Infantile Huntington's Disease

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SUMMARY: A unique case of Huntington's disease is reported because of the extremely early onset and death, and the atypical mode of presentation including severe behavioural problems and a negative family history. Although rare, Huntington's disease must be considered along with the established degenerative disorders of white and gray matter peculiar to the pediatric population when one examines an infant or child with progressive motor deterioration, rigidity, mental retardation and behavioural abnormalities. Computed tomography is a reliable and non-invasive method of establishing the diagnosis during life.

RÉSUMÉ: Nous présentons un cas unique de chorée de Huntington à cause de la précocité exceptionnelle du début et du décès et à cause du mode de présentation qui inclut des problèmes comportementaux sérieux, sans histoire familiale. Même si ce diagnostic est rare chez l'enfant, il faut le considérer lorsque la présentation inclut une détérioration motrice progressive, une rigidité, un retard mental et des anomalies de comportement. La tomodensitométrie est une méthode diagnostique sûre et non-invasive.

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Huntington's disease is extremely rare in the pediatric population; less than one per cent of cases have the onset of symptoms prior to 10 years of age (Jervis, 1963). When the disease becomes manifest during the first decade of life, the neurological abnormalities are often quite distinct from the progressive choreiform movements and presenile dementia which characterize the adult form. We recently studied a child in whom the symptoms of Huntington's disease began during infancy and whose death at 4 years of age appears to be the youngest recorded in the literature.

Case Report

A 20 month old male was referred because of a severe behaviour disorder. He was the result of an uncomplicated 37 week gestation and weighed 3040 g. at birth. The child's motor and language development was moderately delayed; he did not walk unsupported until age 16 months and had only a few single words at 20 months of age. When 10 months of age, the infant had a sudden alteration in personality characterized by constant crying, irritability and self-destructive behaviour including biting and head banging. Brief seizures consisting of staring and associated paleness became evident.

The neurological examination showed normal cranial nerve function including ocular pursuit. There was no speech and the child could not comprehend simple one step commands. He walked or ran constantly. Gait was slightly broad-based and unsteady, but ataxia could not be demonstrated. Although he tended to walk on his tip-toes, no abnormalities of tone or upper motor neuron signs could be elicited. Negative or normal laboratory studies included examination of the cerebrospinal fluid (CSF), serum lead, urine and plasma amino acid determination, nerve conduction velocities, bone marrow examination and a karyotype. Computed tomography (CT) suggested mild cerebral atrophy and the electroencephalogram (EEG) showed subcortical epileptogenic activity. A series of major tranquilizers were employed unsuccessfully to treat the increasingly severe and prolonged behavioural outbursts, irritability and self-mutilation (fluphenazine enanthate, haloperidol and hydroxyzine). Phenytoin controlled the seizures. By the time he was 2 years of age, the parents could not cope with the child's behaviour and institutionalization became necessary.

The child's ambulation began to deteriorate. He refused to walk following a fall at 3½ years of age which resulted in a fractured tibia. He would fall while sitting and could no longer feed himself. Examination showed progressive increase in tone in the lower extremities with contractures of the Achilles tendons, unsustained clonus at the ankles and brisk reflexes. The muscle tone was decreased in the upper extremities with absent deep tendon reflexes. He displayed random athetoid movements in the upper extremities. Additional negative studies included serum lactate and pyruvate, a skin biopsy for lysozymal enzymes (N-Acetyl Hexosaminidase, β-galactosidase, Acid Phosphatase, β-glucosidase, α-galactosidase. α-glucosidase, α-mannosidase, Arylsulfatase A, and α-fucosidase), serum arylsulfatase A and a screen for mucopolysaccharides. A sural nerve biopsy demonstrated a mild neuropathy mainly affecting the unmyelinated fibers and a repeat CT scan was suggestive of Huntington's disease (Figure 1). The child developed an upper respiratory infection and died at the age of 52 months.

At the time of the initial visit, the father, who had immigrated from Germany, was 38 years of age. The child's mother, who was raised in the United Kingdom, was 32. There is only one sibling, a normal 4 year old boy. The father's family history was reviewed in detail and was negative for neurological disorders, particularly Huntington's disease. The mother's father was a serviceman whose name or whereabouts is unknown even following a recent extensive search. The family history is negative on the maternal grandmother's side. The neurological examination was within normal limits for both parents and sibling. Provocative drug testing of the parents has not been attempted.

