Journal of Neurology (2019) 266:522–524
https://doi.org/10.1007/s00415-018-9115-1

LETTER TO THE EDITORS

Sez6l2-antibody-associated progressive cerebellar ataxia: a differential diagnosis of atypical parkinsonism

Max Borsche[1,3] · Stefanie Hahn[2] · Henrike Hanssen[1,3] · Alexander Münchau[1] · Klaus-Peter Wandinger[3,4] · Norbert Brüggemann[1,3]

Received: 3 October 2018 / Revised: 1 November 2018 / Accepted: 2 November 2018 / Published online: 20 November 2018

Dear Sirs,

Recent advances in the identification of immunological causes for movement disorders have opened a new avenue to causally treat these often severely disabling diseases. Immunological processes may be related to secondary underlying disease causes or may occur without known association to such conditions. The detection of antibodies against intracellular structures or surface antigens may be helpful in the diagnostic workup although their significance with regard to disease mechanisms is controversial. Thus, the presence of an antibody may be unspecific, may serve as a biomarker indicating an underlying autoimmunological process or may directly be involved in the disease process. Complicating matters, antibody-associated neurological syndromes may occur without overt inflammatory signs, particularly in the elderly population [1].

Here, we report the second patient with rapidly progressive cerebellar ataxia and anti-Sez6l2 antibodies. We highlight additional clinical signs that can make the differential diagnosis of an autoimmunological vs. a neurodegenerative disorder difficult. The study was approved by the ethics committee of the University of Luebeck.

Initially, this female patient with a history of Crohn's disease noticed gait difficulties and a slightly slurred speech at the age of 55 years. In the past medical history, the patient underwent proctocolectomy including ileostomy due to Crohn's disease at the age of 46 and adhesiolysis due to obstructive ileus at the age of 54. She used to smoke until the age of 25. At the age of 55, active bowel disease or a short bowel syndrome could be ruled out, both clinically and by means of ileoscopy. Upon examination, square wave jerks, mild appendicular ataxia and a slightly impaired tandem gait and moderate postural instability were present (video 1). Workup for immunological and neoplastic causes including antibody testing (deaminated gliadin, tissue transglutaminase, GAD, amphiphysin, CASPR2, $GABA_B$, Hu, Yo, Ri, VGCC, CV-2, PNMA-2, Recoverin, SOX1, Titin, IgLON5) and PET–CT were normal about 4 months after the onset of ataxia. The following CSF parameters were assessed: normal white blood cell count, total protein and albumin, no evidence of intrathecal immunoglobulin synthesis and the absence of oligoclonal bands. Beta-amyloid levels were, however, decreased in two subsequent lumbar punctures [186 pg/ml and 311 pg/ml (>450)], whereas tau and phospho-tau were in the normal range. Cranial MRI showed bilateral thinning of the superior cerebellar peduncle and a global cerebellar atrophy. Due to the rapid onset and fluctuating disease course, an immunological cause was suspected and IVIG was administered four times resulting in a slight subjective improvement.

At 9-month follow-up, ataxia had deteriorated considerably (SARA score from 9.5/40 to 19.5/40). Her speech was difficult to understand, and she was no longer able to walk unaided. There was psychomotor slowing, stereotypies of the trunk, severe postural instability, hypomimia and bradykinesia (video 2). In addition, she complained about nausea and weight loss. Autonomic failure and retinopathy, however, were absent. Antibody titers were determined by incubation of serially diluted patient's serum (1:10, 1:32,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-018-9115-1) contains supplementary material, which is available to authorized users.

✉ Norbert Brüggemann
norbert.brueggemann@neuro.uni-luebeck.de

1 Institute of Neurogenetics, University of Lübeck, Lübeck, Germany

2 Institute of Experimental Immunology, Euroimmun AG, Lübeck, Germany

3 Department of Neurology, University of Lübeck, Lübeck, Germany

4 Institute of Clinical Chemistry, University Hospital of Schleswig-Holstein, Lübeck, Germany

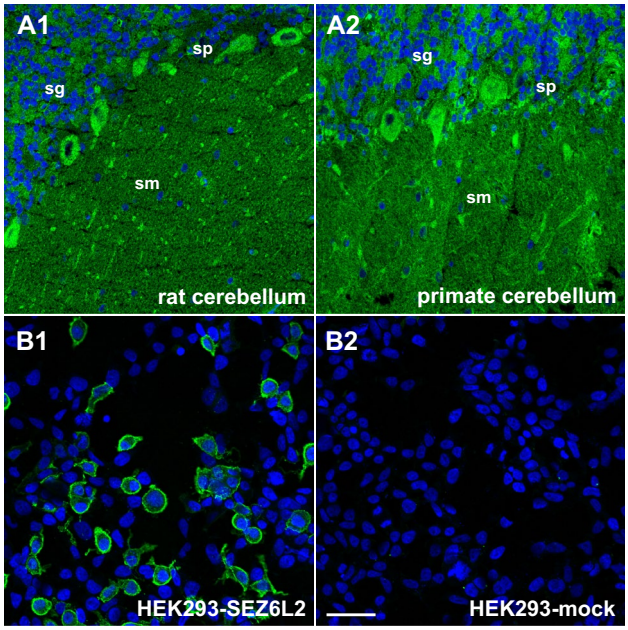

Fig. 1 Immunofluorescence analysis of central nervous tissue and recombinant SEZ6L2. Cryosections of rat (**A1**) and primate cerebellum (**A2**) as well as formalin-fixed recombinant HEK293 cells expressing SEZ6L2 (**B1**) or mock-transfected control (**B2**) were incubated with patient serum (1:100). A fine granular staining of the stratum moleculare (sm) and a blotchy staining of the stratum granulosum (sg) were obtained. Additionally, the cytoplasm of Purkinje cells and their corresponding dendrites displayed a clear immunoreactivity with patient serum. Patient antibodies were detected by Alexa Fluor 488-labelled goat anti-human IgG (green). Nuclei were counterstained by incubation with TO-PRO-3 iodide (blue). Scale bar: 50 µm

