Cerebellum (2013) 12:596–599
DOI 10.1007/s12311-013-0460-4

LETTER TO THE EDITOR

Clinical Course of Two Italian Siblings with Ataxia-Telangiectasia-Like Disorder

Silvia Palmeri · Alessandra Rufa · Barbara Pucci · Emiliano Santarnecchi · Alessandro Malandrini · Maria Laura Stromillo · Marco Mandalà · Francesca Rosini · Nicola De Stefano · Antonio Federico

Published online: 23 February 2013

Abstract Ataxia-telangiectasia-like disorder (ATLD) due to mutations in the MRE11 gene is a very rare autosomal recessive disease, described so far in only 20 patients. Little is known about the onset of the first symptoms or the clinical course of the disease. The present report contributes to the diagnosis of ATLD and its prognosis at onset. We report 30 years of clinical and ophthalmic observations and the results of quantitative magnetic resonance (MR), MR spectroscopy (proton magnetic resonance spectroscopic imaging) and neuropsychological assessment in the first Italian siblings identified with ATLD. Although the disease had early onset and the clinical picture was initially severe, suggesting ataxia-telangiectasia, neurological impairment, ocular motor apraxia and neuropsychological tests showed very slow deterioration in adult age. The patients developed eye and head motor strategies to compensate ocular motor apraxia. MR measurements and MR spectroscopy disclosed widespread neuronal and axonal involvement. ATLD should be considered in patients with ocular apraxia and ataxia in infancy. The long follow-up provided insights into clinical outcome, with functional neuroimaging studies shedding light on the pathogenetic mechanisms of this rare disease.

Keywords Ataxia-telangiectasia-like disorder · ATLD · Ocular apraxia · Autosomal recessive ataxia · Mre11 mutation

Introduction

Among autosomal recessive cerebellar ataxias, ataxia-telangiectasia-like disorder (ATLD) has only been described in six patients in Europe [1, 2], in ten Saudi Arabians [3], in two Japanese [4] and in two Pakistanis [5]. The mutant gene, MRE11, encodes a protein with nuclease and DNA-binding activity involved in repair of DNA double-strand breaks [6]. We report clinical, ophthalmic, neuropsychological and neuroradiological findings over a period of 30 years in the only two Italian ATLD patients so far observed [2]. Our aim is to contribute data on this very rare condition.

Patients and Methods

The two siblings were born to unrelated parents. At 3 years of age, the elder son (patient 1) developed unsteadiness. On beginning school at 6 years of age, he was unable to write on a straight line. From 6 to 12 years of age, we observed

Electronic supplementary material The online version of this article (doi:10.1007/s12311-013-0460-4) contains supplementary material, which is available to authorized users.

S. Palmeri · A. Rufa · E. Santarnecchi · A. Malandrini · M. L. Stromillo · F. Rosini · N. De Stefano · A. Federico
Department of Neurological, Neurosurgical and Behavioural Sciences, Medical School University of Siena, Siena, Italy

B. Pucci
Department of Neurosciences, Medical School University of Siena, Siena, Italy

M. Mandalà
Department of Human Pathology and Oncology, Medical School University of Siena, Siena, Italy

S. Palmeri (✉)
Neurological and Neurometabolic Unit, S. Maria alle Scotte Hospital, Viale Bracci,
53100 Siena, Italy
e-mail: silvia.palmeri@unisi.it

Table 1 Global and regional brain and cerebellar volumes and proton MRS measures in both patients and healthy controls

ATLD	NBV	NCV	NCbV	Cerebellar NAA/CR
Patient 1	1,383	517	107	1.42
Patient 2	1,425	560	95	1.12
HC (mean ± SD)	1,543±45	598±24	201±16	1.85±0.1

HC healthy control, *NBV* normalized brain volume, *NCV* normalized cortical volume, *NCbV* normalized cerebellar volume, expressed in cubic centimetre, *NAA/CR N*-acetylaspartate to creatine ratio

progressive manifestations of head ataxia, oculomotor apraxia, unaided ataxic gait, dysarthria, hypotonia, dysmetria, action tremor and choreo-athetotic movements with expressionless face, drooling and joint laxity. Oculomotor evaluation at 12 years showed dissociation of head rotation and eye movements, dysmetric saccades with increased latency and gaze-evoked nystagmus (GEN). The sister (1 year younger) was normal until 6 years of age, when she developed the same progressive neurological manifestations. Oculomotor evaluation at 11 years of age showed similar abnormalities to the brother but without nystagmus. Both had normal afferent visual function. Neither showed telangiectasia. Laboratory tests including α-fetoprotein and immunoglobulins were normal. A CT scan showed vermian cerebellar atrophy.

From 12 years of age to adulthood, we did not observe any clear worsening of the clinical picture except for gait. At 27 and 26 years, respectively, MRI showed generalized cerebellar atrophy and EMG revealed slight signs of axonal sensory neuropathy; visual evoked potentials, brainstem auditory evoked responses and somatosensory evoked potentials were normal. Nerve biopsy (patient 1) showed rare axonal degeneration and slight reduction in myelinated fibre number. At 37 and 36 years, respectively, sequence analysis of cDNAs and genomic DNA of the MRE11 gene revealed compound mutations at codon 1442C→A, resulting in base exchange T481K, and 1714C→T, which introduced a premature stop codon (R571X) at exon 15 [2]. Previous molecular analysis of the ATM and NBS1 genes was normal.

