Movement Disorders
CLINICAL PRACTICE

CASE SERIES

Neurodegeneration With Brain Iron Accumulation (NBIA) Syndromes Presenting With Late-Onset Craniocervical Dystonia: An Illustrative Case Series

Florian Brugger, MD,[1,2] Georg Kägi, MD,[1,2] Massimo Pandolfo, MD,[3] Niccolò E. Mencacci, MD,[4] Amit Batla, MD,[1] Sarah Wiethoff, MD,[4,5] Kailash P. Bhatia, MD, FRCP[1,]*

Abstract: Neurodegeneration with brain iron accumulation (NBIA) mostly has its disease onset in childhood, adolescence, or early adulthood and usually presents with predominant bulbar and axial dystonia along with signs such as spasticity, indicating an involvement of additional neurological systems. Because of their early onset and presentation with a combination of dystonia plus other neurological symptoms, they are usually not considered as differential diagnosis for late-onset isolated (idiopathic) craniocervical dystonia. In this case series, we present 4 genetically proven cases of NBIA (including neuroferritinopathy, pantothenate-kinase-associated neurodegeneration, and aceruloplasminemia) with late disease onset, which resembled isolated adult-onset craniocervical dystonia at disease onset. We also want to highlight the importance of taking NBIA into consideration when dealing with putatively isolated late-onset dystonias and of picking up unusual signs at later stages of the disease.

Dystonias are a heterogeneous group of disorders characterized by sustained or intermittent involuntary muscle contractions causing abnormal, often repetitive movements, postures, or both.[1] Isolated (idiopathic) dystonia is further classified according to age of onset and distribution.[1] Young-onset dystonia usually affects lower limbs and can generalize, whereas adult-onset dystonia tends to affect the craniocervical region and usually remains focal.[1] However, age of onset is variable, with a mean of 55.7 years for blepharospasm, 43.0 years for laryngeal dystonia, and 40.7 years for cervical dystonia.[2] Besides isolated dystonias, there are a large number of combined dystonias attributed to a variety of secondary and heredodegenerative causes.[1,3] Among these are disorders attributed to excess brain iron accumulation (NIBA; formerly named Hallervorden-Spatz syndrome [HSS]). This group encompasses conditions attributed to mutations in the *PANK2* (pantothenate-kinase-associated neurodegeneration; PKAN), *ATP13A2* (Kufor-Rakeb), *PLA2G6*, *WDR45*, *C19ORF12*, *FLT1* (neuroferritinopathy), *CP* (acaeruloplasminaemia), *DCAF17* (Woodhouse-Sakati-syndrome), and *FA2H* genes (SPG35) and others. Generally, these conditions have a childhood or young-adult onset and often a poor prognosis.[4] Hayflick et al. demonstrated, in their seminal article on the NBIA spectrum, that there are two main forms of HSS: The typical form is mostly attributed to *PANK2* gene mutations and starts in infancy (mean age of onset: 3.4 years) with a combination of prominent bulbar and axial dystonia, parkinsonism, chorea, pyramidal features, gait difficulties, and cognitive decline with rapid progression. The second, more atypical form starts around the age

[1]Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, National Hospital for Neurology and Neurosurgery, London, United Kingdom; [2]Department of Neurology, Kantonsspital St. Gallen, St. Gallen, Switzerland; [3]Department of Neurology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium; [4]Department of Molecular Neuroscience, UCL Institute of Neurology, London, United Kingdom; [5]Center for Neurology and Hertie Institute for Clinical Brain Research, Eberhard-Karls-University, Tübingen, Germany

***Correspondence to:** Prof. Kailash P. Bhatia, Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, Queen Square, London WC1N 3BG, United Kingdom; E-mail: k.bhatia@ucl.ac.uk
Keywords: NBIA, craniocervical dystonia, isolated dystonia.
Relevant disclosures and conflicts of interest are listed at the end of this article.
F.B. and G.K. contributed equally to this publication.
Received 8 February 2016; revised 8 April 2016; accepted 10 April 2016.
Published online 18 July 2016 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12393

doi:10.1002/mdc3.12393

of 14, but usually not later than 28 years. This form has also a slower disease progression and *PANK2* mutations are observed less frequently.[5] Similarly, in *PLA2G6*, age of onset is during infancy, adolescence, or young adulthood.[6] Other NBIAs (e.g., neuroferritinopathy) have an older age of onset, usually in their thirties.[7] Hence, NBIAs do not generally come into the differential diagnosis of isolated craniocervical dystonia. Here, we present 4 patients with genetically proven NBIA with late disease onset and symptoms at early presentation that resembled the presentation of adult-onset isolated (idiopathic) craniocervical dystonia.

