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Research article

Subjective cognitive decline in conjunction with cerebrospinal fluid anti-ATP1A3 autoantibodies and a low amyloid β 1–42/1–40 ratio: Report and literature review

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ABSTRACT

Background: Animal studies reveal the role of the sodium/potassium transporting ATPase α-3 subunit (ATP1A3) in maintaining the resting membrane potential and thus in synaptic information processing and potentially cognitive disorders. However, autoantibodies against AT1A3 have not previously been reported in patients with subjective cognitive decline.

Case presentation: We report the case of a 57-year-old female who underwent neuropsychological testing, magnetic resonance imaging (MRI) and 18 F fluorodesoxyglucose positron emission tomography (FDG-PET) imaging, and cerebrospinal fluid (CSF) analysis. Neural autoantibodies were assessed in serum and CSF. We found a normal cognitive profile together with a self-reported cognitive decline, and such consistent with subjective cognitive decline (SCD). Analysis of the cerebrospinal fluid revealed anti-ATP1A3 autoantibodies. ATP1A3 autoantibodies were also detected in serum. Analysis of amyloid pathology markers in the CSF showed a slightly reduced amyloid β1–42/ amyloid β1–40 ratio. In view of the possible paraneoplastic autoantibodies, whole-body FDG-PET was performed, which did not reveal a malignancy-specific lesion. FDG-PET of the brain also showed no hypometabolism. We diagnosed SCD based on CSF-affirmed possible Alzheimer's pathologic change with ATP1A3 autoantibodies in CSF and serum.

Conclusions: To our knowledge, this is the first report of CSF and serum ATP1A3 autoantibodies associated with SCD although an incidental finding cannot be fully excluded. In addition, amyloid pathology was detected via CSF biomarkers, suggesting that ATP1A3 autoantibodies are a potentially promising biomarker in SCD with an Alzheimer's pathologic change if confirmed in large-scale studies.

1. Background

Autoimmune cognitive impairment is an emerging disease entity [1,2] that is likely underdiagnosed but represents an important differential diagnostic challenge in memory clinics. We report here on a patient with autoantibodies against sodium/potassium transporting ATPase α-3 subunit (ATP1A3) associated with cognitive impairment. ATP1A3 encodes the Na+/ K+ ATPase-α3 isoenzyme, which is exclusively expressed in neurons within the brain [3]. This isoenzyme serves as a catalyst of the sodium-potassium pump by offering different binding sites for Na+ , K+ , ATP and cardiac glycosides as pump inhibitors. Sodium (Na+)/potassium (K+) ATPase's electrical activity is necessary for homeostasis and to maintain the Na+K+ gradient across the plasma membrane to enable physiological excitability and signal transduction. The ATP1A3 isoform is important for restoring an electrochemical gradient during neuronal activity [4,5] due to ATP1A3's expression exclusively in neurons. The ATP1A3 is increased after memory training in animal models [6] and reduced in hippocampal sclerosis in epilepsy

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patients [7]. Mutations of the ATP1A3 gene can be found in rapid-onset dystonia, parkinsonism, and alternating hemiplegia in childhood [8,9]. However, autoantibodies against the ATP1A3 target have not been reported so far in memory clinic patients. Neural autoantibodies are present in dementia or cognitive impairment [10,11], as well as in neurodegenerative dementias such as Alzheimer's disease [12] as a bystander or initial cascade of neuroinflammation, thereby contributing to either the progression of dementia or neuroprotection. Autoantibodies against brain proteins have been shown to be particularly high in patients with Alzheimer's disease [13], although their role is still unclear. A recent study showed that high NMDAR autoantibodies may even have a neuroprotective function [14]. It is therefore worthwhile to investigate the spectrum of neuronal autoantibodies in more detail to better understand their pathophysiology in autoimmune-mediated cognitive disorders. Although we detected only one association, we are tempted to propose that AT1A3 autoantibodies may contribute to cognitive impairment, even if it is subjective in nature, suggesting autoimmune-mediated cognitive impairment. Subjective cognitive decline (SCD) means a subjective perception of cognitive dysfunction with no objective neuropsychological verification of cognitive decline. This SCD definition dates from 2014 [15] and was classified as SCD-I (Subjective Cognitive Decline-Initiative) at the time. It is important that there be persistent subjectively perceived decline in mental performance not associated with an acute event, but one that lasts for a longer time period. Such subjective mental deterioration cannot be revealed through objective standardized cognitive tests, however [16]. We address ATP1A3's function in synaptic information processing to speculate that blocking the ATP1A3 protein might trigger subsequent memory impairment. Animal experiments involving knock-out mice support the hypothesis that a mutation involving a change in ATP1A3 gene function can trigger cognitive deficits [17]. Complete blockage of ATP1A3 by an autoantibody followed by dysfunctional ATP1A3 could be functionally like ATP1A3 alteration caused by a mutation and might also lead to cognitive deficits. In our patient with SCD, we decided as a rationale to determine anti-ATP1A3 autoantibodies because of their known role in cognitive deficits and memory formation [6].

