Psychological Medicine, 1978, **8**, 357–360
Printed in Great Britain

EDITORIAL

The brain in Huntington's chorea[1]

The primary genetic defect in Huntington's chorea has not yet been identified, but some new insight into the brain abnormalities that exist in this tragic disorder has come from recent findings of histopathological and neurochemical changes in post-mortem brain.

Although atrophy occurs throughout the whole brain in chorea, the greatest loss of cells occurs in the basal ganglia (Corsellis, 1976). The increased number of glial cells seen particularly in the caudate nucleus and putamen have been counted by Lange *et al.* (1976), who found the total glial cell number in each nucleus to be the same as in normal brain; however, the concentration of glial cells is increased due to the loss of neuronal cells. The basal ganglia at death weigh approximately 50% of normal, whereas the whole brain weight is usually reduced by about 20%. Loss of cortical cells occurs in layers 3, 5 and 6, and although the atrophy is not as marked as in the basal ganglia, this accounts for most of the whole brain weight loss.

Since an increased number of post-mortems have been carried out on patients dying with Huntington's chorea during the last few years, Professor Corsellis and his colleagues have found that about 7% of the cases diagnosed as having Huntington's chorea have some other neurological condition. The condition most often mis-diagnosed as Huntington's chorea is Alzheimer's disease. The confusion may occur because this disorder can also be dominantly inherited and may sometimes present with abnormal movements. However, the rapid progression of the dementia that dominates the clinical presentation in Alzheimer's disease ought to distinguish these 2 disorders. Three cases in the series diagnosed as Huntington's chorea had cerebellar changes consistent with the autosomal dominant form of cerebellar ataxia. It is important that every patient diagnosed as having Huntington's chorea have this confirmed eventually by autopsy, and the neuropathological report subsequently filed in the clinical notes, since these records will continually be examined by future physicians caring for the offspring.

Although the disorder is most frequently first diagnosed when choreiform movements begin between the ages of 37 and 47 years, an examination of the atypical clinical features and the brain when the disorder presents at the 2 age extremes may provide some insight into the biochemical genetics of this disorder.

The juvenile form of this disease is thought to reflect a genetic variant, since rigidity rather than chorea is usually present. Epileptic convulsions may also occur in children, and these manifestations may occur before either parent is suspected of having Huntington's chorea. The progression of the disease in children is rapid, with death usually occurring within 10 years from the onset of symptoms. Juvenile chorea tends to occur sporadically among families; however, it is clear that the juvenile cases will most often have inherited the disorder from their father (Merritt *et al.* 1969). It has been noted that the offspring of affected males have the onset of their disease and die almost a decade earlier than their father, whereas the offspring of affected females have their onset and death at the same age as their mother (Bird *et al.* 1974). It seems very likely that there must be an inherited sex-related factor modifying the disorder. The biochemical defect which is inherited as an autosomal dominant may have the same penetrance in all cases regardless of age but the amount of inherited modifying factor may vary and determine the rate of cell death in the brain. In children the onset is often 2 decades earlier than their affected parent and the cell death is obviously very rapid. Histopathological examination reveals extreme atrophy of the basal ganglia, with the caudate nucleus often reduced to a thin ribbon (Byers *et al.* 1973).

With the onset of choreiform movements in the sixth or seventh decade there is a very slow

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progression of the disease without the development of dementia that is associated with chorea under the age of 50 years. Elderly choreic patients often live for more than 20 years with their chorea and usually die from natural causes. The basal ganglia will not appear as atrophic as in the younger, more typical, cases. Cell death must be progressing at a very slow rate. The late onset of this mild form of Huntington's chorea without mental deterioration tends to maintain this pattern through several family generations, a useful and encouraging point to remember when counselling the offspring.

Psychotic features may precede the onset of choreiform movements by as much as a decade. These behaviour abnormalities are more common in families in which the onset of chorea is earlier than usual, with psychotic features often occurring in the late teens or early twenties. Patients may be admitted to a psychiatric hospital with the diagnosis of schizophrenia and 10 years later, when the choreiform movements appear or when another member of the family develops chorea, the diagnosis becomes clear.

Several chemical transmitters and related enzymes are fairly stable in post-mortem brain and a number of these have been measured in human brain. Brain cooling has been shown to start immediately after death and, provided the cadaver has been placed in a refrigerator, this rate of cooling progresses until the centre of the brain reaches 4 °C, usually about 24 hours after death (Spokes & Koch, 1978). Enzyme activities usually decline to some stable level during this first 24 hours. Control tissues are handled similarly and since it usually takes 24 hours to complete the administrative post-mortem details, cases will usually be autopsied after stability has been attained. The pre-mortem conditions of the patient are more difficult to control. Choreic patients are usually in a psychiatric hospital receiving neuroleptic drugs for some months or years before death. They often develop bronchopneumonia prior to death. Although most of the control brain tissues used for comparison in the past have been from non-neurological cases dying from natural causes, a recent large collection of brain tissues from patients dying in mental hospitals with the diagnosis of schizophrenia can serve as another group for comparison.