Case 1

This 54-year-old man developed blepharospasm around 3 years before first referral. Around the same time, he also noticed mild walking difficulties. Around 1 year later, he noticed some twitches around his face and he developed swallowing difficulties and his speech became slurred. Furthermore, urinary incontinence, erectile dysfunction, and orthostatic hypotension were reported. Subsequently, his symptoms, particularly his gait and balance, got gradually worse. By the time we saw him, he presented with orofacial dyskinesia and tongue dystonia. There was a dystonic deviation of his face and jaw to the left and cervical dystonia with a torticollis and antecollis. There were bradykinesia and rigidity on all four limbs. His walking was broad-based and his steps occasionally froze.

An MRI revealed T2 and susceptibility weighted imaging (SWI) abnormalities suggestive of iron deposition in the thalamus, substantia nigra red nucleus, and cortex along with partial cavitation in the lentiform nucleus. His ferritin level was decreased (14; normal range 30–400), and a genetic test showed presence of the most common heterozygous mutation in *FTL1*, c.460dupA, confirming a diagnosis of neuroferritinopathy.

Case 2

This 82-year-old British woman presented at the age of 59 with perioral dyskinesias and prominent blepharospasm (Meige syndrome-like; see Video S1, Segment 1). A few months later, she recognized mild balance problems. At the age of 66, her speech became slower and slurred.

At the age of 74, when we saw her first, she presented with prominent craniocervical dystonia with levator inhibition and blepharospasm, more prominent on her right side. Her blepharospasm was partially helped with a sensory trick. There were perioral dyskinesia and prominent bulbar involvement. She had mild bilateral bradykinesia and dystonic hand posturing, and her gait was hypokinetic and unsteady. A MRI scan at this time showed cystic changes in the globus pallidus internus and caudate along with mineralization in the caudate, cerebral peduncles, thalami, striatum, and the cortex. Subsequently, it was noticed that her balance, speech problems, and bradykinesia had worsened. Furthermore, she had developed mild memory difficulties and severe dysphagia requiring percutaneous endoscopic gastrostomy insertion.

In the beginning, when she was inquired for relatives affected similarly, she denied any family history. Later, however, it became clear that there was a family history for neuroferritinopathy in her father, one aunt, one uncle, and two first-degree cousins, although their phenomenology is different to hers. Genetic testing revealed the presence of the same c.460dupA duplication in *FTL1*.

Case 3

This 65-year-old gentleman first noticed difficulties with keeping his eyes open at the age of 55. A neurologist made the diagnosis of blepharospasm and gave him botulinum toxin injections bilaterally to his orbicularis oculi, but without striking benefit. By the time we saw him (now age 64), he presented with intermittent blepharospasm with levator inhibition and a mild jerky retrocollis. When he touched his upper eyelids, he was able to overcome his symptoms (i.e., sensory trick; see Video S1, Segment 2). The remainder of his neurological examination was unremarkable. Because of the fact that he had received radiotherapy for acromegaly in the past and that his symptoms were atypical given his sex and age of onset, an MRI of the brain was requested, which revealed an "eye of the tiger" sign on the T2-weighted sequence. The diagnosis of PKAN was confirmed by detection of biallelic mutations in *PANK2* (details of the mutations unavailable).

Case 4

The case of acaeruloplasminaemia has already been reported elsewhere, but without a video.[8] Her neurological symptoms started at the age of 57, when she noticed an increased blinking frequency followed by involuntary mouth opening, jaw clenching, and lip and tongue protrusion. Two years earlier, she had been diagnosed with diabetes mellitus type 2. At her first referral at the age of 59, she presented with bilateral blepharospasm and oromandibular dystonia (Meige syndrome-like) with otherwise normal neurological and cognitive examination (see Video S1, Segment 3). An MRI scan of her brain revealed mineralization suggestive of iron deposition in the striatum, red nucleus, dentate nucleus, and posterior thalamus. Serum caeruloplasmin and copper were undetectable. Genetic testing revealed two mutations in the *CP* gene (c.146 + 1 G>A+ c.2602delG).

