Salmen Anke (Orcid ID: 0000-0002-4751-299X)
León Betancourt Alejandro Xavier (Orcid ID: 0000-0001-8375-9810)
Rebsamen Michael (Orcid ID: 0000-0002-8441-1485)
Hoepner Robert (Orcid ID: 0000-0002-0115-7021)

Anti-neurochondrin antibody as a biomarker in primary autoimmune cerebellar ataxia – a case report and review of the literature

Schwarzwald A, MD[1,2], Salmen A, MD PD[1], León Betancourt A, MD[1], Diem L, MD[1], Hammer H, MD[1], Radojewski P, MD[3], Rebsamen M[3], Kamber N, MD[1], Chan A, MD Prof[1], Hoepner R, MD PD[1], Friedli C, MD[1]

1: Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Switzerland

2: Clinic Bethesda, Neurorehabilitation, Parkinson Centre, Epileptology, Tschugg, Switzerland

3: Support Center for Advanced Neuroimaging (SCAN), University Institute of Diagnostic and Interventional Neuroradiology, University of Bern, Inselspital, Bern University Hospital, Bern, Switzerland

Corresponding author: Anina Schwarzwald, Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Freiburgstrasse, 3010 Bern, Switzerland, Tel.: 0041 31 632 21 11, E-Mail: ani.schwarzwald@bluewin.ch

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Abstract

Introduction

Neuronal autoantibodies can support the diagnosis of primary autoimmune cerebellar ataxia (PACA).

Methods

Case presentation and literature review of PACA associated with anti-neurochondrin antibodies.

Results

A 33-year-old man noticed 05/20 reduced control of the right leg. First at our hospital 09/21, he complained about gait imbalance, fine motor disorders, tremor, intermittent diplopia and slurred speech. He presented a pancerebellar syndrome with stance, gait and limb ataxia, scanning speech and oculomotor dysfunction. Within three months the symptoms progressed. Initial cerebral magnetic resonance imaging (MRI) 06/20 was normal, but follow-up imaging 10/21 and 07/2022 revealed marked cerebellar atrophy (29% volume loss). Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis of 11 M/L (normal range 0-4), and oligoclonal bands type II. Anti-neurochondrin antibodies (IgG) were detected in serum (1:10'000) and CSF (1:320, by cell-based indirect immunofluorescence assay and immunoblot, analysed by EUROIMMUN laboratory). After ruling out alternative causes and neoplasia, diagnosis of PACA was given and immunotherapy (steroids and cyclophosphamide) was started 01/22. In 03/22 a stabilization of disease was observed.

Conclusion

Cerebellar ataxia associated with anti-neurochondrin antibodies has only been described in 19 cases; however, the number of unrecognised PACAs may be higher. As anti-neurochondrin antibodies target an intracellular antigen and exhibit a mainly cytotoxic T cell mediated pathogenesis, important therapeutic implications may result. Because of the severe and rapid clinical progression, aggressive immunotherapy was warranted. This case highlights the need for rapid diagnosis and therapy in PACA, as stabilization and even improvement of symptoms is attainable.

Introduction

Immune-mediated cerebellar ataxias (IMCA) are well described and not rare. In a prospective study published in 2017 from the United Kingdom, IMCAs accounted for up to 26% in 1500 patients with progressive ataxia observed over a period of 20 years.[1] The most common causes of IMCAs in those 1500 patients were gluten-sensitive ataxias (20%), paraneoplastic cerebellar degenerations (PCD) (2%), and ataxias directly associated with pathogenic neuronal antibodies, anti-glutamate decarboxylase (GAD)-associated ataxia (2%) and myoclonus-opsoclonus ataxia syndrome (1%). Twenty percent (295/1500 patients) of progressive cerebellar ataxias were classified as familial, whereas eighty percent (1205/1500 patients) were classified as sporadic ataxias. Of these eighty percent sporadic ataxias, no specific cause was found in 19% despite intensive investigations (including genetic testing using next-generation sequencing (NGS) for 175 genes); which were then described as idiopathic sporadic ataxias. Today, it is presumed that the majority of these idiopathic sporadic ataxias are immune-related. Due to the lack of a specified aetiology, the category "primary autoimmune cerebellar ataxia (PACA)" was first mentioned.[1] However, the exact prevalence and incidence of PACA is unknown.

In 2020, an international task force of experts in the field of IMCA established diagnostic criteria for PACA.[2] The aim was to allow clinicians to diagnose PACA "when encountering a

patient with progressive ataxia and no other diagnosis given that such consideration might have important therapeutic implications". Among a few others, one criterion included the "presence of autoantibodies, which are suggestive of an autoimmune process but not yet shown to be either directly involved in the pathogenesis of ataxia or to be markers of ataxia with a known trigger". Such antibodies are for example anti-MAG (myelin-associated glycoprotein), anti-Septin-5, anti-Homer-3 or, as in our case, anti-neurochondrin among others.[2]

Anti-neurochondrin antibodies were described for the first time in three patients with cerebellar ataxia in 2016.[3] Neurochondrin is the target intracellular antigen of these antibodies, which is expressed in the brain (mainly in the cytoplasm of cerebellar Purkinje cells, neurons of the brain stem, parts of the amygdala and parts of the hippocampus), as well as in the peripheral and autonomous nervous system, in bone (osteoblasts and -clasts) and in cartilage. It is assumed that anti-neurochondrin antibodies themselves are not pathogenic, but likely hint at a cytotoxic T-cell-mediated pathogenesis and are thus to be regarded as an epiphenomenon.[3–7]

We here present the case of a 33-year-old patient who first presented himself in September 2021 at the University Hospital in Bern with a subacute and progressive pancerebellar syndrome and in whom we detected anti-neurochondrin antibodies in the serum and cerebrospinal fluid, indicating PACA. We aim to describe this case and perform a review of the literature on anti-neurochondrin associated neurological disorders.

Methods/Literature research

The literature search was conducted in Pubmed, last on April fourth 2022. For further detail see figure 1.

Quantification of cerebellar volume was performed using DL+DiReCT[8], which allows deriving brain morphometric measures from high-resolution, contrast-enhanced T1-weighted MRI[9].

Ethics statement

We obtained written informed consent by the here presented case prior to publication.

Case presentation

The first neurological symptoms of this male Caucasian patient started in May 2020 (aged 32 years) with a new occipital headache persisting for two weeks, which was unusual for the patient. Over the course of a few weeks, he developed a slowly progressive, subjective leg weakness and described a loss of control of the right leg and further trouble in fine motor skills of the right arm with a tremor of the right hand (which he noticed especially while writing). He had no previous medical history and no family history of neurological, rheumatological or oncological diseases. He has been a smoker for 13 years and reported a moderate alcohol consumption (0.3-0.6 l beer per week). He did not complain about constitutional symptoms. The patient was working as a driver. No direct exposition to toxic substances is expected or was reported. He is married and is now a father of a healthy child.

