

Dopa-responsive dystonia and hyperprolactinaemia: a novel association in two sisters

Janabel Galea, Mario J Cachia

Abstract

Dopa-Responsive Dystonia (DRD) is a rare hereditary condition of childhood-onset dystonia which responds dramatically to treatment with levodopa. It was first described in 1971 as a "hereditary progressive basal ganglia disease with marked diurnal fluctuation". We describe a novel association between DRD and hyperprolactinaemia occurring in two sisters at the onset of puberty.

Introduction

We report on two sisters, diagnosed with dopa-responsive dystonia (DRD) at the ages of 8 and 11 years, who later developed hyperprolactinaemia.

Key words

Dystonia, dopa-responsive dystonia, hyperprolactinaemia

Janabel Galea* MD

Department of Oncology, Sir Paul Boffa Hospital, Malta
Email: peg@vol.net.mt

Mario J Cachia MD, FRCP

Consultant, Department of Medicine, St Luke's Hospital, Malta
Email: mario.j.cachia@gov.mt

* corresponding author

Case report

These sisters had been seen for many years by various paediatricians for delayed developmental landmarks and hypotonia.

By the age of 9 months, the elder sister, who had a normal birth history, had been repetitively admitted to hospital due to severe recurrent upper respiratory tract infections. The girl was noted to have delay in gross motor development with hypotonia, poor head control and a weak hand grip. She could not sit upright unsupported. No abnormal movements were noted. She attained unsupported sitting at 18 months. An EEG and EMG at the time were normal.

At the age of 1 year, she could only tolerate liquid foods and vomited daily. On examination she had occasional left and upward conjugate deviation of both eyes with slight nystagmus; direct and consensual light reflexes were normal. She had slow tongue movements with dysarthria and dribbling of saliva. Muscle power was graded 3/5 in all 4 limbs. A coarse intentional tremor and clasp-knife rigidity were present in both upper limbs; hypotonia more evident in the lower limbs. Brisk reflexes were present; plantar reflexes normal. High arched feet with prominent calcanei were also noted. Co-ordination was unaffected but gait was ataxic. A CT scan of the brain revealed small frontal atrophic changes. Hypotonic cerebral palsy was the working diagnosis at this time.

At the age of 2 she was continent of both urine and faeces, was still on liquid foods and vomited regularly. Her vocabulary had broadened up to 20 words. Her vision and hearing remained unaffected.

She attended speech therapy for her dysarthria with minimal improvement. The palmer grasp was still present, but she was able to co-ordinate her finger movements. She could build a tower of 10 blocks.

By age 3, her speech had improved and she could communicate in short phrases. Dribbling of saliva was still present. Proper chewing of foods had not yet been developed and she was still vomiting daily, often in copious amounts. Weight gain was hence insignificant.

At age 5, diurnal fluctuation of fatigue was evident. A year later hypotonia had not improved and pyramidal signs were present. She had an ataxic gait, with no swinging movements of the upper limbs. There was also mild cognitive impairment.

Her sister, who was 2 years younger, also presented at a young age with similar symptoms. At birth she suffered an

oculogyric crisis and during infancy, she had gross motor delay and recurrent upper respiratory infections. She was hypotonic with subsequent development of generalised spasticity and prominent truncal ataxia. Physical examination also revealed bilateral flat feet with *genu varum* and *pes cavus* with *calcaneo valgus*. She was continent of both urine and faeces. At the time, the working diagnosis was spastic quadraparesis with global developmental delay and immature speech.

At this stage, the possibility of dopa-responsive dystonia was considered in both girls. When the elder sister was 11 years of age, a small dose of co-careldopa (levodopa and carbidopa) was prescribed to both sisters as a diagnostic and therapeutic trial. Her younger sister showed excellent response to the treatment. However, the elder sister's improvement was more gradual and to a lesser degree. Their handwriting and waddling gait improved. They fell less frequently and were less lethargic in the evenings. Mild dystonic positioning of the left hand present in both sisters remained but this also gradually improved. They attended school with facilitation. Interestingly, both sisters remained hypotonic even after treatment. They eventually developed marked scoliosis.

The elder sister's sexual development started at the age of 9 years and menarche occurred at 16 years.

No further menses followed except for occasional spotting of altered blood. She was reviewed and hyperprolactinaemia was identified with a prolactin level of 8275mU/L (Normal serum level 40-530mU/L). At this point she was referred to an endocrine clinic for further evaluation. Physical examination revealed acne, galactorrhoea, mild scoliosis, hypotonia with mild dystonia in all 4 limbs and a waddling gait. Tunnel vision was noted on ophthalmic assessment. An MRI scan of the brain and pituitary gland identified no intracranial pathology. She was started on bromocriptine 1.25mg daily. After starting treatment, she developed regular menses, no further galactorrhoea was reported but hirsutism was still present. Her gait improved further but lower limbs still showed a waddling gait. Prolactin levels returned to normal. The MRI scan, which was repeated a year later, confirmed no identifiable pathology. At the time, the patient was stable on co-careldopa 110mg daily and bromocriptine 2.5mg daily.