Neuropathologic Findings

The brain in the fresh state weighed 1030 g. The hemispheres appeared symmetrical. There was mild dilation and no asymmetry of the ventricles (Figure 2). The cortical gray matter and underlying white matter appeared normal; however, the corpus striatum was distinctly abnormal (Figure 3). On microscopic

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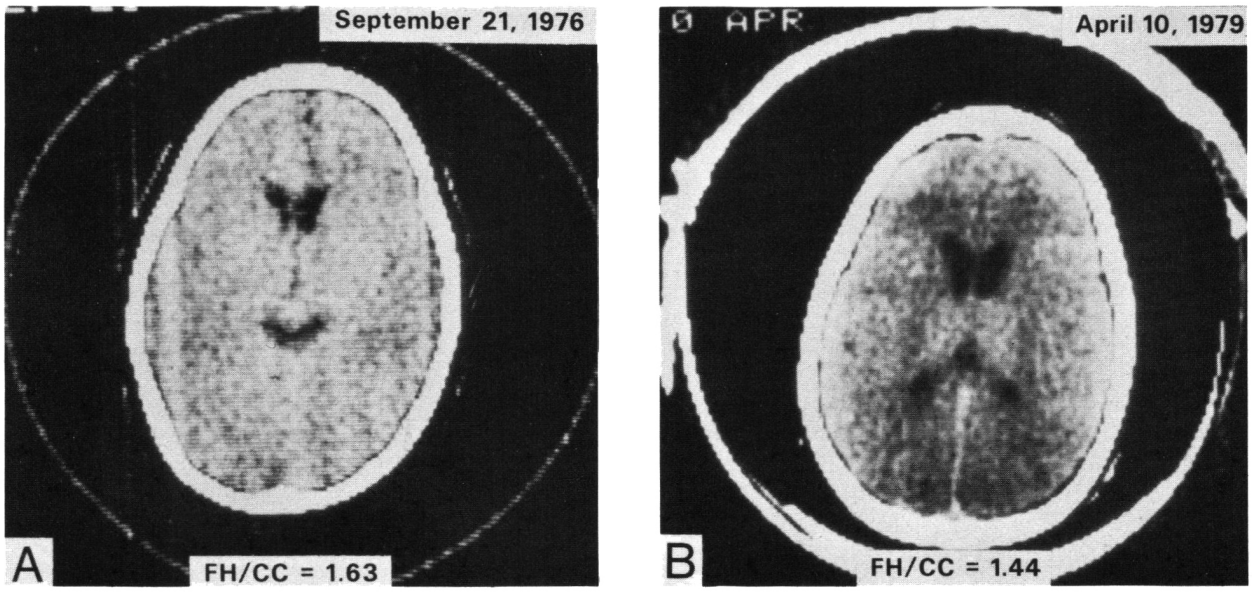

Figure 1 — A) — The initial CT scan shows mild ventricular enlargement which was suggestive of cerebral atrophy. The bifrontal (FH) to bicaudate (CC) ratio was 1.63. *B)* — A repeat CT at age 4 years shows findings compatible with Huntington's disease. Note the "squaring off" of the frontal horns and the FH/CC of 1.44 (see text).

examination the most striking findings were located in the basal ganglia. The predominant cell type in both the caudate and putamen was the astroglial cell (Figure 4). The overlying temporal and frontal cortex showed marked subpial and molecular layer gliosis. There was also the occasional focus of perivascular gliosis. There was no observable loss of cortical neurons in this area. The globus pallidus was slightly reduced in size, particularly along the internal capsule border where a significant reduction in myelin was noted. The cellularity of the globus pallidus was increased primarily due to oligodendroglial cells, but the neurons seemed normal. Examination of the brain stem showed gliosis in the region of the vestibular nuclei with no loss of neurons. The Purkinje cells of the cerebellum were normal but there was marked pallor of the myelin in the region of the central white matter of the hemispheres.

Discussion

Huntington's disease is a progressive degenerative disorder of the central nervous system of unknown etiology which is inherited as an autosomal dominant. The onset of symptoms is most typically between 35-55 years of age (mean age of 44 years). The incidence of Huntington's disease is approximately 1/25,000 and its prevalence in Western Canada has been estimated to be 8.4/100,000 (Shokeir, 1975). Adults with Huntington's disease demonstrate persenile dementia and progressive chorea. Following a variable course, death usually results from a pulmonary infection. The pathology of the central nervous system is similar in adults and children and is characterized by atrophy of the caudate nucleus, putamen and frontal cortex with sparing of the globus pallidus (McMenemy, 1969).

