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Mini-Review: Multiple developmental forms of parkinsonism. The basis for further research as to the pathogenesis of parkinsonism

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Summary. A range of extrapyramidal disturbances have been reported in children following early brain damage. In adults, damage to the basal ganglia can elicit abnormal motor activity in either direction; it would seem reasonable that the same would apply to damage occurring at an earlier developmental stage. The Viennese paediatrician Widhalm described a hypokinetic/parkinsonoid syndrome ('infantile hypokinetic-hypertonic syndrome with Parkinson symptomatic') presented by a significant minority of the children with extrapyramidal movement disturbances, corresponding to the mild rigid-akinetic type of Parkinson's disease. In contrast to classical parkinsonism, but consistent with some forms of post-encephalitic parkinsonism, the syndrome was reversible, although only after L-DOPA therapy. Widhalm's observation that at least one form of childhood parkinsonism can be cured with L-DOPA also suggests that the amino acid plays a more active role than mere replacement therapy in children, perhaps also acting as a neurotrophic agent. It is proposed that environmental factors, including viral and risk factors associated with pregnancy and birth, together with genetically determined lability, may increase the incidence of early hypokinesia/parkinsonism in particular and of Parkinson's disease in later life by disturbing the immature basal ganglia at critical developmental stages. The spectrum disorder of Parkinson's disease thereby occurs as a number of various etiopathologically distinct syndrome subtypes, including early onset developmental forms caused by in utero or early post partum trauma.

Keywords: Parkinsonism, basal ganglia, L-DOPA, hypokinesia, predisposing factors, prenatal/perinatal events, brain development.

The pre- and immediately postnatal periods of life are recognized as being critical in the normal development of specific brain regions; exposure to viral

infection or other environmental stressors during this period has been associated with abnormalities at both the structural and biochemical levels. The specific consequences of such exposure reflect interactions between genetic susceptibility of the individual, relative vulnerabilities of particular brain regions and the developmental stage at which exposure occurs.

A range of extrapyramidal disturbances have been reported to occur in children following early brain damage, many of which become clinically obvious only at the time when the child commences school (see, for example, Huffmann, 1968). Most texts which discuss the post-recovery sequelae of encephalitis or meningitis in early childhood emphasis the behavioural hyperactivity, increased impulsiveness and loss of self-control as the usual problems confronting the parent and physician. A spectacular example of this phenomenon was the encephalitis lethargica epidemic of the 1920s; whereas adults who survived the initial illness were marked by a variety of neurological stigmata, most commonly a form of non-remittent parkinsonism, children and young adults were more likely to exhibit behavioural and social abnormalities which often achieved a level requiring institutional confinement.

It is perhaps surprising that little has been reported concerning extrapyramidal syndromes of *reduced* motor activity following similar in utero or early childhood traumatic events. In adults, damage to the basal ganglia can elicit abnormal motor activity in either direction; it would seem reasonable that the same would apply to damage occurring at an earlier developmental stage. It is conceivable, on the other hand, that children who exhibit reduced motor activity might not attract the same attention as their hyperactive friends, as their behaviour might not be regarded as problematic from a pedagogic point of view; a peaceful, internally directed child might be seen by both parents and physicians as at worst somewhat shy, at least until the point when more serious consequences of the disorder were manifested.

Nevertheless, a search of the literature reveals that a few such cases have been reported, albeit as exceptions. A particularly interesting case was recorded in a Bavarian government report in 1891 during the great influenza epidemic:

One encountered the children awake, sitting in bed and staring without blinking and unconcentrated into space. They reacted to questions, but only hesitantly and unwillingly, giving answers which were as short as possible. Movements of the extremities of these children can be made which are reminiscent of cataleptics, whose limbs remain in a certain position, and which appear as if executed by an automaton. For example, a ten year old boy, who sat in his bed and from whom any form of response was difficult to elicit, moved a piece of bread placed in his hand in three stages towards his mouth (Anonymus, 1891).

This boy, like many of those described in the 1891 report, were said to have later completely recovered, although this follow-up must have occurred little more than a year after the initial illness.

During the encephalitis lethargica epidemic, it was noted that some children exhibited "apathy" and affective deficits following the acute illness; Thiele also remarked that the presentation of hyperactivity and what he specifically designated as "parkinsonism" did not necessarily exclude one another, reporting examples of boys in whom the amyostatic syndrome was

irregularly punctuated by outbursts of motor and psychic hyperactivity (Thiele, 1926). Hypokinesia and even parkinsonism was also occasionally reported for children born from mothers with encephalitis lethargica.

