Parkinsonism and Related Disorders 62 (2019) 253–255

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Correspondence

Variant ataxia-telangiectasia with prominent camptocormia

ARTICLE INFO

Keywords:
Variant ataxia-telangiectasia
Generalized dystonia
Sensory trick
ATM

Ataxia telangiectasia (A-T) is a multisystemic early-onset disorder caused by biallelic mutations in the *ATM* gene [1]. The A-T phenotype consists of ataxia, hyperkinesias, oculomotor apraxia, polyneuropathy, intellectual disability, immunodeficiency, pulmonary symptoms and marked risk for malignancy. Classic A-T is progressive, leading to reduced life expectancy with loss of ambulation by age 10 [1]. A milder phenotype with slower rate of progression is called variant ataxia telangiectasia (vA-T). Sometimes vA-T mimics primary generalized dystonia with ataxia being absent and with normal neuroimaging and immunoglobulin (Ig) levels. However, elevated α-fetoprotein (AFP) occurs in both classical A-T and vA-T [2,3]. We report a case of vA-T with two novel observations [1]: a severe generalized dystonia presentation, and [2] a novel sensory trick ("duck walk") to alleviate walking-associated camptocormia.

This 41-year-old Lithuanian woman, born to non-consanguineous parents, was affected by a complex movement disorder starting at age 1.5 years. The patient obtained a university degree in education but worked as a librarian from age 28 to 32 retiring due to debilitating dystonia. Despite previous extensive work up at different centers no diagnosis was reached. Two maternal aunts were affected by solid tumors (breast and gastric cancer) and a paternal uncle died of leukemia. At onset her gait was described as unsteady and the patient was prone to falls. At age 16y the patient presented with craniocervical dystonia and dysarthria; dystonia progressed, becoming generalized. Prior testing for *TOR1A*, *THAP1*, *TH*, and *GCH1*, and Huntington's disease was negative; Wilson's disease was also ruled out. The patient was examined at our center at age 35 and went through neuroimaging, laboratory and genetic analyses as well as neurophysiological tests. Oral and written consent was obtained for this report. The patient never underwent spinal surgery. Upon examination the patient displayed disabling camptocormia that resolved when the patient lay down or leaned against a wall. She squatted as a sensory trick to reduce the camptocormia magnified during ambulation ("duck walk"; Video). Movements also induced or exacerbated blepharospasm, leg posturing, and retrocollis. There were no telangiectasias or obvious signs of ataxia or oculomotor abnormalities, but broad-base gait during childhood was documented in her medical records. There was no evidence of either recurrent infections or pulmonary symptoms. EMG displayed neurogenic abnormalities but MRI of the spinal cord was normal. Laboratory analyses revealed elevated AFP (75 μg/l, normal value < 8) but normal Ig levels and normal karyotype. Sequencing and multiplex ligation-dependent probe amplification of *SETX* was normal ruling out ataxia with oculomotor apraxia type 2 (AOA2). Western blotting of a lysate of a lymphoblastoid cell line (LCL) made from the patient's blood demonstrated a very low level of ATM with low-level ATM kinase activity (Fig. 1). Previously described mutations c.3214G > T; p.Glu1072Ter and c.8147T > C; p.Val2716Ala in *ATM* were then identified [2,5] in her DNA. Together, the presence of these two *ATM* mutations and low level ATM kinase signaling confirmed the diagnosis of vA-T.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.12.017.

Several unsuccessful pharmacological attempts to treat her dystonia were made over the years. Treatment with DBS was proposed but the patient declined due to the poor outcome reported for a patient with dystonia associated with vA-T [4].