Discussion

Here, we describe 4 genetically proven NBIA cases with initial symptoms resembling adult-onset idiopathic dystonia. Cases 2 and 4 presented with initial symptoms similar to a Meige syndrome, whereas cases 1 and 3 mainly suffered from blepharospasm. At the time of their first presentation, their clinical picture was well in keeping with a form of isolated (idiopathic) dystonia given the distribution and age of onset of the dystonia. However, the occurrence of additional features in the course of their disease was a red flag, which eventually led to the diagnosis of NBIA. In cases 1, 2, and 4, these red flags were balance problems. Of note, case 3 never showed any atypical clinical features during the whole follow-up period. However, an MRI scan of the brain was requested to exclude any structural lesion,

doi:10.1002/mdc3.12393

because the combination of a blepharospasm in a male starting in his fifties and his past medical history of brain radiation appeared a bit unusual.

These cases highlight the importance of looking out for unusual clinical features in patients with putative isolated (idiopathic) dystonia. In general, when dealing with typical isolated dystonia, few, if any, additional diagnostic tests are required, although, in young-onset dystonia, treatable conditions such as dopa-responsive dystonia and Wilson's disease must be excluded.[9] Features suggestive of combined (nonidiopathic) dystonias, such as abnormal birth, dysmorphia, delayed developmental milestones, seizures, hemidystonia, sudden onset, and prominent orobulbar dystonia, and the presence of neurological signs indicating the involvement of other neurological systems, however, should prompt a more extensive diagnostic workup.[9] In NBIAs, an MRI with SWI or T2* sequences are the diagnostic test of choice. There, iron depositions are variably observed in the striatum, thalamus, brainstem, cerebellum, and/or cortex.[4] The presence of an eye-of-the-tiger sign, as in case 3, seems to be almost pathognomonic for PANK2 mutations.[5] Measurement of ferritin levels and ceruloplasmin may also support the diagnostic workup, but definite confirmation can only be achieved by genetic testing.[4]

The symptoms of our cases are somewhat unusual for NBIA. In the majority of the cases, neuroferritinopathy initially presents with focal chorea or dystonia. Dystonia mostly affects arms and legs, but blepharospasm has been described, though much less frequently.[7] In aceruloplasminemia, patients usually presented with cognitive symptoms accompanied by craniofacial dyskinesias, but also in this entity, blepharospasm may occur as a first symptom.[10] In PKAN, the most common presentations are gait difficulties in the typical form and dystonia in the atypical form. Of note, in NBIA, dystonia may involve bulbar functions from the early beginning on and may also show a prominent axial involvement at later stages.[5] A disease onset beyond the age of 40 (i.e., the lower age limit for late-onset dystonia[1]), however, has been described in all three entities before. A late onset can be observed in up to half of the patients with aceruloplasminemia and neuroferritinopathy, whereas this is quite uncommon for PKAN.[5,7,10] To our best knowledge, among the NBIA cases with a disease onset beyond the age of 40 published in the literature, there are only a few descriptions of patients, which are likely to resemble late-onset idiopathic craniocervical dystonia. Of note, all of them carry a mutation in the CP gene[11,12] (Table S1).

In summary, we describe 4 cases of late-onset NBIA who presented with symptoms resembling adult-onset isolated idiopathic craniocervical dystonia. These cases highlight the importance of looking out for atypical clinical signs suggestive of nonprimary dystonia to come to the correct diagnosis.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

F.B.: 1A, 1B, 1C, 3A
G.K.: 1A, 1B, 1C, 3A
M.P.: 1A, 1B, 1C, 3B
N.E.M.: 3B
A.B.: 1C, 3B
S.W.: 3B
K.P.B.: 1A, 1B, 1C, 3B

Disclosures

Ethical Compliance Statement: We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: The authors report no sources of funding and no conflicts of interest.

Financial disclosures for previous 12 months: F.B. received a travel grant from the International Parkinson and Movement Disorder Society and holds a research grant from Merz pharma Switzerland and the Swiss Neurological Society. G.K. is supported by grants from the Swiss Parkinson's Disease Association, the Halley Stuart Trust, and the Schweizerischen Herzstiftung. M.P. is supported by grants from the Belgian National Scientific Research Funds (FNRS), the Friedreich Ataxia Research Alliance, and BioMarin Pharma. He is a member of the scientific advisory board of Voyager Therapeutics and BioBlast and is a consultant for BioMarin. N.E.M. is supported by a Medical Research Council (MRC)/Wellcome Trust grant. S.W. is supported by the Brain Research Trust. K.P.B. holds research grants from the Gossweiler foundation, National Institute for Health Research Research for Patient Benefit, an MRC Wellcome Strategic grant (ref. no.: WT089698), and Parkinson's Disease UK (ref. no.: G-1009); has received honoraria/financial support to speak/attend meetings from GlaxoSmithKline, Boehringer Ingelheim, Ipsen, Merz, Sun Pharma, Allergan, Teva Lundbeck, and Orion pharmaceutical companies; and receives royalties from Oxford University Press and a stipend for *Movement Disorders Clinical Practice* editorship.