Even more interesting for the current discussion is the report by the Viennese paediatrician Widhalm (1985) on extrapyramidal problems in children. Most of these cases had experienced overt problems early in life, such as asphyxia during delivery, prenatal disturbances, premature birth or early childhood meningoencephalitis, often in combination with a difficult pregnancy (heavy bleeding or vomiting, pyelonephritis with high blood pressure). In particular, Widhalm described a hypokinetic/parkinsonoid syndrome ("infantile hypokinetic-hypertonic syndrome with Parkinson symptomatic") presented by a significant minority of the children with extrapyramidal movement disturbances he had observed (65 of 623 patients over a period of $12\frac{1}{2}$ years). Of these 65 patients, there were no reported organic problems during pregnancy or birth in less than one-fifth of cases. Extrapyramidal symptom severity was rated as "mild" in 44% of cases and "moderate" in a further 43%; hypokinesia was presented by all patients, while rigidity (18%) and tremor (8%) were exhibited only by a minority. This picture corresponded in general with a milder form of the rigid-akinetic type of Parkinson's disease as described by Gerstenbrand and Ransmayr (1986). Widhalm's detailed analysis of his patient group also revealed that most of these children presented other neurological, behavioural and somatic abnormalities, cognitive disturbances (97%), concentration weakness (47%), strabism (58%), behavioural difficulties (31%) and repeated severe headaches (29%) being most prominent. Further, only 19% of these children exhibited normal EEG patterns.

Significantly, therapy with the standard antiparkinsonian agent L-DOPA (dosed according to age, ranging from 250–500 mg/day for preschool children to 1,000–1,500 mg/day for adolescents) proved to be effective with regard to extrapyramidal signs ("very good" or "good" improvement) in all mild and moderate cases, and in five of the eight severe cases; a further two patients in the latter group responded "moderately" to this approach. Dyskinesia was presented as a side effect after 8–30 months of L-DOPA therapy, prompting dose reduction and ultimately total withdrawal of L-DOPA after maximally three years treatment. However, it was found that at this point near normal motor function was maintained without further pharmacological intervention. An especially impressive recovery within months of the initiation of therapy was a 15 year old youth whose motor problems had been unsuccessfully approached via physiotherapeutic measures over a period of years. Four patients whose parents declined L-DOPA therapy, in contrast, showed no improvement during the observation period.

Widhalm interpreted his observations as being indicative of a particular sensitivity of the brainstem to the types of injury he had identified as linked with childhood parkinsonism. The reversibility of the syndrome in most cases by L-DOPA therapy was consistent with other reports of reversible damage to specific brain regions subsequent to interrupted perfusion, but was nevertheless regarded by the author as requiring explanation. As early as the 1950s, various authors had described the specific patterns of brain damage following

perinatal hypoxia, with a special sensitivity of the brainstem attributed to lower metabolic activity. In 1979, Davis and colleagues reported that even mild hypoxia was sufficient to disturb the synthesis and storage of catecholamines in the neonate brain. According to Rorke (1982), the perinatal period is particularly critical for the basal ganglia and other grey matter nuclei (such as the hippocampus and thalamus) with respect to hypoxic damage, consistent with Widhalm's findings.

As far as the current authors are aware, Widhalm's paper, published as a supplement to the *Wiener Medizinische Wochenschrift*, never attracted any attention, despite the questions it raises and his remarkable success in the treatment of childhood parkinsonism. This is regrettable, as his report, while concerned with childhood extrapyramidal disorders, may have consequences for the area in general. For instance, it clearly indicated that perinatal events can lead to a syndrome which includes features of classical parkinsonism, including its responsiveness to L-DOPA. In contrast to classical parkinsonism, but consistent with some forms of post-encephalitic parkinsonism (such as that associated with Japanese encephalitis), the syndrome was reversible, although apparently only when L-DOPA therapy was introduced. This phenomenon may be construed as indicating that mechanisms are available which may compensate for the effects of acute damage to the substantia nigra under certain conditions, the identification of which would be crucial for the understanding of adult idiopathic Parkinson's disease. Widhalm's observation that at least one form of childhood parkinsonism can be cured with L-DOPA also suggests that the amino acid plays a more active role than mere replacement therapy in children, perhaps also acting as a neurotrophic agent with consequences for the long term development of the basal ganglia (see, for example, Ferrario et al., 2002).

As discussed above, it would be conceivable that cases similar to those described by Widhalm might be otherwise classified – for instance, as "withdrawn" or "agreeable" children – where the possibility delineated by Widhalm was not considered. Szwaja and Strayer (2001) have also noted that "hypoactive" children are usually classified as "self centered", which detracts considerably from identifying the core nature of the problem. Further, it is also conceivable that mild insults, such as subclinical encephalitis, might be overlooked altogether; Widhalm also identified children with the described syndrome whose gestation and birth presented no ostensible difficulties. This is all the more critical, as correction of the problem would appear to be simple, and should be implemented as soon as possible. In this respect, the recent report that L-DOPA, in contrast to the fears of some workers, may actually retard the progression of familial Parkinson's disease (Gwinn-Hardy et al., 1999) is of interest.