1. Discussion

This is a challenging presentation although elevated AFP and the EMG abnormalities were important diagnostic clues for vA-T. AFP is a useful biomarker for A-T regardless of presentation and should be part of the diagnostic work-up for early-onset dystonia. However, while elevated AFP is found in up to 95% of patients with A-T it is also elevated in AOA2 and ataxia with oculomotor apraxia type 4 (AOA4) but to lower levels than in A-T [1,6]. Absence of both telangiectasias and obvious ataxia make the present case even more challenging. Residual ATM kinase activity, as demonstrated in the LCL for this case, correlated with a milder phenotype in vA-T [7]; in addition, all patients with vA-T had normal Ig levels in contrast to the hypoimmunoglobulinemia commonly found among patients with classic A-T [2]. Other than ataxia and dystonia, variable degrees of chorea and myoclonus have been reported in genetically proven A-T [7,8]. ATM is part of the pathway required for the damage response to double DNA strand breaks. Of note, mutations in other genes involved in DNA repair (*APTX*, *SETX*, and *PNKP*) and causing other neurodegenerative ataxia disorders with oculomotor apraxia (AOA1, AOA2 and AOA4) do not pose an increased risk for malignancy. Despite the milder motor and neuromuscular features, the risk for malignancy is still increased even though the age of occurrence of this complication is also later than in classical A-T [2].

https://doi.org/10.1016/j.parkreldis.2018.12.017
Received 23 October 2018; Received in revised form 5 December 2018; Accepted 15 December 2018

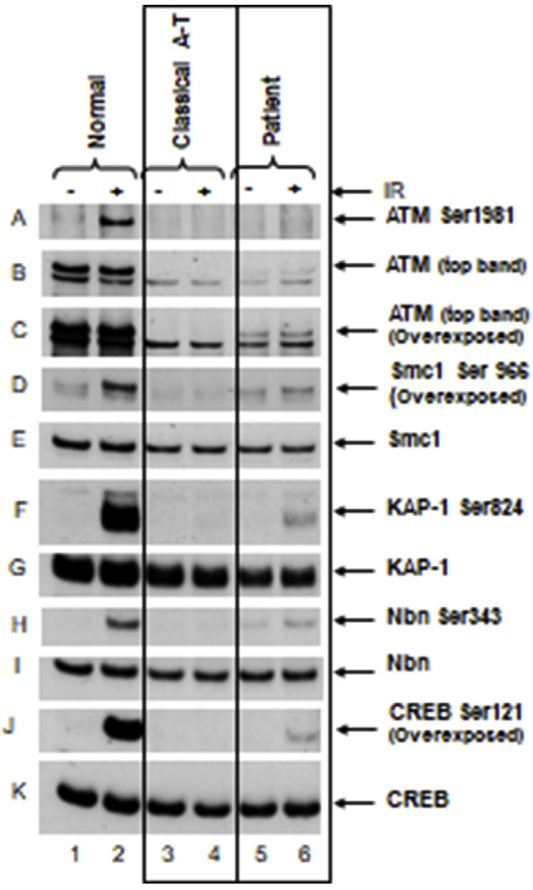

Fig. 1. Western blots showing retention of some ATM kinase activity in the patient's lymphoblastoid cell line (LCL) (lane 6) and normal LCL (lane 2) unlike a classical A-T LCL (lane 4), as shown by phosphorylation of different targets (panels D, F, H and J). Activation (+) of ATM kinase was by exposure of cells to 2Gy gamma rays.

Striking in this case is the predominant camptocormia and the sensory trick used to alleviate it. Camptocormia affects 3–18% of patients with Parkinson's disease (PD) [9] but the prevalence of camptocormia among patients with A-T is unknown. In PD, advanced age, more severe disease and previous spine surgery have been reported as risk factors for the development of camptocormia [9,10]. Sensory tricks for camptocormia associated with PD include wearing a low-slung backpack and supporting oneself by pushing hands against the thighs. Leaning against a wall to stand erect may also be considered a sensory trick [9]. Despite the remarkable variability in disease severity, the neuropathological features for A-T are similar regardless of presentation [11].

Author contributions

M. Paucar, G. Schechtmann, AMR Taylor and P. Svenningsson: study concept and data collection; M. Paucar wrote the first draft. G. Schechtmann, AMR Taylor and P. Svenningsson: editing of the manuscript.

Study funding

Martin Paucar's research is supported by the Swedish Medical Research Association. P. Svenningsson is a Wallenberg Clinical Scholar.

