Dystonic Opisthotonus: A “Red Flag” for Neurodegeneration With Brain Iron Accumulation Syndromes?

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ABSTRACT: Back arching was reported in one of the very first patients with neurodegeneration with brain iron accumulation syndrome (NBIA)s published in 1936. However, recent reports have mainly focused on the genetic and imaging aspects of these disorders, and the phenotypic characterization of the dystonia has been lost. In evaluating patients with NBIA$s in our centers, we have observed that action-induced dystonic opisthotonus is a common and characteristic feature of NBIA$s. Here, we present a case series of patients with NBIA$s presenting this feature demonstrated by videos. We suggest that dystonic opisthotonus could be a useful “red flag” for clinicians to suspect NBIA$s, and we discuss the differential diagnosis of this feature. This would be particularly useful in identifying patients with NBIA$s and no iron accumulation as yet on brain imaging (for example, as in phospholipase A2, group IV (cytosolic, calcium-independent) [PLA2G6]-related disorders), and it has management implications. ©2013 The Authors. Movement Disorders published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

Key Words: neurodegeneration with brain iron accumulation; NBIA; opisthotonus; retrocollis; extensor axial dystonia; PLA2G6; PANK2

With the advent in genetics, a variety of complicated recessive dystonia syndromes have been identified, and the similarity in their clinical presentations makes the differential diagnosis for clinicians difficult.1,2 Hence, clinical clues and “red flags” may be an important help. Generally, in the differential diagnosis of dystonia, the phenomenology, the distribution combined with the age of onset, and the presence of other features are of great importance. For example, lower limb dystonia in an adult is a clue for secondary/heredo-degenerative dystonia rather than primary dystonia. Moreover, severe oromandibular dystonia points to certain disorders, such as neuroacanthocytosis, neuroleptic drug-induced dystonia, neurodegeneration with brain iron accumulation syndromes (NBIA$s), or Lesch-Nyhan. Much less has been written about the diagnostic value and differential diagnosis of extensor truncal dystonia (or dystonic opisthotonus).

NBIA$s cause complicated dystonia syndromes and are characterized by excessive iron deposition in the...
brain, particularly affecting the basal ganglia and mainly the globus pallidus. The 2 core NBIAs are the neuroaxonal dystrophies pantothenate kinase (PKAN)-associated and phospholipase A2, group IV (cytosolic, calcium-independent) (PLA2G6)-associated neurodegeneration (PLAN), whereas additional disorders recently have been described. In evaluating patients with NBIAs in our centers, we have observed typical action-induced dystonic opisthotonus, in which the trunk tends to arch backward when the patient stands and occasionally even when lying down and attempting to move. Here, we discuss the differential diagnosis of dystonic opisthotonus and the occurrence of this feature in NBIAs. We wish to highlight that dystonic opisthotonus may be a clinical clue that, together with other signs (such as oromandibular dystonia), should raise suspicion to test for these disorders.

**How Common is Dystonic Opisthotonus in NBIAs?**

Numerous early and later case reports, in which clinical descriptions are detailed, describe neck arching and back arching in NBIAs; in fact, back arching was noted in 1 of the very first described patients with this syndrome published in 1936 by Ludo von Bogaert. This confirms that dystonic opisthotonus may be a common feature of NBIAs. We wish to highlight that dystonic opisthotonus may be a clinical clue that, together with other signs (such as oromandibular dystonia), should raise suspicion to test for these disorders.

**Differential Diagnosis of Dystonic Opisthotonus**

The differential diagnosis of dystonic opisthotonus includes mainly secondary dystonias, while it is uncommon in primary dystonia. Classically, retrocollis has been described in tardive dystonia caused by use of dopamine receptor antagonists; approximately 36% to 50% of patients with tardive dystonia have retrocollis, and about half of these also have extensor...
Dystonic Opisthotonus and NBIA Syndromes

| Differential diagnosis of dystonic opisthotonus | Further clues for the differential diagnosis |
|-------------------------------------------------|---------------------------------------------|
| Drug-induced dystonia\(^{23,28,53}\) | Often also retrocollis |
| NBIAs | Oromandibular dystonia |
| Glutaric aciduria\(^{36,40}\) | Consanguinity |
| Maple syrup urine disease\(^{35,37,38}\) | Perinatal history |
| Wilson's disease | Kayser-Fleischer rings |
| Lesch-Nyhan\(^{24}\) | Oromandibular dystonia |
| Dopa-responsive dystonia (DYT)\(^{33}\) | Perinatal history |
| Tyrosine hydroxylase deficiency | Oculogyric crisis |
| Aromatic L-amino acid decarboxylase deficiency | Perinatal history |
| Sepiapterin reductase deficiency\(^{52}\) | Delayed motor milestones |
| Primary extensor truncal dystonia\(^{26}\) | No further signs |
| Others (eg, meningitis, encephalitis, etc) | Dependent on the underlying cause |

MRI, magnetic resonance imaging; NBIAs, neurodegeneration with brain iron accumulation syndromes.

truncal dystonia,\(^{23,27,28}\) which worsens during movement, especially walking.\(^{23,27-29}\)

Because Wilson’s disease is a common differential diagnosis in patients with young-onset dystonia syndromes, we screened 100 patients who had symptomatic neurologic Wilson’s disease who were followed in the Wilson’s disease clinic (Kokilaben Dhirubhai Ambani Hospital, Mumbai, India) for retrocollis and opisthotonus. We reviewed the medical records and serial videos that were taken at approximately 3-month intervals over the last 7 years. Consistent with other reports,\(^{40}\) axial symptoms related to dystonia were observed, and some patients presented with extensor truncal dystonia.