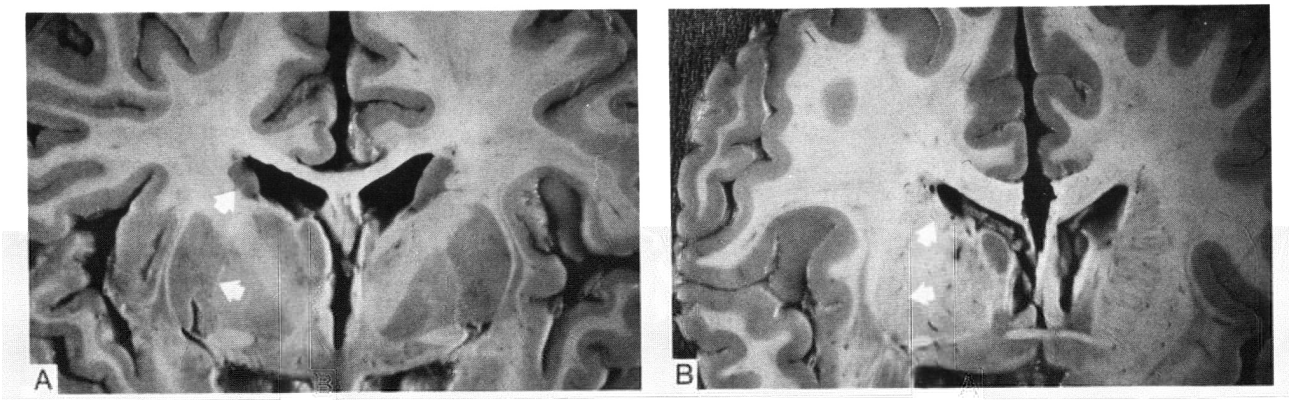

Figure 2 — A) — Coronal section from the brain of a child (4 years old) who died from leukemia. This slightly skew cut has been made in order to match the section from the patient with Huntington's disease as closely as possible. A small portion of thalamus indents the lateral margin of the left lateral ventricle. *B)* — Coronal section from the patient. Note the severe atrophy of the caudate and putamen nuclei (arrows) as compared to the control brain. White scars replace the normal appearance of gray matter in these areas. The cortex shows no evidence of significant atrophy.

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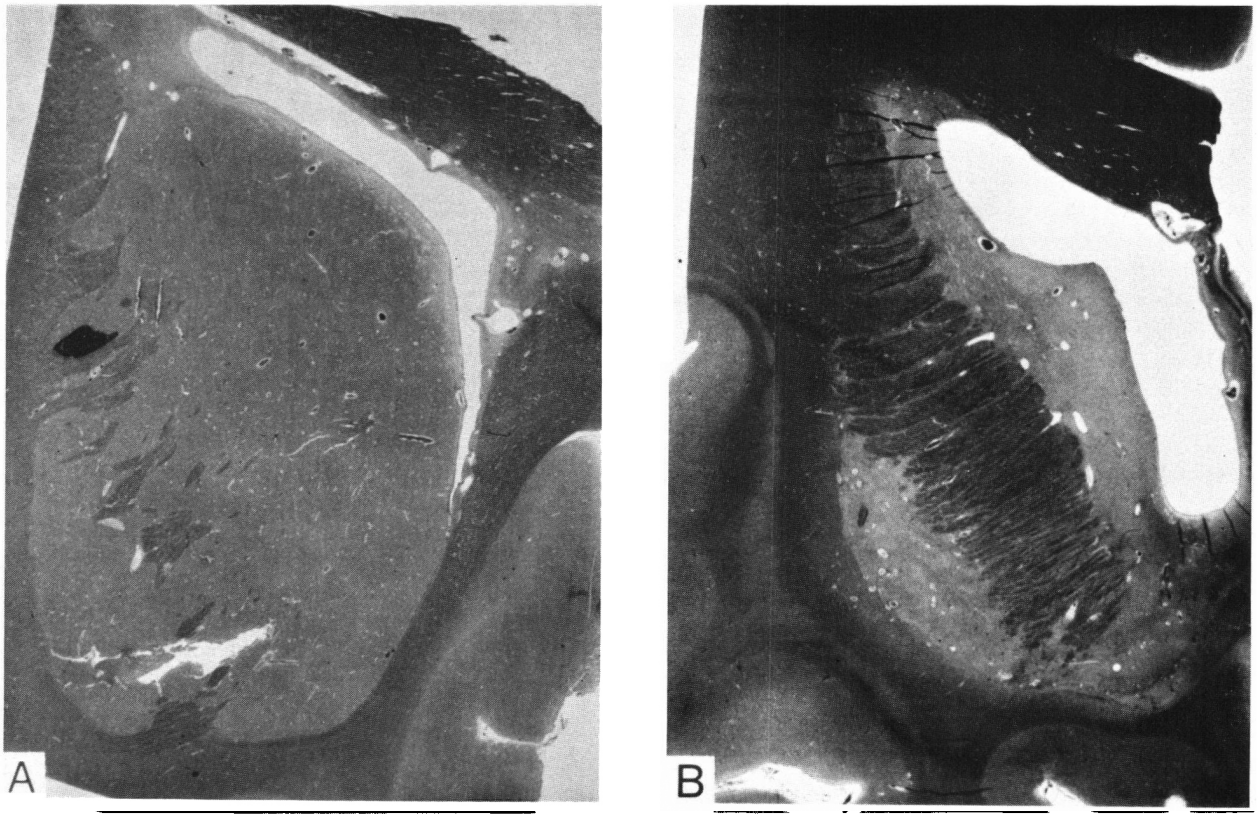