A first neurological assessment was performed in June 2020 by a registered doctor of neurology describing an ataxia in the heel-to-shin test and a clumsiness while hopping on the right foot with a slight slump of the right leg in the gait tests. The initial brain MRI (06/2020) and MRI of the spinal axis (06/2020) both showed no pathologies. Motor evoked potentials (MEP) to the lower extremities were unrevealing. However, in August 2020 CSF-specific oligoclonal bands (type II)[10] were found in the CSF examination (no original documentation available, no

information on CSF cell count). No definite diagnosis was established and the patient received no treatment. In May 2021, he presented himself for a follow-up at the same neurologist and reported an accentuation of his gait unsteadiness and subjective fine motor disturbance of the right hand in the meantime. In the clinical examination, a progressive gait ataxia and ataxia of the lower extremities were found.

Again, brain MRI and multiple electrophysiological examinations (MEP to the lower extremities, somatosensory evoked potentials (SSEP) to the lower extremities and visually evoked potentials (VEP) (05/2021) remained unrevealing. However, persisting CSF-specific oligoclonal bands were indicating a chronic inflammation of the central nervous system. This finding and the progressive symptoms finally led to the transfer to our outpatient department with the suspicion of a chronic inflammation of the central nervous system (CNS).

When the patient first presented at our neuro-immunological outpatient department in September 2021, he reported a further progression of his gait unsteadiness and troubles in fine motor skills of the right hand. Furthermore, he noticed a new tremor of the left hand, speaking difficulties and transient diplopia when watching to the left. He involuntarily had lost four kilograms within the last five months, but night sweats and fever were denied. He was still an active cigarette smoker, but refrained from alcohol and consumed no other drugs. In the neurological examination, he presented a pancerebellar syndrome with a predominantly left-sided ataxia of stand, gait and limbs, an oculomotor dysfunction with fluctuating nystagmus as

well as a scanning, slightly slurred speech. The SARA-Score (Scale for the Assessment and Rating of Ataxia)[11] was 12 of 40 points, indicating moderate cerebellar ataxia.

The results of the additional blood examinations are listed in tables 1.1-1.3. Except for borderline elevated anti-nuclear antibodies (ANA) of 1:80 (reference <1:80), an extensive screening for rheumatological disorders (vasculitis, connective tissue disease, myositis, systemic sclerosis, lupus erythematosus, antiphospholipid syndrome) remained unrevealing, as were screening tests for celiac disease, gluten ataxia, metabolic, paraneoplastic and hormonal causes of ataxia (see table 1.1). All of the tested onconeuronal and limbic antibodies were negative (see table 1.2) and also a broad microbiological examination (see table 1.3) remained unrevealing.

A repeated lumbar puncture showed a pleocytosis of 11 M/L (normal range 0-4), with a disturbed blood-brain barrier (albumin ratio 7.57, reference <6.5) and persisting CSF-specific oligoclonal bands (type II).[10] In the CSF, no evidence of infectious causes (by using BioFire multiplex polymerase chain reaction (PCR) as well as John Cunningham polyoma virus (JCPy virus) PCR) could be found (see table 1.3). Limbic and onconeuronal antibodies remained negative in CSF too (see table 1.2).

Repeated brain MRI in October 2021 showed a marked cerebellar atrophy especially of the superior vermis and cerebellar hemispheres. The MRI of the spinal axis remained normal (see figure 2).

A broad tumour screening with a whole-body computer tomography (CT), urological examination, gastroscopy and colonoscopy showed no signs of an underlying malignancy (for details see table 1.1). A Helicobacter pylori positive gastritis was found in the gastroscopy, for which eradication therapy was then established. The CT scan suggested an enlarged thymus and perfusion inhomogeneity in liver segment VIII. On further MRIs, the finding of the enlarged thymus was most likely compatible with a residual thymus, whereas the lesion in liver segment VIII was caused by a transient hepatic attenuation difference (THAD)/shunt, a so-called pseudolesion. Further, we performed an analysis for rare autoantibodies, which can be associated with a progressive cerebellar disorder. High-titre anti-neurochondrin immunoglobulin G (IgG) antibodies of 1:10'000 (reference <1:100) were detected in the serum and in the CSF (1:320, reference 1:100) by cell-based indirect immunofluorescence assay (IFA) and immunoblot (cell-based immunohistoprecipitation) (performed at the EUROIMMUN laboratory (Lübeck, Germany)). Due to this appropriate finding, we omitted genetic testing (to exclude e.g. spinocerebellar atrophy).

In December 2021, only three months after first presenting to our institution, the cerebellar syndrome showed further progression; by then the patient could only walk with a wheeled walker. The SARA score was already 20.5 points, indicating a severe dependency in activities of daily living (ADL).

We diagnosed PACA related to anti-neurochondrin antibodies (see following literature review). In January 2022 we started an immunosuppressive therapy with oral glucocorticoids and

subsequently a higher potent immunotherapy with cyclophosphamide (weight-adjusted 15mg/kg/body weight, initially three doses every two weeks, then three doses every three weeks, according to the CYCLOPS protocol[12]). By this time, the SARA score had increased to 23 points. We used this score as a clinical follow-up parameter. In the follow-up examination two months after the start of cyclophosphamide in March 2022, there was a small improvement, or at least a disease stabilisation (SARA score of 21 points). A marked cerebellar volume loss of 29% was observed over two years (see figure 3). For an overview of the progression of cerebellar ataxia by SARA score, see figure 4. Whether this improvement in SARA score represents a true treatment response, day-to-day fluctuation or inter-rater variability cannot be determined with certainty. Apart from increased sweating, no side effects of the immunosuppressive medications were noted. Additionally, he has physical therapy twice a week and occupational therapy once a week. Due to the scanning dysarthria, speech therapy was also prescribed. After conclusion of the cyclophosphamide induction scheme, an intensive neuro rehabilitation is planned near-term.