Disclosures

M. Paucar, G. Schechtmann, M. Taylor, and Per Svenningsson report no disclosures relevant to the manuscript.

Acknowledgements

The authors are grateful to the patient for kind participation and for consenting to this report. We are also grateful to Professor Jan Ygge for performing a neuro-ophthalmological examination.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.12.017.

References

[1] Mar 19 [Updated 2016 Oct 27], R. Gatti, S. Perlman, Ataxia-telangiectasia, [Internet], in: M.P. Adam, H.H. Ardinger, R.A. Pagon, et al. (Eds.), GeneReviews®, University of Washington, Seattle, Seattle (WA), 19991993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK26468/.
[2] M.M. Verhagen, W.F. Abdo, M.A. Willemsen, F.B. Hogervorst, D.F. Smeets, J.A. Hiel, et al., Clinical spectrum of ataxia-telangiectasia in adulthood, Neurology 73 (6) (2009 Aug 11) 430–437.
[3] R. Saunders-Pullman, D. Raymond, A.J. Stoessl, D. Hobson, K. Nakamura, S. Pullman, et al., Variant ataxia-telangiectasia presenting as primary-appearing dystonia in Canadian Mennonites, Neurology 78 (9) (2012 Feb 28) 649–657.
[4] I. Beaulieu-Boire, C.C. Aquino, A. Fasano, Y.Y. Poon, M. Fallis, A.E. Lang, et al., Deep brain stimulation in rare inherited dystonias, Brain Stimul 9 (6) (2016 Nov - Dec) 905–910.
[5] M. Mitui, E. Bernatowska, B. Pietrucha, J. Piotrowska-Jastrzebska, L. Eng, S. Nahas, et al., ATM gene founder haplotypes and associated mutations in Polish families with ataxia-telangiectasia, Ann. Hum. Genet. 69 (Pt 6) (2005 Nov) 657–664.
[6] M. Paucar, H. Malmgren, M. Taylor, J.J. Reynolds, P. Svenningsson, R. Press, A. Nordgren, Expanding the ataxia with oculomotor apraxia type 4 phenotype, Neurol Genet 2 (1) (2016 Jan 21) e49.
[7] M.M. Verhagen, J.I. Last, F.B. Hogervorst, D.F. Smeets, N. Roeleveld, F. Verheijen, et al., Presence of ATM protein and residual kinase activity correlates with the phenotype in ataxia-telangiectasia: a genotype-phenotype study, Hum. Mutat. 33

(3) (2012 Mar) 561–571.
[8] H.A.G. Teive, C.H.F. Camargo, R.P. Munhoz, More than ataxia - movement disorders in ataxia-telangiectasia, Park. Relat. Disord. 46 (2018 Jan) 3–8.
[9] K.M. Doherty, B.P. van de Warrenburg, M.C. Peralta, L. Silveira-Moriyama, J.P. Azulay, O.S. Gershanik, et al., Postural deformities in Parkinson's disease, Lancet Neurol. 10 (6) (2011 Jun) 538–549.
[10] D. Tiple, G. Fabbrini, C. Colosimo, D. Ottaviani, F. Camerota, G. Defazio, A. Berardelli, et al., Camptocormia in Parkinson disease: an epidemiological and clinical study, J. Neurol. Neurosurg. Psychiatry 80 (2) (2009 Feb) 145–148.
[11] M.M. Verhagen, J.J. Martin, M. van Deuren, C. Ceuterick-de Groote, C.M. Weemaes, B.H. Kremer, et al., Neuropathology in classical and variant ataxia-telangiectasia, Neuropathology 32 (3) (2012 Jun) 234–244.

Martin Paucar*
Department of Neurology, Karolinska University Hospital, Stockholm, Sweden
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
E-mail address: martin.paucar-arce@sll.se.

Gaston Schechtmann
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden

Alexander MR. Taylor
Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, United Kingdom

Per Svenningsson
Department of Neurology, Karolinska University Hospital, Stockholm, Sweden
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

* Corresponding author.