We propose that the syndrome described by Widhalm in individuals under twenty years of age may represent a developmental form of parkinsonism attributable to the interplay of environmental and genetic factors, and that its incidence is probably underestimated due to greater community concern with overactive children. The ontogeny of catecholaminergic systems in the human basal ganglia has been investigated by a number of laboratories in recent

years (for example: Segawa, 2000; Galvin et al., 2001; Itoh et al., 2001), and the processes involved represent a complex interplay of programmed neuronal maturation and apoptosis, subject to modulation by a range of intrinsic factors, such as growth factors, cytokines and hormones (Adams et al., 2000; Rice and Barone, 2000). Further, evidence has been presented that the indirect basal ganglia pathway is not fully developed until late childhood (cited in Segawa, 2000), offering further opportunities for perinatal damage. Although it is recognized that intrauterine and early postnatal infections and hypoxia, for example, are associated with changes in the levels of such factors – to what extent they reflect the occurrence or extent of infection or ischemia is unresolved – their involvement in the pathophysiology of childhood neurological disease remains relatively unexplored (Nelson and Willoughby, 2002). Age-dependent neurotoxicity due to exotoxic mechanisms following administration of any of a number of agents, including alcohol, sedatives, tranquilizers, anticonvulsants and anesthetics, has also been recently described (Olney et al., 2000; Weiss, 2000).

Parkinsonism may be a complication of a number of viral infections including Coxsackie, herpes zoster, measles, poliomyelitis, Japanese encephalitis, and influenza B, and lesions of the substantia nigra have been reported in both Japanese encephalitis and St. Louis encephalitis (Casals et al., 1998). Mattock and colleagues (1988) speculated that intra-uterine influenza might cause Parkinson's disease, suggesting that:

intra-uterine influenza may be cytotoxic to the developing foetal substantia nigra, and that an affected individual may be born without evident disability but with limited striatal neurochemical reserves and a reduced nigral cell count. Nigral failure might thus be delayed by decades as cells are lost and postnatal environmental exposures may modify their rate of decline and hence the interval before overt disease ensues.

Parkinson's disease would develop after mildly neurotoxic influenza following a latent interval, while a particularly toxic influenza with extensive nigral damage would occur after a short latent interval and perhaps before the age of thirty. It was similarly reported in a brief communication that childhood poliomyelitis was a significant risk factor for the later development of parkinsonism, even where the poliomyelitis was of the non-paralytic form (Nielsen et al., 2002).

Genetic factors also play a role in the response of the basal ganglia to environmental changes during maturation, although spectacular deficits, such as the recently reported tyrosine hydroxylase deficiency (Grattan-Smith et al., 2002), are rare. Lücking et al. (2000) reported that of thirteen patients with very early onset Parkinson's disease (20 years or younger) ten were homozygous or heterozygous for mutations in the Parkin gene, whereas only two of 64 patients (3%) with an age at onset of 31 to 45 years showed this pattern. Yokochi (2000) similarly discussed the genetic bases of pediatric extrapyramidal disorders, including L-DOPA-responsive dystonia and juvenile parkinsonism, and noted that the two entities were genetically distinct entities; it was also noted, however, that fewer than half of juvenile parkinsonism cases carry the relevant Parkin gene mutation. Prenatal maternal stress also affects the

functional development of the fetus, so that later behaviour is determined not only by genetic factors and the postnatal environment but also by the maternal environment during gestation (Weinstock et al., 1988).

In summary, it is proposed that environmental factors, including viral and risk factors associated with pregnancy and birth, together with genetically determined lability, may increase the incidence of early hypokinesia/parkinsonism in particular and of Parkinson's disease in later life by disturbing the immature basal ganglia at critical developmental stages, detectable by changes in the function and organization of brain circuitry, including changes in monoaminergic and excitatory amino acid systems. Developmental forms of parkinsonism might thus occur following any of a number of disparate events affecting early brain maturation:

- *genetically determined parkinsonism*, including Parkin gene mutations
- *induced by in utero or perinatal viral (or other?) infection*, such as maternal influenza during pregnancy
- *in utero or perinatal trauma or maternal stress*, including those factors identified by Widhalm

Only in a minority of cases of pre- or perinatal infection or trauma, determined by individual differences in susceptibility, will such exposure result in childhood parkinsonism. As with poliomyelitis, it is to be assumed that only a small percentage of those exposed to the causative insult, even of those in whom brain maturation is not complete, will present clinically significant deficits; nonetheless, we feel justified in proposing that the spectrum disorder of Parkinson's disease occurs as a number of various etiopathologically distinct syndrome subtypes, including early onset developmental forms caused by in utero or early post partum trauma. We are not suggesting that our proposal would explain more than a small minority of parkinsonian cases, but nevertheless feel that the vulnerability of the basal ganglia to various noxa, especially during development, renders likely the existence of developmental forms of childhood parkinsonism. While there are many references in the literature to genetically determined cases of early onset parkinsonism, consideration of other early life events resulting in developmental changes resulting in basal ganglia deficits have not attracted so much attention in recent years. We hope that our small contribution may at least (re)generate some awareness of such possibilities.

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