Literature review

PACA was first discussed as a separate entity in 2008.[13] Autoimmunity was suggested, because patients with rapidly progressive cerebellar ataxias, classified as idiopathic sporadic ataxia had an overrepresentation of the human lymphocyte antigen (HLA) phenotype DQ2 (74% vs. 35% in the healthy population), which is strongly associated with autoimmune diseases, such as celiac disease and gluten ataxia, type 1 diabetes mellitus, stiff person syndrome, autoimmune

thyroid syndrome and autoimmune polyendocrine syndromes.[1,14] Moreover, patients with PACA more frequently presented with other autoimmune diseases (47% vs. 3% in the general population and 5% in genetic ataxias, respectively). In up to sixty percent of the cases, autoantibodies (not yet specified) against cerebellar structures could be identified (vs. five percent in genetic ataxias). It was assumed that PACA is a treatable disorder due to its autoimmune pathogenesis, however, no specific immunotherapy as a treatment option had been reported on by then.

In April 2020 an international task force of experts on IMCA published diagnostic criteria for PACA (aside from IMCA). For the diagnostic pathway, we kindly refer to Hadjivassiliou et al.[2]

The detection of autoantibodies suggestive of an autoimmune process is of particular significance and eventually has therapeutic implications.

In the literature, nineteen cases in total with autoimmunity by the detection of anti-neurochondrin antibodies have been described so far (including our case).[3,4,7,15–19] The clinical presentation was cerebellar ataxia in fourteen of nineteen cases described (73.7%)[3,4,16,18,19] and brainstem encephalitis in five cases (26.3%).[3,4] At least four of those five patients with brainstem encephalitis simultaneously had a cerebellar syndrome. One patient with a brainstem syndrome had an accompanying thoracic myelitis.[4] Movement disorders were described in two paediatric cases[15–17], as were three cases of encephalopathy in paediatric patients.[15] In addition, small fibre neuropathy was detected in one patient.[4] One patient with cerebellar ataxia suffered previously from psychosis.[4] The age at diagnosis of all published cases ranged from 2.6 to 69

years. The median age of all published cases (including our case) is 30.8 years, excluding the paediatric cases (younger than 16 years), the mean age is 41.8 years. Twelve out of nineteen patients were male (63.2%). A summary of the epidemiological and clinical data of all published cases with anti-neurochondrin associated autoimmunity is listed in table 2.1.

In the patient with brainstem encephalitis and myelitis, the laboratory findings included anti-neurochondrin antibodies and elevated SSA (Ro) antibodies, CCP (cyclic citrullinated peptide) and ANA compatible with Sjögren's syndrome.[4] In the patient with the preceding psychosis, elevated SSA and ANAs were also found, additionally to a hypothyroidism.[4] In only one of the published cases, a carcinoma was detected; a low-differentiated uterine carcinoma in a patient aged 69 years.[4] In sixteen cases (including our case), data of CSF analysis are available (16/19 (84.2%)).[3,4,7,12] CSF pleocytosis is described in 11/16 (68.8 %) and the detection of CSF specific oligoclonal bands and elevated IgG index, respectively in 11/16 cases (68.8%).[3,4,19,16] Normal CSF findings were described in three neuropediatric cases[15,18]. In eighteen of nineteen patients (94.7%), data of the MRI findings were available. Ten of eighteen (55.6%) had documented a cerebellar atrophy in the course of the disease, especially an atrophy of the vermis.[3,4,19] Five MRIs were described as normal[4,15] (5/18, 27.8%), four of them were neuropediatric patients and the last one was the patient with the small fibre neuropathy. A summary of the diagnostic findings of all published cases with anti-neurochondrin associated autoimmunity is listed in table 2.2.

Eighteen of nineteen patients with autoimmunity and detection of anti-neurochondrin antibodies received an immunotherapy after diagnosis (94.7%); only one patient remained untreated.[4] Fourteen cases were treated (among others) with steroids[4,15,16,18,19] (14/18, 77.8%), eleven with intravenous immunoglobulins (IVIG)[3,4,17,18] (11/18, 61.1%), five (including our case) with cyclophosphamide[3,4,19] (5/18, 27.8%), four with azathioprine[3,4,15] (4/18, 22.2%), four with rituximab[4,18] (4/18, 22.2%), two with mycophenolate[16,19] (2/18, 11.1%) and two with plasmapheresis[4,19] (2/18, 11.1%). All forms of therapies are listed in table 2.3.

The time from disease onset to therapy initiation ranged from a few days to ten years and the follow up time from 0.13 to 60 months (mean 18.4 months). Since disease severity in most of the cases described was not quantified by an objective value such as the SARA score (only 3 others[3] besides our case), it is not possible to describe at what level of disease a therapy was started. Ten of nineteen cases had (at least a slight) clinical improvement (including our patient) (52.6%).[3,4,15,17,18] A stabilization of the disease was achieved in four cases [3,4,16,19], whereas a further progression was also observed in four cases (4/19, 21.1%)[4] and one patient died from complications of the neurological progression during the follow up (1/19, 5.3%)[4].

Due to the limited available data, it is not possible to predict the optimal choice of therapy. However, in the so far reported anti-neurochondrin associated neurological disorders, three of four (but all three of three adult) patients (75%) who were treated by B cell depletion predominantly showed progression of the disease[4] (one paediatric patient under B cell depletion showed improvement[18]), while patients receiving drugs not selectively targeting B cells seemed

to show more frequently an improvement and a stabilization of the disease, respectively (including our case) (cyclophosphamide four of five (80%), azathioprine three of four (75%), mycophenolate two of two (100%)).[3,4,15,16,19] Steroids and IVIG were mostly used in combination with other immunotherapies especially for treatment initiation, so their actual effect in isolation is difficult to estimate (improvement and stabilization, respectively in nine of fourteen cases (including our case) (64.3%) who received steroids and seven of eleven patients (63.6%) with IVIG).

Discussion

The diagnostic criteria of PACA are fulfilled in our case. The patient presented a subacute onset of his symptoms and a rapidly progressive cerebellar ataxia. MRI showed a progressive, marked cerebellar atrophy with a marked quantified cerebellar volume loss of 29% within 24 months (see figure 3), whereas MR spectroscopy was not performed. CSF analysis revealed a lymphocytic pleocytosis with elevated protein, repeatedly CSF-specific oligoclonal bands and an elevated IgG index. Other autoimmune diseases were not found in our patient, neither are they present in the family history. Anti-neurochondrin antibodies with high titres were detected in both serum and CSF. Alternative diagnoses were largely excluded.

As the anti-neurochondrin antibodies are not thought to be directly pathogenic because of the intracellularly located target antigen, a mostly T-cell mediated autoimmune process is the most likely aetiology.[3,20] Therefore, we chose with cyclophosphamide an immunotherapy that is mainly directed against immune cell proliferation. Under this therapeutic regimen, a clinical

stabilization of the beforehand rapidly progressive disease could be achieved. Morphometrically, progressive cerebellar atrophy was detected within two years.