At 45 and 44 years, respectively, the patients showed a stable clinical picture except for severe ataxia. Patient 1 also manifested dystonia of the limbs (as shown in video clips). Both had frequent falls but could walk arm in arm with another person. Total ataxia score was 68/100 according to the International Cooperative Ataxia Rating Scale [7]. Clinical oculomotor examination showed impaired horizontal saccades and pursuit, as well as abnormalities of fixation, VOR and gaze holding. Saccades were fast and inaccurate in both patients and associated with various kinds and degrees of eye oscillations, including GEN, rebound nystagmus and saccadic intrusions. Disrupted pursuit, abnormal VOR and oculocephalic dissociation were also evident. Magnetic resonance (MR) measures [8, 9] showed that normalized volumes of the whole brain, cortex and cerebellar tissues were at least 2 standard deviations below the mean of healthy controls. Single-voxel proton MR spectrometry also detected significantly lower values of cerebellar *N*-acetylaspartate (a marker of axonal integrity)/creatine (Table 1, Fig. 1). Conventional MRI and single-voxel proton MRS examinations were obtained in a single session using a Philips Gyroscan operating at 1.5 T.

Neuropsychological evaluation (WAIS-R) at 18 and 16 years of age showed total IQs of 70 and 80 (standard

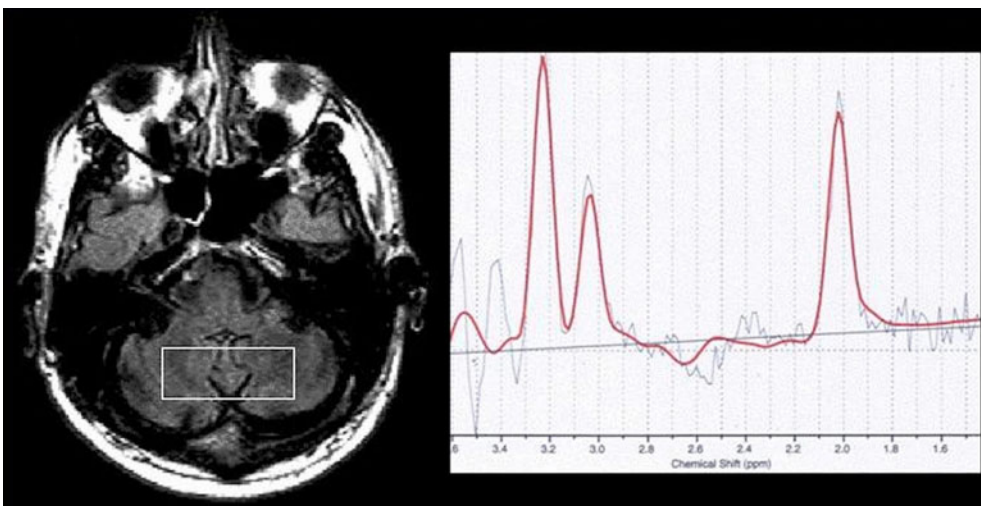

Fig. 1 Conventional MRI scan of patient 1 with the cerebellar volume of interest (VOI) used for spectroscopy and the proton MR spectrum of the same VOI

score 100±15), normal verbal IQ and performance IQ below average (50 and 69), impaired by manual difficulties. In a second evaluation (42 and 41 years, respectively), patient 2 showed slight worsening of total, verbal and performance IQ. This time a battery of neuropsychological tests was also done for better evaluation of cognitive functions (Frontal Assessment Battery; Rey's 15 words learning and recall; Rey's complex figure recall; Rey's complex figure copy, phonemic and semantic fluency; Raven's Progressive Matrices; and Hamilton Rating Scale for Depression). Frontal abilities, visuospatial long-term memory, verbal production and selective and divided attention and praxis, especially in planning complex geometric figures, were below average for both. MMSE was normal. No mood disorders were found. An interview on quality of life (QoL) and daily living activities (Katz's ADL, Lawton's IADL) revealed a decline in ability to dress, to leave the house autonomously, to use public transport, to go to the bank and so forth; however, both were employed for about 4 h/day. Their Likert QoL scores (scale 1–10) were 6 and 7, respectively.

Discussion

The severe clinical picture observed at onset of the disease suggested ataxia-telangiectasia (A-T), despite the absence of telangiectasia [10]. Progression was rapid from onset to 12 years of age and slowed thereafter. Molecular genetic study of the MRE11 gene led to the diagnosis of ATLD at 37 and 36 years, respectively [2]. Moderate cognitive deficits, mostly concerning executive functions, had deteriorated slightly at the second evaluation. With regard to motor impairment, our patients, the English patient and the two Saudi Arabian adult patients, can still walk in adulthood. They are not wheelchair-bound, as patients affected by A-T or Friedreich's ataxia would be. Although autonomy is difficult, our patients scored 6 and 7 for overall quality of life (best quality = 10).

