

Clinical study

Levodopa responsive Parkinsonism in adults with Angelman Syndrome

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Summary Two intellectually disabled adults with Angelman Syndrome are reported who developed intermittent episodes of a severe resting tremor, cogwheel rigidity and bradykinesia in their late teens. The Parkinsonism was not due to medications and there was a dramatic improvement with levodopa therapy. The association between Angelman Syndrome and Parkinsonism has not previously been described. © 2001 Harcourt Publishers Ltd

Keywords: Angelman Syndrome, Parkinsonism, intellectual disability, tremor

INTRODUCTION

Angelman Syndrome is a well recognised cause of intellectual disability in children who present with ataxia, severe speech and cognitive delay, and a happy disposition, hence the initial designation as the 'Happy Puppet' Syndrome.^{1,2} Although originally described in 1965 the condition only received widespread recognition when it was discovered that it was due to a maternally derived deletion on Chromosome 15q 11–13.³

Most diagnosed patients with the syndrome are still children or adolescents and little is known about the natural history of the condition in adults.⁴ Two adults with Angelman Syndrome are described who presented with early onset Parkinsonism and showed a good response to levodopa medication. This association with Angelman Syndrome has not previously been described.

CASE REPORT

Case 1

A 23 year old male, resident in a home for intellectually disabled adults, had a 4 year history of episodes of a severe resting tremor. During these episodes he required the full attention of an attendant to walk, whereas in between episodes he was independently ambulant. A clinical diagnosis of Angelman Syndrome, recently made on the basis of his coarse facial appearance, prognathism and ataxia, was confirmed by a cytogenetic study that showed the characteristic deletion on 15q 11–13. He had a past history of generalised tonic clonic seizures that were treated with sodium valproate, clonazepam and carbamazepine.

On examination there was a prominent resting tremor of the arms with cogwheel type rigidity and bradykinesia. He had mild lower limb spasticity with an ataxic gait and persistent drooling, all of which are typical clinical features in Angelman Syndrome.

There was no improvement in the Parkinsonism features when sodium valproate was ceased because of concerns it may have contributed to the Parkinsonism. However, there was a dramatic improvement when twice daily levodopa/carbidopa, (100 mg/

10 mg), was commenced. The resting tremor and cogwheel rigidity disappeared and he once again became independently ambulant. Subsequently all anticonvulsants were ceased without recurrence of seizures although he required a slightly higher dose of levodopa.

Case 2

A 43 year old woman was a resident of the same institution as case 1 and presented with a 25 year history of episodic tremors which lasted for hours that precluded independent ambulation when present. She was intellectually disabled with epilepsy and a spastic diplegia of unknown cause. Medications consisted of phenytoin, clonazepam, ethosuximide and thyroxine.

On examination, she was microcephalic, with coarse facial features and persistent drooling. There was a florid resting tremor with cogwheel rigidity.

In the lower limbs the tendon reflexes were increased and she was unable to walk without assistance.

Due to clinical similarities to case 1, a cytogenetics analysis was performed and this confirmed the clinical suspicion of Angelman Syndrome. She was then treated with levodopa/carbidopa and a significant improvement occurred, such that she became independently ambulant and was able to feed herself. Subsequently, phenytoin and ethosuximide were ceased but clonazepam and carbamazepine were continued because of infrequent seizures. The dose of levodopa/carbidopa (100 mg/10 mg) was increased to five tablets daily.

DISCUSSION

Both patients had bradykinesia with a marked resting tremor and cogwheel rigidity, which improved dramatically on levodopa. It is unlikely these symptoms were caused by Idiopathic Parkinsons disease as the presence of pre-existing cerebellar signs and a severe intellectual disability, as are found in Angelman Syndrome, are considered exclusion criteria for the disease.⁵ However, it is also possible that dysfunction or degeneration of presynaptic dopaminergic systems may be a common mechanism in both conditions.

Anticonvulsants can cause a variety of movement disorders with both phenytoin and valproate reported to cause Parkinsonism.⁶ Although patient 1 had been treated with sodium valproate and patient 2 with phenytoin, neither of these drugs were given at high

Received 4 February 2000

Accepted 19 May 2000

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doses and the clinical features of Parkinsonism persisted after these anticonvulsants were ceased.

Both patients had also been treated intermittently over the years with modest doses of major tranquilisers, but were not considered to have tardive dyskinesia, as there were no orofacial movements and the tremors were intermittent rather than continuous.⁷ In addition the improvement seen on L-Dopa therapy is not usually found in tardive dyskinesia.⁸

Autosomal dominant Parkinson's disease has been mapped to 4q21–22 in one family associated with a mutation of the alpha-synuclein gene, while a susceptibility locus for this disorder appears to be at 2p13.⁹ Autosomal recessive juvenile Parkinsonism has been linked to a probable deletion at 6q25–27,⁹ but there has been no report of any association between the Angelman site on 15q11–13 and Parkinson's disease. Angelman Syndrome is believed to be due to a mutation of the ubiquitin protein ligase gene, which is maternally derived.¹⁰

Tremor had been observed in 11 of 13 adults with Angelman Syndrome whose ages ranged from 20 to 53 years.⁴ However, there was no mention of bradykinesia or cogwheel rigidity, and it's unclear how severe the tremor was for these patients. In the current cases described the tremor was intermittent but severe and totally inhibited the ability to walk unaided or feed independently when it was present. Initially, the tremor had been misinterpreted by the nursing staff as seizure activity, but videotape and clinical review of the patients when they were symptomatic confirmed the movement disorder. The occurrence of the marked intermittent

resting tremor was a clue to the actual diagnosis of Angelman Syndrome in case 2.

The true incidence of Parkinsonism in adults with Angelman Syndrome remains to be determined, but given the significant disability which it causes and the excellent response to levodopa then this condition should be considered in all adults with the syndrome.

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