1:100, 1:320, 1:100, 1:3200) or CSF (1:1, 1:3, 2, 1:10, 1:32, 1:100) on transfected HEK 293 cells expressing the Sez6l2-antigen (Fig. 1). Titers were determined as the highest sample dilution still resulting in antibody binding. Subsequently, the patient was treated with rituximab resulting in a stable disease state over a time period of 12 months as of now (video 3). Nausea and stereotypies of the trunk were no longer present and she regained her premorbid weight. She was able to walk longer distances with a walker.

Sez6l2 antibodies were previously described in another patient with rapidly progressive cerebellar ataxia [6]. In mice, a high expression of Sez6l2 was shown in the cerebellar cortex [4], and Sez6l2 antibodies were capable of inhibiting the complex formation of GluR1 and Sez6l2 [7]. Interestingly, the original patient shared several similarities with our case including sex (female), age (50 vs. 60 years), rapid disease progression, normal routine CSF results and cerebellar atrophy. In contrast to the first case, retinopathy was not present in our patient, whereas the combination with the above-mentioned additional clinical features were reminiscent of an atypical form of parkinsonism, in particular the cerebellar subtype of progressive supranuclear palsy (PSP-C). In keeping with a neurodegenerative disorder, beta-amyloid levels were decreased. The rapid disease progression, however, the inconclusive phenotype in conjunction with the presence of Sez6l2 antibodies and stabilization of the disease course due to immunomodulation and—suppression strongly suggested an autoimmunological cause in our patient.

Taken together, the clinical phenotype of antibody-associated movement disorders may show considerable overlap with neurodegenerative diseases such as atypical forms of parkinsonism. In this context, IgLON5 antibodies were recently identified in patients with an inflammatory encephalopathy in whom clearly neurodegenerative changes were observed in post-mortem investigations of the brain [2, 3, 5]. The rapid disease course, however, should prompt the clinician to thoroughly assess paraneoplastic and autoimmunological causes including Sez6l2 antibodies.

Funding None.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

References

1. Escudero D, Guasp M, Arino H, Gaig C, Martinez-Hernandez E, Dalmau J, Graus F (2017) Antibody-associated CNS syndromes without signs of inflammation in the elderly. Neurology 89:1471–1475
2. Gaig C, Graus F, Compta Y, Hogl B, Bataller L, Bruggemann N, Giordana C, Heidbreder A, Kotschet K, Lewerenz J, Macher S, Marti MJ, Montojo T, Perez-Perez J, Puertas I, Seitz C, Simabukuro M, Tellez N, Wandinger KP, Iranzo A, Ercilla G, Sabater L, Santamaria J, Dalmau J (2017) Clinical manifestations of the anti-IgLON5 disease. Neurology 88:1736–1743
3. Gelpi E, Hoftberger R, Graus F, Ling H, Holton JL, Dawson T, Popovic M, Pretnar-Oblak J, Hogl B, Schmutzhard E, Poewe W, Ricken G, Santamaria J, Dalmau J, Budka H, Revesz T, Kovacs GG (2016) Neuropathological criteria of anti-IgLON5-related tauopathy. Acta Neuropathol 132:531–543
4. Miyazaki T, Hashimoto K, Uda A, Sakagami H, Nakamura Y, Saito SY, Nishi M, Kume H, Tohgo A, Kaneko I, Kondo H, Fukunaga K, Kano M, Watanabe M, Takeshima H (2006) Disturbance of cerebellar synaptic maturation in mutant mice lacking BSRPs, a novel brain-specific receptor-like protein family. FEBS Lett 580:4057–4064
5. Sabater L, Gaig C, Gelpi E, Bataller L, Lewerenz J, Torres-Vega E, Contreras A, Giometto B, Compta Y, Embid C, Vilaseca I, Iranzo A, Santamaria J, Dalmau J, Graus F (2014) A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study. Lancet Neurol 13:575–586

6. Yaguchi H, Yabe I, Takahashi H, Okumura F, Takeuchi A, Horiuchi K, Kano T, Kanda A, Saito W, Matsumoto M, Nakayama KI, Hatakeyama S, Sasaki H (2014) Identification of anti-Sez6l2 antibody in a patient with cerebellar ataxia and retinopathy. J Neurol 261:224–226

7. Yaguchi H, Yabe I, Takahashi H, Watanabe M, Nomura T, Kano T, Matsumoto M, Nakayama KI, Watanabe M, Hatakeyama S (2017) Sez6l2 regulates phosphorylation of ADD and neuritogenesis. Biochem Biophys Res Commun 494:234–241