Figure 3 — A) — The corpus striatum is of normal size in this control brain. Note the relative size of the lateral ventricles in the two brains (Luxol fast blue x 6). *B)* — Corpus striatum from the patient showing marked atrophy. The internal capsule appears relatively prominent in comparison. There is no significant demyelination (Luxol fast blue x 6).

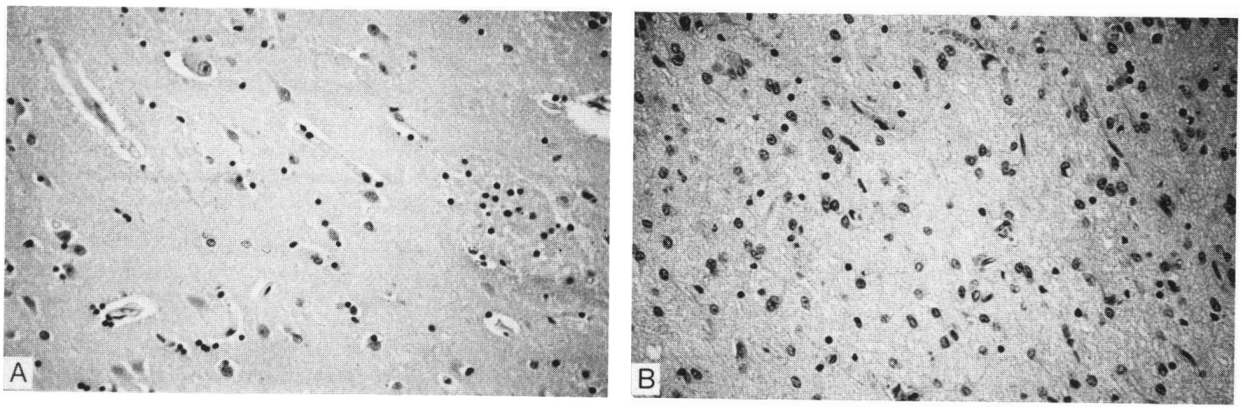

Figure 4 — A) — Caudate nucleus from control brain showing normal proportions of small and large neurons (Haematoxylin and Eosin x 600). *B)* — Caudate nucleus showing gliosis with no residual neurons in the child with Huntington's disease (Haematoxylin and Eosin x 600).

There are several clinical features that distinguish Huntington's disease in the child. Rigidity and dystonia are the most common neurological findings in the pediatric group and choreo-athetosis, at least in the initial stage of the disease, is conspicuous by its absence. Severe astrogliosis of the globus pallidus with a normal complement of neurons was noted by Byers et al (1973) in the majority of the examined cases as well as in the present report, an uncommon finding in patients with the adult variety. The involvement of the globus pallidus may account for the rigidity and dystonia so often encountered in the childhood form of Huntington's disease.

Mental deterioration is much more rapid in children and behavioural problems may be significant. Seizures, usually of the grand mal type, are common in the pediatric group and are typically resistant to anticonvulsants. A pathological cause for the seizures has not been determined and it is therefore assumed that the developing brain is more susceptible to recurrent seizures in association with the pathological changes particularly in the frontal and temporal cortex.