Perry *et al.* (1973) were the first to report that the concentration of gamma-aminobutyric acid (GABA), a neuroinhibitory transmitter, was decreased in the caudate nucleus and putamen of post-mortem brain from patients dying with chorea. Bird & Iversen (1974, 1976) found that the biosynthetic enzyme for GABA, glutamic acid decarboxylase (GAD), was decreased in the striatum and substantia nigra but not in the frontal cortex of the brain from choreics. The activity of tyrosine hydroxylase (T-OH), the biosynthetic enzyme for dopamine (DA), however, was normal in the striatum or even increased, particularly in the substantia nigra (Bird & Iversen, 1976).

We have focused considerable attention on the substantia nigra, an area which has had little histopathological examination in the past, since it is always normally pigmented. The substantia nigra is divided into 2 regions, the more dorsal region being the zona compacta which is normally darkly pigmented and contains the cell bodies of the dopamine neurones whose axons form a pathway to the striatum. Dendrites extend from the dopamine cell body throughout both regions of the substantia nigra. The less pigmented ventral region of the substantia nigra, the zona reticulata, receives axons from neuroinhibitory GABA cells in the striatum, and the terminals of these axons are in contact with the dendrites from the dopamine cells. The dopamine concentration in the zona compacta is normally twice that of the zona reticulata (Hornykiewicz, 1963) and concentration of GABA is two-fold higher in the reticulata zone than the compacta zone (Kanazawa & Toyokura, 1975). The substantia nigra in the brain from a patient with chorea is often more darkly pigmented than normal and the zona reticulata is much more atrophic than the zona compacta because of the loss of striatal afferents.

These pathological and neurochemical findings in Huntington's chorea correlate well with the clinical features in this disorder, since loss of neuroinhibition in the substantia nigra could result in excessive dopaminergic activity that is known to be associated with the abnormal movements. Pharmacologic agents used to reduce these movements are usually those which interfere with the post-synaptic receptor for dopamine, e.g. phenothiazines and butyrophenones, or agents which interfere with the storage of dopamine in dopaminergic terminals, e.g. tetrabenazine (Nitoman).

Whether the administration of GABA-like drugs would be therapeutic in chorea would depend on the integrity of the natural receptors for GABA. Enna *et al.* (1976), using radio-active labelled GABA as a ligand, have shown that the density of GABA receptors in the substantia nigra is increased two-fold. Other evidence suggests that the receptors for GABA are located on the dendrites of the dopamine cells, so Enna's study does correlate with the increased concentration of dopamine neurones in the substantia nigra in the brain from choreics.

The activity of choline acetyltransferase (ChAc), the biosynthetic enzyme for acetylcholine, is also decreased in the basal ganglia from some cases who die with chorea (Bird & Iversen, 1974). This decrease is related to the degree of basal ganglia atrophy and is especially marked in the juvenile cases. The cholinergic neurone probably serves as one of the sites for post-synaptic receptors for dopamine and, therefore, the loss of this cell type may explain why the juvenile cases, and indeed many of the adult cases, develop rigidity as the terminal event in their disease. This may also explain why L-DOPA administration to rigid choreics is not effective.

Other clinical indications of the imbalance between GABA and dopamine concentrations may be reflected through the hypothalamus where dopamine acts as a transmitter for cells that produce a number of releasing factors. Gonadotropic releasing factor (GnRF) is under catecholamine control and has been used clinically to treat infertility. GnRF is significantly increased in the hypothalamus of the post-mortem brains from female choreics (Bird *et al.* 1976), and this may explain the increased fertility of the choreic female when compared to her non-affected sibling (Reed & Palm, 1951). The increased libido that many choreic women have may also be due to an increased production of GnRF. Increased serum growth hormone concentration (Phillipson & Bird, 1976) and decreased serum prolactin (Hayden *et al.* 1977) have been reported in patients with chorea, findings consistent with excess dopaminergic activity. There will no doubt be other neuroendocrine alterations discovered in the future that will be secondary to the altered GABA/dopamine ratio in the brain.

Many of the various clinical manifestations of Huntington's chorea have been shown to be associated with specific histological and neurochemical findings in the brain. These clinical features are common to other neurologic and psychiatric disorders and, therefore, future collaboration between clinicians and basic scientists in the examination of post-mortem brain should help to elucidate the defects in a wide spectrum of diseases.

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