Cerebellar ataxias can affect young individuals in the middle of their productive age, as in our here presented case, and have a major negative impact on quality of life as well as far-reaching important socio-economic consequences. Well-characterized IMCAs are quite frequent and effective therapies in some entities are known (e.g. gluten-free diet for gluten-sensitive ataxia in the context of coeliac disease), but still a large number of progressive cerebellar ataxias suspected to be immune-mediated remains unexplained. The diagnosis of these idiopathic sporadic ataxias couldn't be given so far due to a missing diagnostic biomarker. To establish the diagnosis of PACA brings with it corresponding therapeutic options in the form of immunosuppressive therapies. It is therefore of paramount importance to try to understand the pathomechanism in a given case to provide the best possible treatment. The diagnostic criteria for PACA must be further disseminated and established in order to allow rapid diagnosis and start of an appropriate immunotherapy as soon as possible after diagnosis, because the mantra "time is cerebellum" also applies in the case of PACA.[21] Once the cerebellar reserves (namely reduced synaptic plasticity and a loss of "functional units" by cell death of Purkinje cells) have been consumed and the cerebellar atrophy is advanced, the motor deficits are usually irreversible.[21]

So far, only eighteen cases (together with the here presented case nineteen cases) with autoimmunity associated with anti-neurochondrin antibodies have been described, most often

with clinically evident cerebellar or brainstem syndromes.[3,4,15–19] Anti-neurochondrin antibodies belong to those antibodies supporting the diagnosis of PACA[2]. Only one study has investigated the response to therapy with mycophenolate in a small cohort of patients with PACA, however without defining the specific autoantibodies associated with the autoimmune disease.[22] The most effective immunotherapy in PACA has not been further investigated. Does one certain immunotherapy, like mycophenolate used in the latter study, have a positive therapeutic effect in every form of PACA? Considering that other antibodies already described in PACA, ARHGAP26 and Homer-3 are intracellular antigens[23–25], like Neurochondrin, a T-cell-mediated pathogenesis is assumed in these cases as well. Sj/ITPR1 is another antibody described in PACA, which is primarily an intracellular antigen, but under certain circumstances can also be found on the cell surface.[23,24] The pathogenic relevance of anti-Nb/AP3B2 (neuronal (B2) and adaptor protein 3, subunit B2, respectively) has not yet been investigated in detail; in 1991, the target antigen was described as being localised in the cytoplasm or the cell membrane.[23,26]

Conclusion

Here, we summarize all published cases of anti-neurochondrin antibody associated neurologic disease with their clinical and paraclinical findings and therapeutic approaches. To date, however, there are no specific guidelines on the optimal treatment. Multicentre efforts to

improve knowledge about PACA in general and anti-neurochondrin associated PACA in special are urgently needed.

Ethical Approval and consent to participate and for publication

We obtained written informed consent by the here presented case prior to publication.

Availability of data and materials

Data and material are available upon reasonable request to the corresponding author.

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Competing interests and Authors Disclosures

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Author contributions

A. Schwarzwald was responsible for conceptualization, methodology, literature review, investigation and drafted the original and revised the manuscript.

A. Salmen was responsible for revision and editing of the manuscript.

A. X. León Betancourt was responsible for revision and editing of the manuscript.

L. F. Diem was responsible for revision and editing of the manuscript.

H. Hammer was responsible for revision and editing of the manuscript.

P. Radojewski performed the radiological assessment of the MRI.

M. Rebsamen performed the morphometric analysis of MRI.

N. Kamber was responsible for revision and editing of the manuscript.

A. Chan was responsible for revision and editing of the manuscript.

R. Hoepner was responsible for revision and editing of the manuscript.

Friedli C was responsible for conceptualization, methodology, investigation and revision and editing of the manuscript.

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[Figures]

[Tables]

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Table 1.1: Blood examinations of the here presented patient

Type of examination	**Results**	**Reference**
Screening for vasculitis		
ANA	**1:80**	<1:80
PR3-ANCA	<0.5 IU/ml	<5 IU/ml
MPO-ANCA	<1.0 IU/ml	<6.0 IU/ml
Screening for connective tissue disease		

SS-A (Ro)	<0.4 EliA U/ml	<7.0 EliA U/ml
SS-B (La)	<0.3 EliA U/ml	<7.0 EliA U/ml
Sm	negative	negative
RNP	negative	negative
PCNA	negative	negative
DFS-70	negative	negative
Screening for myositis		
Mi-2	negative	negative
Screening for systemic sclerosis		
Scl-70	negative	negative
Centromer A/B	negative	negative
PM-Scl 100	negative	negative
Ku	negative	negative
Screening for antiphospholipid syndrome		
Anti-cardiolipin antibody (IgG)	4.5 CU	<20.0 CU
Anti-cardiolipin antibody (IgM)	3.5 CU	<20.0 CU
Anti-beta2 glycoprotein (IgG)	<6.4 CU	<20.0 CU
Anti-beta2 glycoprotein (IgM)	4.1 CU	<20.0 CU
Screening for thyroid diseases		
TSH	2.97 mU/L	0.27-4.20 mU/L
FT4	18.5 pmol/L	12.0-22.0 pmol/L
FT3	6.62 pmol/L	3.10-6.80 pmol/L
TRAb	<0.3 IU/L	<1.8 IU/L
Anti TG	<33 U/mL	<33 U/mL
Anti TPO	<50 U/mL	<60 U/mL
Screening for systemic lupus		
Lupus anticoagulans	negative	negative
Screening for sarcoidosis		
ACE	26 U/L	20-64 U/L
s-IL2 receptor	249.2pg/mL	<477.0pg/mL
Tumour screening		
AFP	3.4 kU/L	<5.8 kU/L
PSA, total	1.0 µg/L	<1.4 µg/L
Screening for metabolic causes		
Lipids (total cholesterol, HDL and LDL cholesterol, total cholesterol/HDL ratio, triglycerides)	normal	
Holotranscobolamin	87.4 pmol/L	>50 pmol/L
Folic acid	14.6 nmol/L	>8.8 nmol/L
HbA1c	4.9%	4.8-5.9%
Long chain fatty acids	normal	
Caeruloplasmin	0.21 g/L	0.15-0.30 g/L
Copper	16 µmol/L	11.0-22.0 µmol/L
Vitamin B1	12 nmol/L	10-53 nmol/L
Vitamin B6	17 nmol/L	10-111 nmol/L
Screening for bowel diseases		
Deaminated gliadin peptide (IgA)	<5.2 CU	<20 CU
Deaminated gliadin peptide (IgG)	<2.8 CU	<20 CU
Endomysium (IgG)	<1.5	<.1.5
Tissue transglutaminase	2.2 CU	<20.0 CU