Of the 20 patients described in the literature, our two patients and 14 others have not developed tumours. Two Japanese siblings with a phenotype close to A-T died of lung adenocarcinoma at 9 and 16 years of age [4]. Tumours are not specifically reported for the Pakistani patients [5].

Despite the early age of onset, the disease and oculomotor function evolved quite favourably in our patients. The ophthalmic features, resembling those of two adults described by Khan [11], currently show a combination of horizontal torsional GEN. The latency of goal-directed saccades was very high at onset. This condition, known as oculomotor apraxia, is common in A-T patients and is characterized by inability to perform voluntary saccades. It decreased progressively in our patients and was replaced by voluntary goal-directed eye and head movements towards the target. Irrespective of ocular motor changes, visual function did not worsen in the course of follow-up in our siblings, who are currently able to read books, watch TV and use the computer. This indicates that they have developed ocular and head motor strategies to preserve their vision during the course of the disease.

MR measures and proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) findings compared with conventional MRI suggest widespread neuroaxonal damage not confined to cerebellar neurons. These findings are in line with the autopsy study of Oba et al. [12], which showed lack of MRE11 immunoreactivity in Purkinje neurons, the cerebral cortex and basal ganglia of ATLD patients.

Conclusion

Comprehensive observation of two siblings with ATLD, carrying MRE11 gene compound mutations, over a period of 30 years, improved current knowledge of this rare early onset ataxia. The disease seems to have early onset with severe features, normal Ig and α-fetoprotein, low incidence of malignancies, slow evolution, mild neuropathy, ophthalmic features similar to A-T, slight deterioration of cognitive function in adulthood and MR and ^{1}H-MRSI evidence of widespread neuroaxonal damage not confined to cerebellar neurons.

Acknowledgments We thank Prof. G.C. Guazzi for allowing us to examine old clinical data of the patients and for the helpful clinical discussion.

Conflict of interest None.

Ethical approval All subjects gave their informed consent prior to inclusion in the study.

References

1. Stewart GS, Maser RS, Stankovic T, Bressan DA, Kaplan MI, Jaspers NGJ, et al. The DNA double-strand break gene hMre11 is mutated in individuals with ataxia-telangiectasia-like disorder. Cell. 1999;99:577–87.
2. Delia D, Piane M, Buscemi G, Savio C, Palmeri S, Lulli P, et al. MRE11 mutations and impaired ATM-dependent responses in an Italian family with ataxia-telangiectasia-like disorder. Hum Mol Genet. 2004;13(18):2155–63.
3. Fernet M, Gribaa M, Salih MAM, Seidahmed MZ, Hall J, Koening M. Identification and functional consequences of a novel MRE11 mutation affecting 10 Saudi Arabian patients with ataxia telangiectasia-like disorder. Hum Mol Genet. 2005;14(2):307–18.
4. Uchisaka N, Takahashi N, Sato M, Kikuchi A, Mochizuchi S, Imai K, et al. Two brothers with ataxia-telangiectasia-like disorder with lung adenocarcinoma. J Pediatr. 2009;155:435–8.

5. Chaki M, Airik R, Ghosh AK, Giles RH, Chen R, Slaats GG, et al. Exome capture reveals ZNF423 and CEP164 mutations, linking renal ciliopathies to DNA damage response signaling. Cell. 2012;150(3):533–48.
6. D'Amours D, Jackson SP. The Mre11 complex: at the crossroads of DNA repair and checkpoint signalling. Nat Rev Mol Cell Biol. 2002;3:317–27.
7. Trouillas P, Takayanagi T, Hallett M, Currier RD, Subramony SH, Wessel K, et al. International Cooperative Ataxia Scale for pharmacological assessment of the cerebellar syndrome. J Neurol Sci. 1997;145:205–11.
8. De Stefano N, Dotti MT, Mortilla M, Federico A. Magnetic resonance imaging and spectroscopic changes in brains of patients with cerebrotendinous xanthomatosis. Brain. 2001;124(Pt 1):121–31.
9. Smith SM, Zhang Y, Jenkinson M, Chen J, Matthew PM, Federico A, et al. Accurate, robust and automated longitudinal and cross-sectional brain change analysis. NeuroImage. 2002;17:479–89.
10. Riise R, Ygge J, Lindman C, Stray-Pedersen A, Bek T, Rodningen OK, et al. Ocular findings in Norwegian patients with ataxia-telangiectasia: a 5 year prospective cohort study. Acta Ophthalmol Scand. 2007;85:557–62.
11. Khan AO, Oystreck DT, Koenig M, Salih MA. Ophthalmic features of ataxia telangiectasia-like disorder. J AAPOS. 2008;12 (2):186–9.
12. Oba D, Hayashi M, Minamitani M, Hamano S, Uchisaka N, Kikuchi A, et al. Autopsy study of cerebellar degeneration in siblings with ataxia-telangiectasia-like disorder. Acta Neuropathol. 2010;119(4):513–20.