At the age of 13 years the younger sister was also screened for hyperprolactinaemia, which was initially normal but started to rise on follow up visits. Her prolactin levels had increased to 1119mU/L. Menarche had occurred at the age of 12. Her presenting complaint was hirsutism. There were no visual field defects. An MRI showed a small microadenoma. She was initially treated with bromocriptine, but some months later changed to cabergoline. Her prolactin levels normalised.

Discussion

Dopa-Responsive Dystonia (DRD) is a hereditary condition characterised by childhood-onset dystonia with diurnal fluctuation of symptoms, being worse towards the evening. This condition responds dramatically to treatment with levodopa. It

was first described in 1971 by Segawa *et al*, who described the condition as "hereditary progressive basal ganglia disease with marked diurnal fluctuation."¹

There are 2 types of DRD, autosomal-dominant and recessive, the former being the commonest form.

DRD is characterised by dopamine deficiency in the striatum.² There is decreased dopamine activity at the nigrostriatal terminals in patients suffering from DRD.² This is not due to a morphological disorder, as in Parkinson's disease, but is related to a functional disorder of the nigrostriatal dopamine (DA) neuron, with the striatum being free of a primary lesion.³

Tyrosine hydroxylase (TH) acts on tyrosine to produce dopamine. TH is a rate limiting enzyme in the synthesis of dopamine.² Tetrahydropterin (BH4), its cofactor, is synthesised from GTP in a 3-enzyme pathway, which includes GTP cyclohydrolase I (GCH).⁴ Neurohistochemical examinations show low BH4 concentrations resulting in decreased TH activity and its protein in the striatum or at the terminal of the nigrostriatal neuron.³ There are normal levels of TH protein and its activity in the substantia nigra.³ Low BH4 levels could be congenital but is commonly an indirect result of mutations in the GCH-I gene.³ This gene codes for Guanosine Triphosphate (GTP) cyclohydrolase I enzyme. Various mutations in the GCH-I gene have been identified.⁴ Furukawa observed that the locus of mutations is different between different families but identical within a family.⁵ GCH activity in patients with DRD would be low, resulting in a slow production of BH4, which does not meet up to its daily consumption.⁶

However, physical signs and symptoms present in DRD patients are attributed to dopamine deficiency in the striatum rather than deficiency of BH4.⁶ Symptoms are worse towards the evening due to depletion of the BH4 pool.⁶

Reduced neopterin levels distinguish DRD from degenerative nigro-striatal dopamine deficiency disorders.⁷ Neopterin levels are reduced in the striatum, putamen and even in the CSF of patients with DRD.⁴ Neopterin indirectly reflects the activity of GCH in the brain as it is a metabolite of an intermediate in the biosynthesis of BH4.⁶

Signs and symptoms develop in early childhood. The main characteristic is gait disturbance with postural dystonia. The patient tends to walk in an equines posture. As the patient gets older and if no treatment is given, the dystonia spreads to affect the trunk and all four limbs. Muscle tone is increased and tendon reflexes tend to be exaggerated. The progression of dystonia tends to subside by the fourth decade.³ Postural tremor develops in the third decade. Resting tremor is not present as in patients with Parkinson's disease. There are no mental or psychological abnormalities. Autonomic nervous symptoms are not present.³

The clinical course of DRD is dependant on the age of onset. For example, those patients whose symptoms start in adulthood tend to develop a hand tremor without dystonia and diurnal variation.³

DRD is usually diagnosed by the administration of small doses of levodopa resulting in marked symptomatic improvement, with relatively few side-effects related to levodopa treatment and no long-term complications, such as those seen in Parkinson's disease.¹ There are laboratory tests available but are not routinely performed. Biochemical tests include the measurement of neopterin and biopterin levels and neurotransmitter metabolites, HVA and 5HIAA, in the cerebrospinal fluid and the phenylalanine loading tests. Imaging studies are performed but are not conclusive.⁴

Treatment mainly involves the administration of a combination of levodopa and carbidopa. The two girls mentioned in the above report were started on this treatment with good results. A randomised controlled study, involving patients with Parkinson's disease, carried out by Montastruc *et al.* shows that treatment with high doses of bromocriptine for the first 3 years followed by the administration of levodopa delays the onset of motor complications. It gives better symptomatic relief than with levodopa alone.⁸

The cause for the co-existence of hyperprolactinaemia identified in both sisters with DRD in the above case report still has to be established. A study carried out on patients suffering from metastatic carcinoma of the prostate identified paradoxical stimulation of prolactin secretion on administration of levodopa to these patients.⁹ There could be unidentified pathways susceptible to dopamine deficiency which, on administration of levodopa, affects the neuroendocrine regulation of prolactin release. Dopamine is a prolactin-inhibiting factor.¹⁰ In a study it was noted that hyperprolactinaemia was present in patients with autosomal recessive BH4 deficiency and with the recessively inherited severe form of TH deficiency.¹⁰ Prolactin levels are normal in the autosomal dominant GTPCH-deficient DRD. The hypothalamic dopamine loss in these patients could not be sufficient enough to cause a rise in the serum prolactin.¹⁰

DRD and hyperprolactinaemia in both sisters could be unrelated but may be due to a genetic defect giving rise to the co-existence of both conditions. The fact that both sisters developed hyperprolactinaemia shortly after the onset of menarche makes a genetic link more likely.

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