Abbreviations: ACE: Angiotensin converting enzyme; AFP: Alpha-fetoprotein; ANA: anti-nuclear antibodies; CU: Control unit; DFS-70: "dense, fine speckled"-70; EliA: Enzyme-linked immunosorbent Assay; FT3: Free triiodothyronine; FT4: Free tetraiodothyronine; HDL: High density lipoprotein; IgA, IgG, IgM: Immunoglobulin A, G, M; IU: International unit; LDL: Low density lipoprotein; MPO: Myeloperoxidase; PCNA: Proliferating-cell-nuclear antigen; PM: Polymyositis; PR3-ANCA: Proteinase-3 anti-neutrophil cytoplasmic antibody; PSA: Prostate-specific antigen; RNP: Ribonucleoprotein; Scl:"Scleroderma"; s-IL2: Soluble interleukin; Sm: Smith; SS-A/SS-B: Sjögren's syndrome A/B; TG: Thyreoglobulin; TPO:

Thyreoperoxidase; TRAb: Thyreotropin receptor antibodies; TSH: Thyroid-stimulating hormone. Abnormal values are printed bold.

Table 1.2: Blood and CSF examinations of the here presented patient

Neuro-immunological testing (serologically)	**Results**	**Reference**	***Neuro-immunological testing (CSF)***	**Results**	**Reference**
Brain neuronal nuclear antibodies	<1:80	<1:80	Brain neuronal nuclear antibodies	<1:10	<1:10
Onconeuronal antibodies	negative	negative	Onconeuronal antibodies	negative	negative
Anti Purkinje cells	<1:80	<1:80	Anti Purkinje cells	<1:10	<1:10
Anti Yo	negative	negative	Anti Yo	negative	negative
Anti Amphiphysin	negative	negative	Anti Amphiphysin	negative	negative
CRMP-5 (CV2)	negative	negative	CRMP-5 (CV2)	negative	negative
Ma-1	negative	negative	Ma-1	negative	negative
Ma-2	negative	negative	Ma-2	negative	negative
SOX-1	negative	negative	SOX-1	negative	negative
Tr (DNER)	negative	negative	Tr (DNER)	negative	negative
Zic4	negative	negative	Zic4	negative	negative
NMDA (glutamate receptor)	<1:10	<1:10	Anti Hu	negative	negative
GAD	<1:80	<1:80	GAD	negative	negative
AMPA 1/2	<1:10	<1:10	Anti Ri	negative	negative
Anti neurochondrin	**1:10'000**	<1:100	**Anti neurochondrin**	**1:320**	negative
Lgi-1	<1:10	<1:10	IL-6	negative	negative
CASPR-2	<1:10	<1:10	IL-10	negative	negative
GABA receptor B1/2	<1:10	<1:10			
DPPX	<1:10	<1:10			
Anti glial nuclear antibodies	negative	<1:10			
Anti Homer 3	negative	<1:100			
Anti ITPR1	negative	<1:100			
Anti mGluR1	negative	<1:10			
Anti RhoGTPase-activating protein 26	negative	<1:10			
Anti IgLON5	negative	<1:10			
Anti mGluR5	negative	<1:10			

Abbreviations: AMPA 1/2: Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid;Anti Hu: Anti neuronal nuclear antibody 1 (ANNA1); Anti-IgLON5: Anti-immunoglobulin-like cell adhesion molecule-5; Anti mGluR1/GluR5: Anti-metabotropic glutamate receptor-1/5; Anti Ri: Anti-neuronal nuclear antibody 2 (ANNA 2); Anti Yo: Purkinje cell antibody type 1; CASPR-2: Contactin-associated protein-2; CRMP-5: Collapsin response mediator protein-5; CSF: Cerebrospinal fluid; DPPX: Dipeptidyl-peptidase-like protein-6; GAD: Glutamate decarboxylase; GABA: γ-aminobutyric acid; IL-6/IL-10: Interleukine-6/10; ITPR1: Inositol 1,4,5-triphosphate receptor type 1; Lg-1: Leucine-rich glioma inactivated 1; Ma-1/Ma-2: Paraneoplastic neuronal antigen; NMDA: N-methyl-D-aspartate; SOX-1: Anti-glial nuclear antibody (AGNA) and sex-determining region Y-box; Tr (DNER): Delta/notch-like epidermal growth factor-related receptor; Zic4: Zinc finger protein Abnormal values are printed **bold**.

Table 1.3: Blood and CSF examinations of the here presented patient

Screening for infectious causes (serologically)		***Screening for infectious causes (PCR in CSF)***	
Hepatitis B	negative	Neisseria meningitidis	negative
Hepatitis C	negative	Streptococcus pneumoniae	negative
Hepatitis E	negative	Listeria monocytogenes	negative

HIV type 1 & 2	negative	Haemophilus influenzae	negative
Varicella zoster virus	positive	Streptococcus group B	negative
Epstein Barr virus (EBV)	positive	Escherichia coli	negative
Treponema pallidum	negative	Cryptococcus neoformans/gatti	negative
Borrelia burgdorferi IgG	negative	Herpes simplex type 1	negative
Borrelia burgdorferi IgM	positive	Herpes simplex type 2	negative
Mycobacterium tuberculosis	negative	Varicella zoster virus	negative
Stool		Enterovirus	negative
Tropheryma whipplei PCR	negative	Cytomegalovirus	negative
Screening for infectious causes (ELISA)		Human herpesvirus type 6	negative
CXCL-13	negative	Parechovirus	negative
		Borrelia burgdorferi IgG index	negative
		Borrelia burgdorferi IgM index	negative
		JCV DNA (PCR)	negative

Abbreviations: CSF: Cerebrospinal fluid; CXCL-13: C-X-C chemokine ligand 13; DNA: deoxyribonucleic acid; ELISA: Enzyme-like immunosorbent assay; HIV: Human immunodeficiency virus; JCV: John Cunningham polyoma virus; PCR: Polymerase chain reaction

Table 2.1) Clinical signs and symptoms in patients with detected anti neurochondrin antibodies

