OPEN ACCESS Freely available online

Tremor and Other Hyperkinetic Movements

Letters

Are Gait Stereotypies a Marker for Neurodegeneration in Down Syndrome? A Prospective Observation

José Luiz Pedroso[1]*, Thiago Cardoso Vale[2] & Orlando Graziani Povoas Barsottini[1]

[1] Department of Neurology, Division of General Neurology and Ataxia Unit, Universidade Federal de São Paulo, São Paulo, São Paulo, Brazil, [2] Department of Internal Medicine, Universidade Federal de Juiz de Fora, Juiz de Fora, Minas Gerais, Brazil

Keywords: Down syndrome, Gait stereotypy, Neurodegeneration

Citation: Pedroso JL, Vale TC, Barsottini OGP. Are gait stereotypies a marker for neurodegeneration in Down syndrome? A prospective observation. Tremor Other Hyperkinet Mov. 2016; 6. doi: 10.7916/D85D8S1Q

*To whom correspondence should be addressed. E-mail: jlpedroso.neuro@gmail.com

Editor: Elan D. Louis, Yale University, USA

Received: May 9, 2016 **Accepted:** August 22, 2016 **Published:** September 13, 2016

Funding: None.

Financial Disclosures: None.

Conflict of Interest: The authors report no conflict of interest.

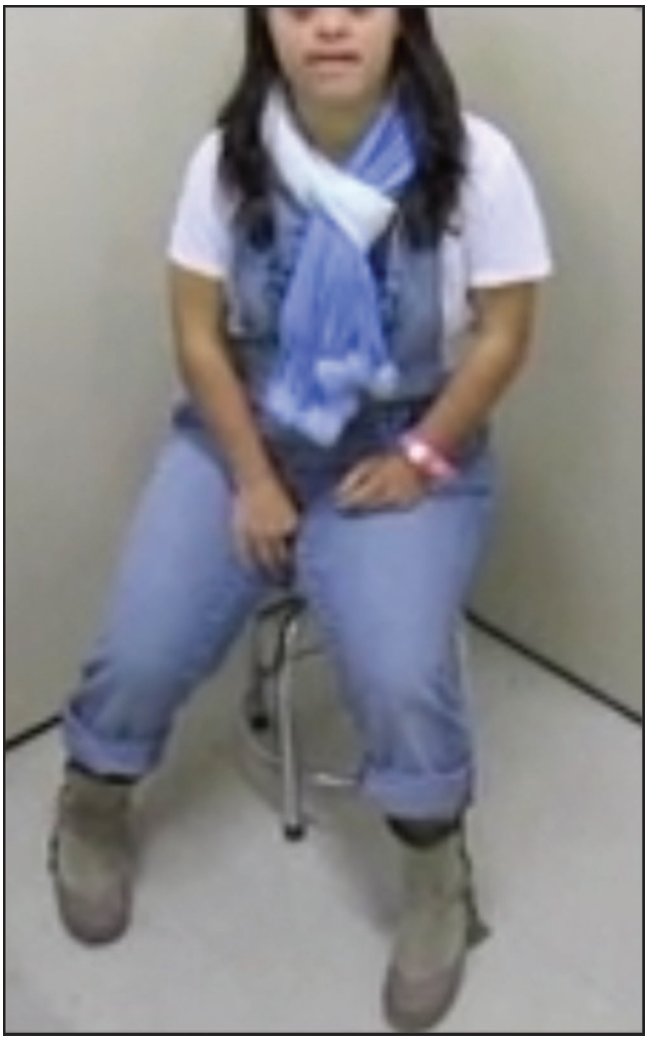
Ethics Statement: All patients that appear on video have provided written informed consent; authorization for the videotaping and for publication of the videotape was provided.

Down syndrome (DS) is the most common genetic cause of intellectual disability. Besides systemic involvement, patients with DS may present with a wide range of neurological manifestations, which include dementia resembling Alzheimer's disease, seizures, vascular disease and stroke, psychiatric comorbidities, and movement disorders.[1–3] Abnormal movements in DS are diverse, and the clinical relevance of these neurological manifestations is misunderstood.[4] In this article, we report a patient with DS that presented with movement disorders characterized by gait stereotypies as the first neurological manifestation, evolving to a severe neurodegenerative process and dementia in the following 3 years. We try to demonstrate on the basis of a single report that early movement disorders, particularly stereotypies and gait abnormalities, may predict neurodegeneration and dementia in DS.

