Neuropsychological Difficulties Associated with Dopa Responsive Dystonia

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Abstract

A young girl with l-dopa responsive dystonia showed significant improvements in motor function but had ongoing complaints of neuropsychological difficulties. A neuropsychological evaluation was undertaken to understand the nature of her difficulties. Intellectual function, attention, executive function, and academic attainment were assessed using published psychometric tests. Verbal and non-verbal reasoning was found to be age appropriate. Particular difficulties were identified with working memory, visual selective attention, dual attention, and processing speed which were having a significant impact upon the child and her family. The importance of a thorough neuropsychological evaluation is discussed in helping to appropriately manage and support the child with this chronic but rare health condition.

Keywords: Dopa, dystonia, neuropsychological

Introduction

Dr Segawa in 1976 described in detail, for the first time, the features of dopa responsive dystonia (DRD) characterized by diurnal fluctuation, mild parkinsonian features, initial limb involvement, and marked response to dopamine. Subsequently, various biochemical and genetic disorders have been discovered. Since then, variations in DRD clinical presentation have been reported worldwide. We describe the case report of a young girl with l-dopa responsive dystonia who, despite showing significant improvements in motor function, had ongoing complaints of neuropsychological difficulties. This case illustrates the importance of a thorough neuropsychological evaluation in helping to appropriately manage and support the child with this chronic but rare health condition.

Case History

A female baby initially presented with feeding difficulties within weeks of her birth. Dystonia and developmental delay became apparent at 8 months of age. Over the next 12 months, she became severely developmentally delayed with marked head lag, dystonia, and rigidity. A diagnosis of DRD was suspected following cerebrospinal fluid biochemical analysis which demonstrated low levels of total neopterin 5 nmol/l (7–65) and homovanillic acid 163 nmol/l (176–851). Consequently, levodopa was initiated at 21 months of age; following this, her symptoms demonstrated dramatic resolution and an overall development, thus, confirming the diagnosis of DRD. Despite exhibiting poor head control and an inability to reach out for objects at 21 months of age, she was able to bottom shuffle by 26 months of age and was able to walk without aid and speak three-word sentences by the age of 2 years and 10 months. The cause of DRD was not clear in this particular case.

However, despite this resolution, the girl was referred for neuropsychological evaluation at the age of 7 years after her family and school noticed significant difficulties with attention, task initiation, and explosive temper outbursts. She was exhibiting variations across the day and on a day-to-day basis with respect to her ability to engage in tasks; she had complained to her parents that she could “not do things as her brain was asleep.” The parents also reported that typical

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reward-based behavioral incentives were not successful in modifying behavior.

The girl completed a neuropsychological evaluation across two morning sessions. The evaluation included measures of visual-motor performance, attention, and executive function. She was observed to be fidgety throughout the assessment sessions. Visual motor integration was measured by the Beery-Buktenica Developmental Test of Visual-Motor Integration 5th Edition (Beery and Beery, 2010), which involved the child copying with geometric designs of increasing difficulty. Her performance fell within the average range (65th percentile). The Test of Everyday Attention of Children-Score (TEA-Ch; Manly et al. 1999) was administered to deduce her level of sustained attention. This test involves children counting the number of “scoring” sounds (with prolonged intervals between consecutive sounds) they hear on an audio tape. Her performance in this component fell within the average range.

Spatial Selective Attention was measured using the “Sky search” from TEA-Ch. This is a timed sub-test where children have to find as many “target” spaceships as possible on a sheet filled with very similar “distractor” spaceships. In the second part of this task there are no “distractors.” Subtracting part 2 from part 1 gives a measure of a child’s ability to make the selection that is relatively free from the influence of motor slowness. Motor slowness was an issue but even when this effect was removed, performance was far below average. In addition to the slowness in spatial selective attention and motor components, she also demonstrated poor spatial selective attention on Map Mission from the TEA-Ch. Divided attention was measured again using “Sky search-DT” from TEA-Ch. Children are asked to combine the two tasks of finding the spaceships and keeping a count of “scoring” sounds. Her performance fell well below the average range in this component too.

Neuropsychological evaluation suggested that while motor difficulties had been ameliorated to some extent by levodopa, the child experienced neuropsychological difficulties. In particular, psychomotor speed was slowed and working memory was poor. Visual selective attention was impaired, even after accounting for the effects of slowed motor speed. The executive aspects of attention (i.e., divided attention) were also impaired.

**DISCUSSION**

DRD was first described by Segawa and colleagues in 1976 (hence the eponym Segawa syndrome) who named the disorder “hereditary progressive dystonia with marked diurnal fluctuation.” It is a condition characterized by the onset in early childhood of walking difficulties due to lower limb dystonia which progresses to generalized dystonia, a diurnal fluctuation of symptoms, the concurrent or subsequent development of Parkinsonism (mainly rigidity and bradykinesia), and a dramatic and sustained response to treatment with levodopa which highlights the importance of appropriately identifying this rare disease.

About 50% of cases are caused by an autosomal dominantly inherited defect in the gene GCH1 (14q22.1-q22.2) that encodes guanosine triphosphate cyclohydrolase 1 (GTPCH1). GTPCH1 catalyzes the rate-limiting step in tetrahydrobiopterin (BH4) biosynthesis, which itself is the essential cofactor for production of tyrosine hydroxylase, tryptophan hydroxylase, and phenylalanine hydroxylase. Tyrosine hydroxylase is the initial and rate-limiting enzyme in dopamine synthesis. Since the discovery of the gene mutation, many different mutations in the GCH1 gene, TH gene (tyrosine hydroxylase), and SR (sepiapterin reductase) genes have been identified to cause DRD, particularly of the autosomal recessive form of DRD.

It is difficult to be certain whether the neuropsychological difficulties experienced in this case relate to DRD or a comorbid condition. A study by Trender-Gerhard et al. reported that the long-term outcomes for people with DRD included problems with concentration, verbal working memory, writer’s cramp, and mood swings. However, few neuropsychological studies have been undertaken to definitively assess this.

Interestingly, there is a small case series of four patients with DRD in Australia, who had mutations in the tyrosine hydroxylase gene. These children also experienced difficulties with attention and their executive function, thus conforming with the hypothesis that neuropsychological manifestations form part of this condition.

DRD has clinical similarities to Parkinson’s disease, which is known to be associated with nigrostriatal and mesocorticolimbic dopamine depletion. The condition is accompanied by subtle cognitive impairments even in the early stages, resembling those seen in frontal lobe pathology. Medication with levodopa at a level to ameliorate the motor symptoms in Parkinson’s disease has been found to have more complex effects on cognition, with some cognitive systems being “overdosed” whereas others are “underdosed.” This means that medication may improve or impair cognitive performance depending on the nature of the task and the level of dopamine function in the underlying neural systems.
cortico-striatal circuitry.[9] It is currently not known if other medications such as methylphenidate used to help children with attentional deficits may help children with DRD and associated attentional difficulties.

In conclusion, additional research is needed to further characterize and understand the neuropsychological manifestations of this rare but complex condition. Steps must be taken to delineate the optimal management of these poorly understood manifestations, such that adequate monitoring and appropriate support can be given to the child and their carers.

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Conflict of interest
There are no conflicts of interest.

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