	Sex (f/m)	Age (y)	Country	Year	Clinical signs and symptoms
1[3]	m	51	Germany	2016	Cerebellar and brainstem syndrome
2[3]	m	23	Germany	2016	Cerebellar and brainstem syndrome and episode of blurred vision, reduced colour vision and painful movement of the right eye
3[3]	f	19	Germany	2016	Cerebellar and brainstem syndrome
4[17]	m	2,6	China	2019	Cerebellar ataxia with recurrent ataxia: 1st episode with gait instability, dysphagia and dysarthria after fever, 2nd episode after fever with static and truncal ataxia, dysarthria, clumsiness of the right arm, intention tremor und dysmetria in both hands, weak muscle tone and missing deep tendon reflexes
5[17]	m	5,2	China	2019	Cerebellar ataxia with progressive dysarthria, gait instability, action tremor and dysmetria
6[17]	m	67	China	2019	Cerebellar ataxia with intermittent dizziness and gait ataxia (1st episode after respiratory infection, 2nd episode without preceding event, 3rd episode with progressive gait ataxia, dysarthria, truncal ataxia und horizontal nystagmus)
7[4]	m	40	USA	2019	Brainstem encephalitis and thoracic myelitis with body pruritus for 2 weeks, then facial palsy and hypaesthesia right, bilateral gaze palsy, dysarthria, vocal cord palsy, T8 sensory level; constipation, hyperreflexia
8[4]	f	33	USA	2019	Cerebellar ataxia with nystagmus, scanning dysarthria, paranoid psychosis 1 year previous
9[4]	f	42	USA	2019	Brainstem encephalitis and cerebellar ataxia with progressive ataxia, abdominal pain and vomiting. Extra ocular muscle paralysis, tinnitus, hearing loss, dysphagia and dysarthria.
10[4]	m	35	USA	2019	Cerebellar ataxia with oscillopsia, periodic alternating nystagmus, skew deviation; progressive imbalance; severe limb dysmetria predominantly of the lower limbs; dysarthria
11[4]	f	53	USA	2019	Cerebellar ataxia, predominantly left; dysarthria, vertigo, saccadic pursuits, dysphagia
12[4]	m	44	USA	2019	Small fibre neuropathy with paraesthesia, constipation, restless legs likely symptoms
13[4]	f	69	USA	2019	Cerebellar ataxia with nausea, vomiting, nystagmus, incoordination
14[14]	m	6	Germany	2019	Encephalopathy with reduced consciousness, disturbed behaviour, memory impairment (episodic memory)
15[14,16]	f	7	Germany	2019	Movement disorder with paroxysmal choreatiform movement disorder of the right and encephalopathy with irritability, aggressiveness,

					impairment of attention and memory, behavioural disorder, loss of impulse control/compulsive disorder;
16[14]	m	14	Germany	2019	Encephalopathy with non-epileptic stupor, severe (intermittent violent) aggressiveness, loss of orientation, progressive daytime sleepiness
17[15]	m	7	Belgium	2021	Cerebellar ataxia, cervical dystonia, choreatiform movement disorder of the upper limbs, action tremor, opsoclonus, dysarthria, acathisia, emotional instability
18[18]	f	34	USA	2022	Cerebellar ataxia, ascending paraesthesia, progressive spastic tetraparesis, need of wheelchair after 9 months
19	*m*	*33*	*CH*	*2021*	*Cerebellar ataxia with gait, stance and limb ataxia, oculomotor disorders, scanning speech*

Abbreviations: CH: Switzerland; f: Female; m: Male; n/r: Not reported; USA: United States of America; y: Years
Country and year of data acquisition and publication, respectively
Italic letters: Our here presented patient

Table 2.2) Diagnostic findings in patients with detected anti neurochondrin antibodies

	Sex (f/m)	Age (y)	CSF findings	MRI findings
1[3]	m	51	Pleocytosis, oligoclonal bands	Cerebellar atrophy
2[3]	m	23	Pleocytosis, oligoclonal bands	Cerebellar atrophy
3[3]	f	19	Pleocytosis, oligoclonal bands	Cerebellar atrophy
4[17]	m	2,6	n/r	Normal cranial and spinal MRI
5[17]	m	5,2	No pleocytosis, no oligoclonal bands	Cerebellar atrophy
6[17]	m	67	Lymphocytic pleocytosis, oligoclonal bands	No cerebellar atrophy
7[4]	m	40	Lymphocytic pleocytosis, protein elevation, oligoclonal bands, elevated IgG index	Early MRI: Cerebellar leptomeningeal enhancement; abnormal T2 sign in the dorsal pons and in the upper medulla. Spinal MRI: Longitudinally intramedullary sign without contrast medium enhancement. Late MRI: 5 years after symptom onset: Vermis atrophy
8[4]	f	33	Protein elevation, oligoclonal bands	Early MRI: Intracranial and spinal normal Late MRI: Cerebellar atrophy
9[4]	f	42	Lymphocytic pleocytosis, protein elevation, oligoclonal bands, elevated IgG index	Early MRI: Abnormal T2 alteration in mesencephalon, pons and middle cerebellar peduncle
10[4]	m	35	Protein elevation	Early MRI: Normal Late MRI: Cerebellar atrophy
11[4]	f	53	Lymphocytic pleocytosis, protein elevation, elevated IgG index	Early MRI: Abnormal T2 alteration in the left frontal and cerebellar cortex Late MRI: Cerebellar/pontine atrophy; hippocampal formation with abnormal T2 alteration
12[4]	m	44	Not tested	MRI: Intracranial and spinal normal
13[4]	f	69	n/r	Early MRI: Bilateral striatal und hippocampal T2 abnormalities
14[14]	m	6	Normal	Normal
15[14,16]	f	7	Normal	Normal
16[14]	m	14	Pleocytosis	Normal
17[15]	m	7	Pleocytosis, oligoclonal bands	n/r
18[18]	f	34	Lymphocytic pleocytosis, oligoclonal bands, elevated IgG index	Slight cerebellar atrophy, non-enhancing longitudinally extensive T2 lesion along the ventral spine of the grey matter, starting from pons to thoracic spine

19	*m*	*33*	*Lymphocytic pleocytosis, oligoclonal bands type 2, elevated IgG index*	*Initial MRI: Normal* *Follow-up MRI: Cerebellar atrophy*

Abbreviations: CSF: Cerebrospinal fluid; f: Female, IgG: Immunoglobulin G; m: Male; MRI: magnetic resonance imaging; n/r: Not reported; y: Years
Italic letters: Our here presented patient

Table 2.3) Therapies and outcomes in patients with detected anti neurochondrin antibodies

