronal loss in the caudate nucleus and putamen, accompanied by moderate astrocytic proliferation. The rest of the brain was reported as normal.

An apparently distinct entity of necrosis of the striate body has been reported by several authors (Marinesco and Draganesco, 1929; Hawke and Donohue, 1950; Miyoshi *et al.*, 1969). The neurological symptoms began after a febrile illness in childhood. The clinical features included alteration

of consciousness and abnormal muscle tone with involuntary movements and, occasionally, myoclonic seizures. Naked eye examination of the brains disclosed softening of the caudate nucleus and the putamen. Microscopically the softened areas were necrotic with brisk mesodermal reaction. Some of the cases were familial.

Verhaart (1938) described striatal necrosis in a series of patients who also showed similar lesions in other regions of the brain, particularly in the basal ganglia and brain stem. It was suggested (Friede, 1975) that his cases may represent an early description of Leigh's subacute necrotising encephalomyelopathy.

The nosological classification of our cases poses considerable difficulty. Pathologically all 3 showed progressive degeneration of the striate body. In Cases 1 and 2 both the caudate nucleus and putamen were severely affected, while in Case 3 only the caudate nucleus showed severe degeneration with a less pronounced lesion in the putamen. Furthermore, the clinical course of Case 3 differed from the others. Cases 1 and 2 were remarkably similar in the juvenile onset of psychiatric symptoms, seizures, dementia, tremor, and rigidity. Case 3, on the other hand, presented at 9 weeks with seizures that were refractory to anticonvulsant therapy. His clinical course was characterised by psychomotor retardation, hypotonia, and choreoathetosis in addition to severe seizures. He died before his 3rd birthday.

Cases 1 and 2 bear notable similarity to Huntington's disease in their clinical course. However, only Case 1 has a positive family history in that her father developed chorea at age 30, six years after the onset of symptoms, and one year after the death of his daughter. In view of this history and the clinical course Case 1 is, in our opinion, a case of juvenile Huntington's disease, in spite of the fact that the neuropathological lesions in her case were more restricted than those in previous reports (Byers *et al.*, 1973). The pathological features of our cases are more similar to those described by Roessmann and Schwartz (1973). The only significant difference is in the cerebellum. However, we feel that the loss of Purkinje and granule cells in the cerebellar cortex may be secondary, caused either by the intractable seizures or anticonvulsant medication (Hoffman, 1958). This would be supported by the neuronal loss and gliosis in the Ammon's horn in Cases 1 and 3. The clinical presentation and course in Cases 1 and 2 were dissimilar from those of Roessmann and Schwartz. Case 3 was similar to their cases in age of onset but seizures, which were so prominent in our patient, were not noted in those of Roessmann and Schwartz. Our cases also differed in that there was no evidence of siblings being similarly affected.

While our Cases 1 and 2 bear clinical similarity to juvenile Huntington's disease with a positive family history in Case 1, the pathology in all 3 patients resembles more closely the cases of striatal degeneration reported by Roessmann and Schwartz. The diagnostic problem is whether all these cases represent a single disease of wide spectrum with the same biochemical defect or whether the clinical and pathological differences are significant and therefore there is more than one disease. The genetic implications make such a distinction important. Huntington's disease is an autosomal dominant disorder whereas the cases of Roessmann and Schwartz suggest an autosomal recessive pattern. The final classification of striatal degeneration has to await the determination of the underlying biochemical defect.

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