A 32-year-old female, previously diagnosed with DS, presented to our hospital with a 3-year history of gait abnormalities, as reported by the parents. These complaints were characterized by repetitive movements while walking, particularly when she started the movements. When rising from a chair, she went back to the initial position, and when trying to move forward she always went back to the previous position. This phenomenology was interpreted as stereotypic movements called "step forward and step backward" (Video 1). Brain computed tomography and magnetic resonance imaging (MRI) disclosed punctate calcifications in the basal ganglia. A trial with levodopa (up to 800 mg/day) and neuroleptics (Quetiapine 100 mg/day) was started, but no improvement was observed.

In the following 3 years, she developed progressive and severe cognitive dysfunction with worsening speech, culminating in global aphasia and apraxia, inability to perform activities such as drawing and self-bathing, moderate to severe dysphagia, and changes in personality and behavior (severe apathy and no more social interaction with other children). Her memory seemed impaired since she could not recognize some family members. New brain MRI disclosed mild global cerebral atrophy. Blood tests, screening for inborn errors of metabolism, cerebrospinal fluid and electroencephalogram results were normal. Psychiatry evaluation ruled out catatonia. A neurodegenerative process and dementia related to DS was then diagnosed. Rivastigmine (up to 6 mg twice daily) was initiated and rehabilitation was recommended, with poor improvement.

DS (MIM #190685) results from a chromosomal numerical aberration (21 chromosome, full or partial trisomy) confirmed by direct genetic karyotyping.[1] Systemic features include dysmorphic findings, hypothyroidism, and non-cyanogenic congenital cardiopathies. Neurological signs most commonly include variable degrees of cognitive impairment and dementia. Dementia occurs in up to 75% of patients over 60 years. Progressive memory losses are the most pronounced symptoms in the early stages of dementia, but remote memory and other typical features of Alzheimer's disease are compromised only in later stages.[2,3] Other signs observed in DS patients with dementia include behavioral changes, apraxia, progressive aphasia, sphincter dysfunction, and gait abnormalities.[3]



Video 1. Marked Gait Stereotypies. When rising from a chair, she went back to the initial position, and when trying to move forward, she always went back to the previous position. This phenomenology was interpreted as stereotypic movements called "step forward and step back."

When dementia emerges in younger individuals (aged 30–40 years) with DS, it often initially manifests as changes in behavior and personality, including onset of apathy, increasing impulsivity, and executive dysfunction.[4,5] Our patient had memory impairment, personality and behavioral changes, and also executive dysfunction. Prasher[6] described mental deterioration, slowing, confusion, reduced output of speech, and deterioration in gait and personality change as the common early symptoms of dementia among adults with DS.

Abnormal involuntary movements in DS are variable and common, but may be misdiagnosed. The main movement disorders observed in DS include dyskinesia, akathisia, parkinsonism, and stereotypies. Dyskinesia, particularly orofacial dyskinesia, is the most common form of abnormal movements in DS patients. Parkinsonism is unusual, and basal ganglia calcification may play a role in this condition. Interestingly, several types of stereotypies may be observed in DS; the most common are truncal rocking, repetitive waving of fingers in front of the eyes, and rubbing hands together or on the trunk.[7]

Stereotypies were considered in our patient since this phenomenology was characterized by non-functioning and purposeless repetitive movements that interfered with normal activities.[8] Stereotypies in DS should be differentiated from tics, obsessional slowness, and freezing of gait. Unlike tics, stereotypic movements tend to be longer and more likely to be stimulated by excitement and do not cause annoyance to those who suffer from them. Tics display a peculiar variability over time and there are accompanying sensory phenomena consisting of premonitory urges and somatic hypersensitivity.[9] Obsessional slowness is characterized by long hours of engagement in usual daily activities, such as bathing, dressing, and eating. It is a type of severe ritualistic behavior. Motor slowness with poverty of movement and a history of obsessive–compulsive symptoms are characteristic. Poor speech production, bizarre postures, mannerisms, echophenomena, and oculogyric tics are also noted in these patients.[10,11] Freezing of gait is a common and disabling symptom in patients with parkinsonism, characterized by sudden and brief episodes of inability to produce effective forward stepping. These episodes typically occur during gait initiation or turning.[12] It is not frequently described in patients with Down's syndrome. Other abnormal motor behaviors such as mannerisms, paroxysmal dyskinesia, and akathisia were ruled out.