Cerebellar signs are present in about 50 per cent of childhood cases and have been found to be associated with loss of Purkinje cells and neurons in the dentate nuclei. Oculomotor apraxia occurs in approximately 20 per cent of individuals with juvenile Huntington's disease. Hansotia et al (1968) noted that dyslalia was the most common presenting symptom in a review of 20 cases of juvenile Huntington's disease. Finally, the course of

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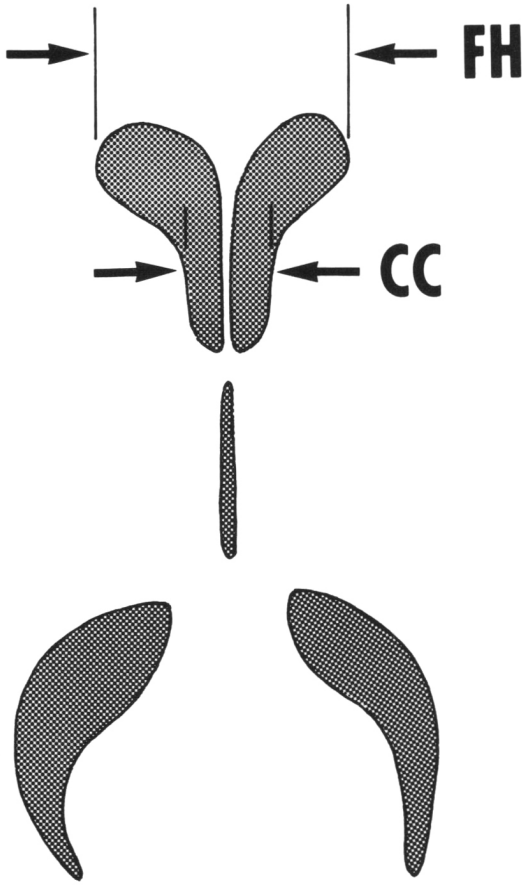

BIFRONTAL(FH)/BICAUDATE(CC) RATIO IN HUNTINGTON'S DISEASE

	Mean	Range
Normal adults	2.48 ± 0.35	1.67 - 3.00
Normal children	3.29 ± 0.22	2.00 - 4.00
Atrophy	2.10 ± 0.33	1.60 - 3.00
Huntington's disease	1.33 ± 0.18	1.08 - 1.57

FH/CC Ratio < 1.60 in Huntington's disease

Figure 5 — The CT findings in Huntington's disease (Modified from Terrence et al (1976)).

the disease is more rapid in children, with an average duration of illness of 8 years as compared to almost 14 years in the adult (Bell, 1934).

Jervis (1963) reviewed the literature and found 20 examples of Huntington's disease where the onset of symptoms was prior to 10 years of age. Subsequently Markham and Knox (1965), Byers and Dodge (1967), Hansotia et al (1968) and Byers et al (1973) described an additional 19 subjects. In almost every patient disturbances of locomotion due to rigidity were the primary presenting symptom. A few were noted to deteriorate in their academic performance and a smaller number displayed behavioural disturbances. Most of the patients had a positive family history for Huntington's disease.

Byers et al (1973) in their neuropathologic review of 14 cases of Huntington's disease in children documented a positive history in 8 families. Although 5 additional families initially denied the presence of the disease, careful follow-up and genetic counselling eventually confirmed the diagnosis by a positive family history. In only one case was a family history not ascertainable. The patient in this report appears to have had the onset of symptoms at the youngest age (10 months) and also died at the earliest age (52 months) of any cases reported in the literature. Although a new mutation is a remote possibility, an inherited gene is statistically much more likely. It is presumed that longterm follow-up of the family will uncover additional cases of Huntington's disease.

CT is a useful non-invasive method of establishing the diagnosis of Huntington's disease during life. Terrence et al (1976) showed that the mean bifrontal to bicaudate ratio (FH/CC) in a group of adult Huntington's patients as 1.33 ± 0.18 whereas the normal adult values were 2.48 ± 0.35 (Figure 5). Johns and Haslam (unpublished data) found the mean value for a group of 8 neurologically normal children between the ages of 2 and 5 years was 3.29 ± 0.22. The initial CT measurements when the patient had few neurological findings fell within the lower end of the cerebral atrophy range (1.63). However, when the CT was repeated 2½ years later at a time when the patient had progressive neurological signs, the FH/CC of 1.44 clearly fell in the Huntington's disease range.

Although Huntington's disease is a rare entity in the pediatric population it should be considered in the differential diagnosis of an infant or child who shows symptoms and signs of a degenerative disorder of the white or gray matter in addition to metachromatic leukodystrophy, Tay-Sachs disease (juvenile onset), neuroaxonal dystrophy, dystonia musculorum deformans, the Tourette syndrome, post-encephalitis, hepato-lenticular degeneration (Wilson's disease), Ramsay-Hunt atrophy of the globus pallidus and Sydenham's chorea. Once the diagnosis of Huntington's disease has been established, it is the physician's responsibility to provide genetic counselling to the family so that the risks for additional cases in future generations are clearly understood.

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