References

1. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* 2013;28:863–873.
2. O'Riordan S, Raymond D, Lynch T, et al. Age at onset as a factor in determining the phenotype of primary torsion dystonia. *Neurology* 2004;63:1423–1426.
3. Albanese A, Asmus F, Bhatia KP, et al. EFNS guidelines on diagnosis and treatment of primary dystonias. *Eur J Neurol* 2011;18:5–18.
4. Schneider SA, Bhatia KP. Excess iron harms the brain: the syndromes of neurodegeneration with brain iron accumulation (NBIA). *J Neural Transm (Vienna)* 2013;120:695–703.
5. Hayflick SJ, Westaway SK, Levinson B, et al. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. *N Engl J Med* 2003;348:33–40.
6. Kurian MA, Morgan NV, MacPherson L, et al. Phenotypic spectrum of neurodegeneration associated with mutations in the PLA2G6 gene (PLAN). *Neurology* 2008;70:1623–1629.

doi:10.1002/mdc3.12393

7. Chinnery PF, Crompton DE, Birchall D, et al. Clinical features and natural history of neuroferritinopathy caused by the FTL1 460InsA mutation. *Brain* 2007;130(Pt 1):110–119.

8. Haemers I, Kono S, Goldman S, Gitlin JD, Pandolfo M. Clinical, molecular, and PET study of a case of aceruloplasminaemia presenting with focal cranial dyskinesia. *J Neurol Neurosurg Psychiatry* 2004;75:334–337.

9. Charlesworth G, Bhatia KP, Wood NW. The genetics of dystonia: new twists in an old tale. *Brain* 2013;136(Pt 7):2017–2037.

10. McNeill A, Pandolfo M, Kuhn J, Shang H, Miyajima H. The neurological presentation of ceruloplasmin gene mutations. *Eur Neurol* 2008;60:200–205.

11. Miyajima H, Takahashi Y, Shimizu H, Sakai N, Kamata T, Kaneko E. Late onset diabetes mellitus in patients with hereditary aceruloplasminemia. *Intern Med* 1996;35:641–645.

12. Shang HF, Jiang XF, Burgunder JM, Chen Q, Zhou D. Novel mutation in the ceruloplasmin gene causing a cognitive and movement disorder with diabetes mellitus. *Mov Disord* 2006;21:2217–2220.

Supporting Information

A video accompanying this article is available in the supporting information here.

Table S1. Summarizes published NBIA cases with a late disease onset. Our NBIA patients presented as putative late-onset isolated idiopathic craniocervical dystonia. In this table, we therefore included only cases from the literature, which experienced their first symptoms after the age of 40 years. This age limit is in agreement with the definition for late-onset dystonia.[1] Only cases with sufficient clinical data and a confirmed mutation in the respective gene were considered. No cases were found for NBIA associated with mutations in the ATP13A2 (Kufor-Rakeb), PLA2G6, WDR45 (BPAN), or C19ORF12 (MPAN) genes. Cases whose clinical description is suggestive of a phenotype resembling isolated idiopathic craniocervical dystonia are highlighted in bold. *Only the locus of the causative gene was found by linkage analysis. Abbreviation: n.a., not available.

Video S1. Segment 1: Patient 2: There is a prominent blepharospasm combined with facial grimacing and intermittent mouth opening dystonia. She has some benefit from touching the outer margin of her right eyes (i.e., sensory trick). There is also an abnormal dystonic posture of both arms. Her gait is slow, shuffling, and unsteady. Segment 2: Patient 3: There is prominent blepharospasm with levator inhibition on both sides. Furthermore, the patient has also signs of mild cervical dystonia with an intermittent, jerky retrocollis. Segment 3: Patient 4: There is craniocervical dystonia with blepharospasm, jaw clenching, and lip protrusion. Repetitive movements of her hands are slightly slow. When walking, she is steady, but leaning to the right side, and her arm swing is reduced on both sides.

doi:10.1002/mdc3.12393