	Sex (f/m)	Age (y)	Immunotherapy	Time from disease onset to therapy initiation (mt)	Follow up (mt)	Outcome
1[3]	m	51	Cyclophosphamide	21	12	Slight improvement (SARA-Score from 27 to 25)
2[3]	m	23	Cyclophosphamide	54	12	Slight improvement (SARA-Score from 25 to 23)
3[3]	f	19	Azathioprine; IVIG	120	12	Stable disease (SARA-Score on high level (32))
4[17]	m	2,6	IVIG; methylprednisolone	8	18	Improvement
5[17]	m	5,2	IVIG; methylprednisolone; rituximab	Therapy initiation within days of the recurrent episodes	5	Improvement
6[17]	m	67	IVIG	NA	0.13	Improvement
7[4]	m	40	Steroids IV; IVIG; rituximab	Within 1 month	60	Progression/wheel-chair bound
8[4]	f	33	Steroids IV; IVIG; rituximab	12	18	Progression/wheel-chair bound
9[4]	f	42	IVIG; azathioprine; steroids IV	Within 1 month	27	Death
10[4]	m	35	IVIG; steroids IV; cyclophosphamide; rituximab	Within 1 month	10	Progression/wheel-chair bound
11[4]	f	53	Steroids IV, prolonged steroids PO; azathioprine	Within 1 month	48	Slight improvement/walking with canes
12[4]	m	44	No immunotherapy	-	2	Stable disease/normal walking
13[4]	f	69	Steroids IV, plasmapheresis	Within 1 month	2	Wheel-chair bound
14[14]	m	6	Steroids, IVIG, azathioprine	n/r	24	Improvement of mood and memory skills
15[14,16]	f	7	Steroids; IVIG, risperidone	n/r	36	Improvement of mood and movement disorder
16[14]	m	14	Steroids; IVIG, risperidone	n/r	24	Marginal improvement
17[15]	m	7	Steroids (Methylprednisolone 30mg/kg per weight for 3 days); after 3rd recurrence permanent steroids monthly with	n/r	n/r	No recurrence since permanent therapy; persistent slight gait ataxia, significant cognitive deficits

			methylprednisolone 500mg/m^2; after 8 months mycophenolate			
18[18]	f	34	Steroids for 5 days; plasmapheresis; Cyclophosphamide; mycophenolate	20	n/r	Stable disease with persistent deficits
19	*m*	*33*	*Steroids PO, Cyclophosphamide*	*20*	*2*	*Slight improvement (SARA score decreased from 23 to 21 within 2 months)*

Abbreviations: f: Female; IV: Intravenous; IVIG: Intravenous immunoglobulins; kg: Kilograms; m: Male; m^2: Square meter; mt: Months; n/r: Not reported; PO: Per oral; SARA: Scale for the Assessment and Rating of Ataxia; y: Years

Italic letters: Our here presented patient

Figure 1) Structured literature search presented in a flow chart

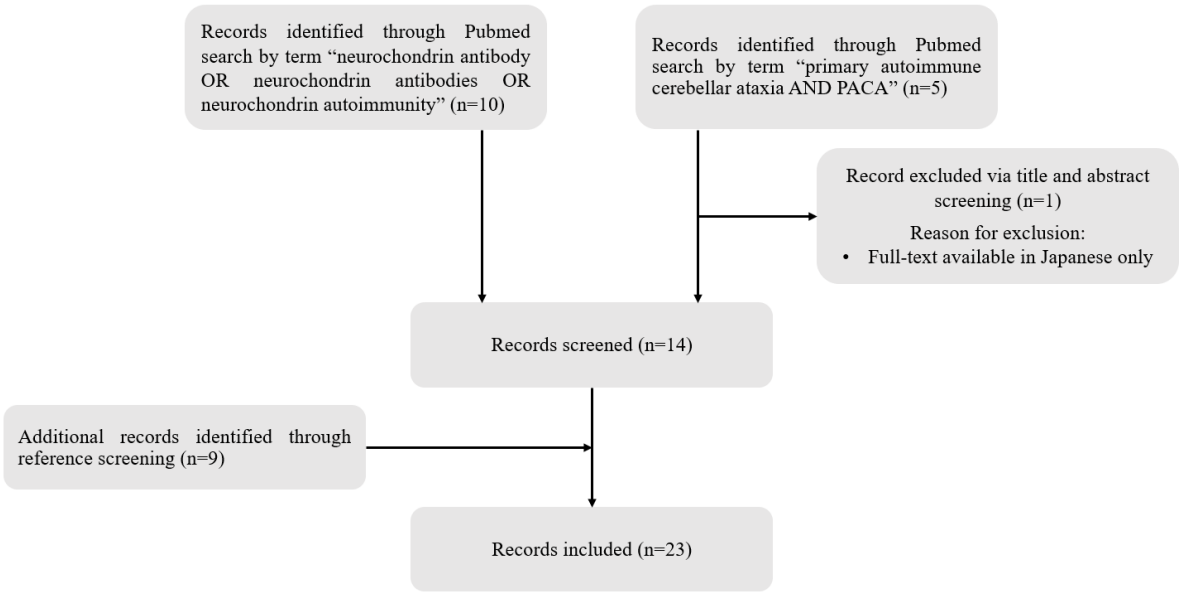


Figure 2) Initial MRI from June 2020, with normal appearing cerebellar structures; Image 2) Follow-up MRI from October 2021 with marked cerebellar atrophy