In patients diagnosed with dystonic cerebral palsy, opisthotonus has been described occasionally, but some patients with so-called cerebral palsy may have other conditions (including NBIAs)\(^{7,31-36}\); thus, “red flags” are important to avoid long delays in diagnosis.\(^{31-34}\) Opisthotonus also has been described in neurometabolic disorders (eg, glutaric aciduria, maple syrup urine disease, Lesch-Nyhan, dopa-responsive dystonias)\(^{33,35-40}\) (Table 1). The very early age at onset, delayed motor milestones, truncal hypotonia, encephalopathic crisis, and intermittent painful dystonic posturing exacerbated by fever or infections are helpful clues to suspect a neurometabolic disease (see Table 1).\(^{39,41}\)

Which Is the Possible Pathophysiology?

The pathophysiologic explanation of the anatomic predilection for oromandibular and extensor truncal dystonia in these patients, as opposed to primary dystonias, remains unknown.\(^{47}\) However, the fact that these features also are present in patients with NBIAs in whom brain imaging does not show iron deposition implies that the clinical picture probably is not directly related to the iron but is related to the underlying neurodegeneration.\(^{5,48,49}\) This is supported by the fact that treatment with an iron-chelator, deferiprone, reduced iron in MRI studies but did not improve clinical symptoms.\(^{49}\) Moreover, the finding that dystonic opisthotonus responds to globus pallidus internus or subthalamic nucleus deep brain stimulation\(^{11,13,50}\) and, in some patients, also to levodopa\(^{51}\) confirms that it is related to basal ganglia dysfunction as opposed to other conditions with nondystonic opisthotonus.

Conclusion

We identified dystonic opisthotonus as a characteristic feature of NBIAs related to PANK2 and PLA2G6 mutations and suggest that this feature, together with other “red flags” for NBIAs (such as severe oromandibular dystonia) should raise suspicion to test for these disorders in patients with young-onset, complicated dystonia syndromes. Hence, these patients should have appropriate imaging, which includes T2* and susceptibility-weighted imaging to look for brain iron accumulation. Phenotypic “red flags” are important for clinicians for many reasons. First, some patients with NBIAs may not initially have evidence of iron accumulation in brain imaging (as in Patients 3 and 4 presented here), and suspicion for genetic testing can be mainly guided by phenotypic clues; otherwise, misdiagnosis for many years may occur.\(^{31,31}\) Second, the identification of these patients may have important management implications in view of current research on new treatment approaches.\(^{49,52}\) The true prevalence of this feature in NBIAs, along with other disorders described here, needs to be evaluated in larger studies.
Legend to the Video

Video 1. Four patients with NBIA and dystonic opisthotonus are shown. None of the patients were receiving neuroleptics before the onset of dystonic opisthotonus.

Segment 1. This Indian man aged 39 years carries homozygous mutations (c.1010A>C; p.Asp337Ala) in the PANK2 gene. He developed decrease in visual acuity and dysthria at age 12 years and lower limb dystonia and dystonic opisthotonus at age 14 years. On examination at age 34 years, he had reduced visual acuity, slow and hypometric vertical and horizontal saccades, generalized dystonia with prominent oromandibular dystonia, and severe dystonic opisthotonus, which was more evident while walking. Brain MRI revealed an “eye-of-the-tiger” sign.

Segment 2. This Indian woman aged 36 years (the sister of patient 1) carries the same mutation. At age 13 years, she developed visual disturbances, dysarthria, and writer’s cramp on the right. On examination at age 36 years, she was anarthric, and she had reduced visual acuity and pigmentary retinopathy with hypometric saccades; she also had generalized dystonia with oromandibular involvement, retrocollis, and dystonic opisthotonus with increased tone in all limbs. Brain MRI revealed an “eye-of-the-tiger” sign.

Segment 3. This Pakistani man aged 21 years, the product of double consanguinity, carries homozygous c.2239C>T (p.R747W) mutations in the PLA2G6 gene. At age 18 years, he developed foot dystonia, cognitive decline, and personality changes. On examination at age 21 years, he had blepharoclonus, jerky saccadic pursuit, and asymmetric pyramidal features with spasticity, hyper-reflexia, and rigidity; bradykinesia; foot dystonia; and marked opisthotonus, which worsened with walking. Brain MRI revealed no iron deposition on T2* imaging.

Segment 4. This Taiwanese woman aged 25 years carries a compound heterozygous mutation of the PLA2G6 gene (p.Asp331Tyr/p.Met358IlefsX). She noticed unsteady gait and easy falls at age 8 years, developed cognitive decline at age 18 years, and developed dystonia at age 22 years. Examination at age 25 years revealed retrocollis and dystonic opisthotonus induced by walking, parkinsonism, ataxic gait, intellectual impairment, and dysarthria. Brain MRI revealed cortical and cerebellar atrophy but no evidence of iron deposition on T2* sequences.

Acknowledgments: We thank the patients for their consent to publish the video.

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