The precise neuroanatomical localization for motor stereotypies is unknown. Some data suggest that these abnormal behaviors may involve neural circuits interconnecting the neocortex with the striatum and areas of the basal ganglia. Several lines of evidence support a neurobiological basis for stereotypies, including a correlation with severity of autism and cognitive impairment, but not in DS.[5] Stereotypies are usually associated with mutism in DS, as in this case.[7]

There are no reliable clinical markers to predict dementia in DS, although some reports have correlated early motor disturbances with subsequent cognitive decline and mutism.[3,7] These data have demonstrated a correlation between severe intellectual impairment in DS and movement disorders, especially dyskinesias and motor stereotypies.[7]

In conclusion, this prospective report demonstrates that movement disorders in DS, particularly gait stereotypies, may predict cognitive decline and may be the first neurological manifestation of the neurodegenerative process. Although there is no effective treatment to avoid brain degeneration in DS patients, neurologists must be aware of this phenomenology as a possible marker for the early stages of dementia, and a closer follow-up might be relevant. It is possible that mild motor manifestation may be misdiagnosed by parents and doctors. Future studies with more patients will be valuable to reinforce this single case report.

References

1. Hwang SW, Jea A. A review of the neurological and neurosurgical implications of Down syndrome in children. *Clin Pediatr (Phila)* 2013;52: 845–856. doi: 10.1177/0009922813493833.

2. Benejam B. Dementia symptoms in Down syndrome. *Int Med J Down Syndr* 2009;13:18–21. doi: 10.1016/S2171-9748(09)70018-2.

3. Lott IT, Dierssen M. Cognitive deficits and associated neurological complications in individuals with Down's syndrome. *Lancet Neurol* 2010;9: 623–633. doi: 10.1016/S1474-4422(10)70112-5.

4. Grieco J, Pulsifer M, Seligsohn K, Skotko B, Schwartz A. Down syndrome: cognitive and behavioral functioning across the lifespan. *Am J Med Genet C Semin Med Genet* 2015;169:135–149. doi: 10.1002/ajmg.c.31439.

5. Ballard C, Mobley W, Hardy J, Williams G, Corbett A. Dementia in Down's syndrome. *Lancet Neurol* 2016;15:622–636. doi: 10.1016/S1474-4422(16) 00063-6.

6. Prasher VP. Age-specific prevalence, thyroid dysfunction and depressive symptomatology in adults with Down's syndrome and dementia. *Int J Geriatr Psychiatry* 1995;10:25–31. doi: 10.1002/gps.930100106.

7. Haw CM, Barnes TR, Clark K, Crichton P, Kohen D. Movement disorder in Down's syndrome: a possible marker of the severity of mental handicap. *Mov Disord* 1996;11:395–303. doi: 10.1002/mds.870110408.

8. Singer HS. Motor stereotypies. *Semin Pediatr Neurol* 2009;16:77–81. doi: 10.1016/j.spen.2009.03.008.

9. Martino D, Madhusudan N, Zis P, Cavanna AE. An introduction to the clinical phenomenology of Tourette syndrome. *Int Rev Neurobiol* 2013;112:1–33. doi: 10.1016/B978-0-12-411546-0.00001-9.

10. Charlot L, Fox S, Friedlander R. Obsessional slowness in Down's syndrome. *J Intellect Disabil Res* 2002;46(6):517–524. doi: 10.1046/j.1365-2788. 2002.00419.x.

11. Ganos C, Kassavetis P, Cerdan M, et al. Revisiting the syndrome of "obsessional slowness". *Mov Disord Clin Pract* 2015;2:163–169. doi: 10.1002/ mdc3.12140.

12. Nonnekes J, Snijders AH, Nutt JG, Deuschl G, Giladi N, Bloem BR. Freezing of gait: a practical approach to management. *Lancet Neurol* 2015;14: 768–778. doi: 10.1016/S1474-4422(15)00041-1.