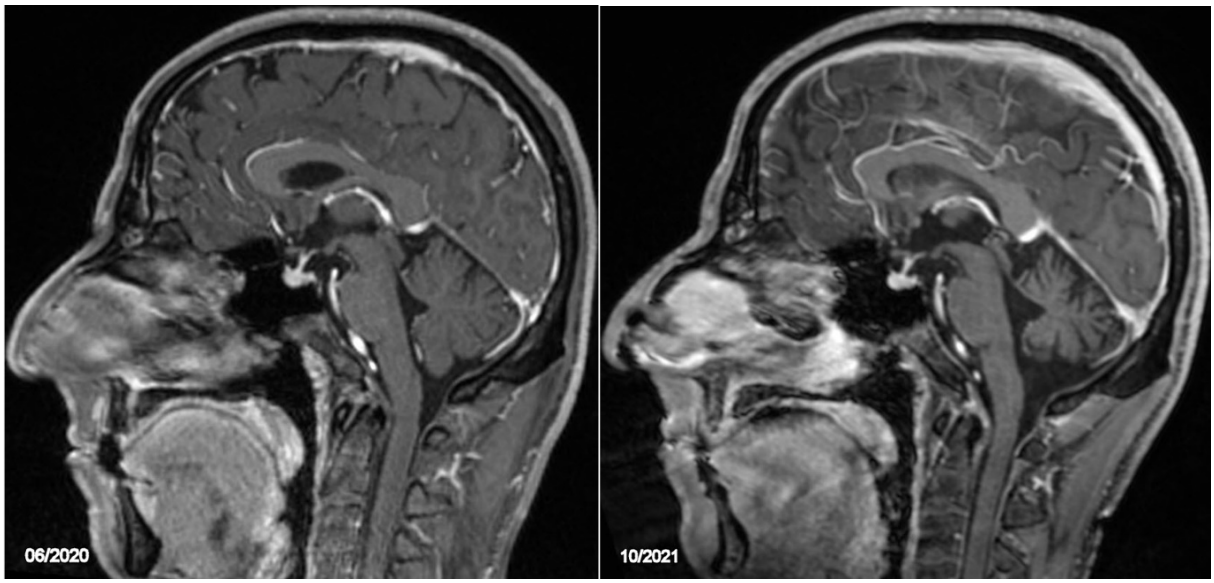
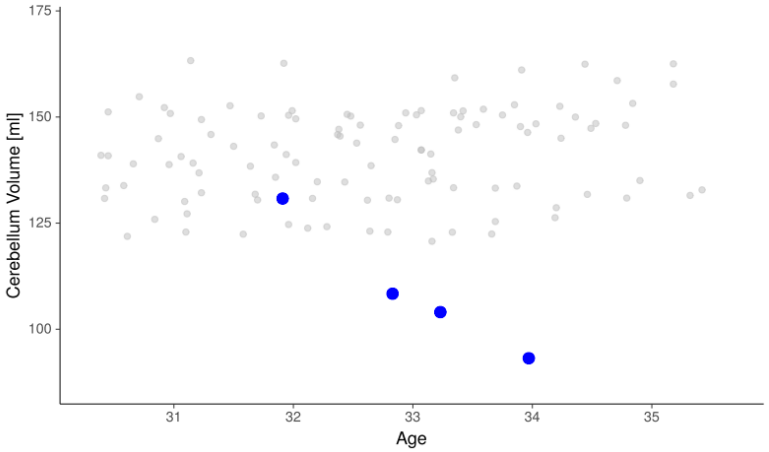
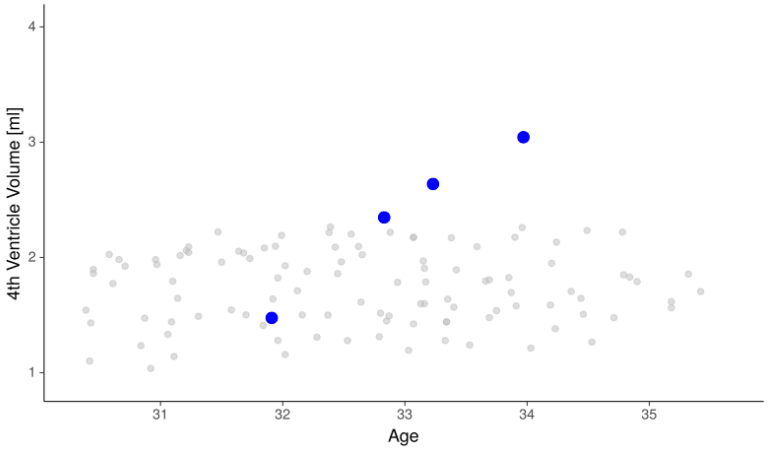


Figure 3: Cerebellar volume measures derived from the MR images (upper panels). After two years, the volume was significantly reduced (93 ml) compared to the baseline image (131 ml). Correspondingly, the volume of the fourth ventricle increases (lower panels). As a reference, corresponding measures from patients with MS are shown as grey dots in the background.

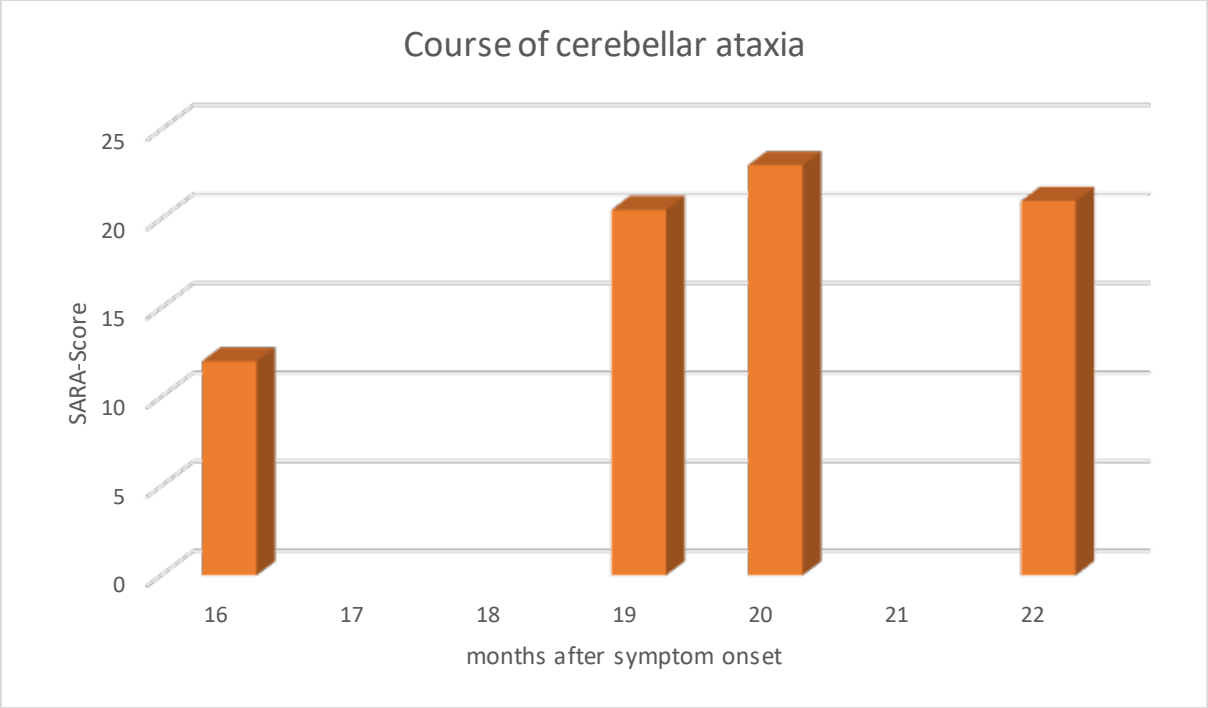


Date	Cerebellum Volume [ml]
06/2020	130.8
05/2021	108.4
10/2021	104.0
07/2022	93.2



Date	4th Ventricle Volume [ml]
06/2020	1.5
05/2021	2.3
10/2021	2.6
07/2022	3.0

Figure 4: Course of cerebellar ataxia measured by SARA score



Abbreviation: SARA: Scale for the Assessment and Rating of Ataxia.

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