2. Case presentation

A 57-year-old female patient presented at our clinic complaining of a slowly progressive cognitive decline for 1–2 years prior to her first presentation at our clinic, which manifested itself primarily in forgetfulness and difficulty finding words, as well as a decline in arithmetic skills. She was independent in daily living activities but had experienced insecurity. She had begun to more frequently control her work steps and to seek external reassurance. In handicraft activities such as knitting, she began to notice that she had to concentrate harder and that it was harder to learn new knitting patterns. She also reported dizziness that had accompanied her cognitive complaints. She also undertook more control steps in her work to avoid making mistakes, and felt insecure overall. She had trouble falling asleep and sleeping through the night, possibly due in part to restless leg syndrome. She is married, has two daughters and a son. She graduated from high school and received a PhD in archaeology. One daughter suffers from Hashimoto's thyroiditis, but beyond that, her family history is free of other somatic or psychiatric diagnoses. Her medical history comprises restless legs syndrome with insomnia, a condition after herniated discs at the level of cervical disk 5/6 after surgery in 2021, bronchial asthma, elevated gastrin serotonin and chromogranin values with no organic correlate, Hashimoto thyroiditis and sleep apnea syndrome treated with a mask. Her restless legs syndrome had existed for three years before her first presentation. Pregabalin alleviated her restless legs syndrome (RLS) symptoms significantly, but difficulty falling asleep and sleeping through the night persisted. However, the sleep disorder's exact cause has not been clarified and could also be multifactorial. Regarding her affective symptoms, a slightly depressed mood with a tendency to brood, and fear of the future were evident. However, the criteria for a depressive episode were not met. She has also reported intrusions and flashbacks related to traumatic experiences in childhood possibly reflecting a posttraumatic stress disorder (PTSD). However, she has had PTSD for decades and had already undergone psychotherapy. The aim of psychotherapy was to stabilize affective symptoms. However, PTSD symptoms are not the reason for her current presentation and have not constituted the predominating features at presentation and her follow-up exam. To clarify the chronology: her PTSD initially developed over decades ago, followed by RLS three years ago and cognitive dysfunction 1–2 years ago. Neurological testing revealed no landmark abnormalities other than the reported staggering vertigo with no evidence of nystagmus. Magnetic resonance imaging of the brain performed before her first presentation in our memory clinic was normal, and no vascular lesions were diagnosed. Neuropsychological examination via the CERAD-plus test battery (Consortium to Establish a Registry for Alzheimer's Disease) mainly revealed results within normal limits except for slightly reduced phonematic word fluency according to age- and education-based normative values (Fig. 1). The CERAD-plus test battery was presented as a z-transformation. A z-value indicates by how many standard deviations a measured value deviates from the mean value of the population under investigation. A value of −1 means that the scale value is one standard deviation below the mean value for a healthy person with the same age, gender, and education level. Also, extensive neuropsychological testing revealed a normal performance in additional tests of orientation, processing speed, divergent thinking, action planning, visuospatial perception, visuoconstructive functions, working memory, figural and verbal memory. Her cognitive test results did not fulfill the criteria of mild cognitive impairment (MCI) [18], but her subjective complaints of cognitive decline with a normal cognitive profile are compatible with SCD. A follow up investigation one year later showed a similar profile concurring with SCD (Table 1). A neurological and psychiatric examination was also carried out that revealed no pathologies. Blood tests were carried out that ruled out reversible causes of cognitive disorders. We conducted a neural spinal tap that revealed anti-ATP1A3 autoantibodies in the CSF at an intensity of 1:1 and in the serum at 1:100 (Table 2). Cell-based assays served to determine anti-ATP1A3 autoantibodies in serum and CSF. We tested for ATP1A3 antibodies in addition to a standard panel of autoantibodies in neuropsychiatric disorders due to their potential role in memory formation and cognitive functions. The specific antibody index for ATP1A3 was 4.41, indicating specific synthesis of ATP1A3 autoantibodies in the CNS. The cell count and protein findings in the CSF were unremarkable. An external analysis of core CSF biomarkers of Alzheimer's disease (AD) in the CSF laboratory in the Department of Psychiatry and Psychotherapy from the University of Erlangen showed a slightly reduced ratio amyloid-β1–42/ amyloid-β 1–40 (Aβ1–42/1–40) (0.058, reference value: > 0.06), but not pathologically altered Alzheimer's disease (AD)-dependent tau proteins such as ptau181, or hybrid ratios such as Aβ1–42/t-tau (Table 2). A ratio below 0.06 was evaluated as a pathological ratio Aß1–42/1–40. This was based on an internal laboratory limit value [19]. The neuronal cell damage markers (p-tau181, Aß1–42/1–40) were assessed with commercially available immunoreaction cartridges for plasma on the fully automated Lumipulse G600II system. In view of possible paraneoplastic autoantibodies, she underwent whole-body FDG-PET (18F fluorodesoxyglucose positron emission tomography), which revealed no malignancy-specific lesion. An FDG PET was performed in combination with a low-dose CT with reconstruction and quantitative evaluation. A standard visual test was performed. Her brain FDG-PET also revealed no hypometabolism. We therefore diagnosed an SCD attributable to a CSF-based Alzheimer's pathologic change involving ATP1A3 autoantibodies in the CSF and serum. Although there is evidence of amyloid pathology (reduced Aß1–42/1–40 ratio) according to the ATN criteria [20], there is no evidence of tau pathology in the sense of an early tau marker such as p-tau181 according to the revised Jack et al. criteria [21]. Thus, an Alzheimer's continuum is currently present, but it lacks

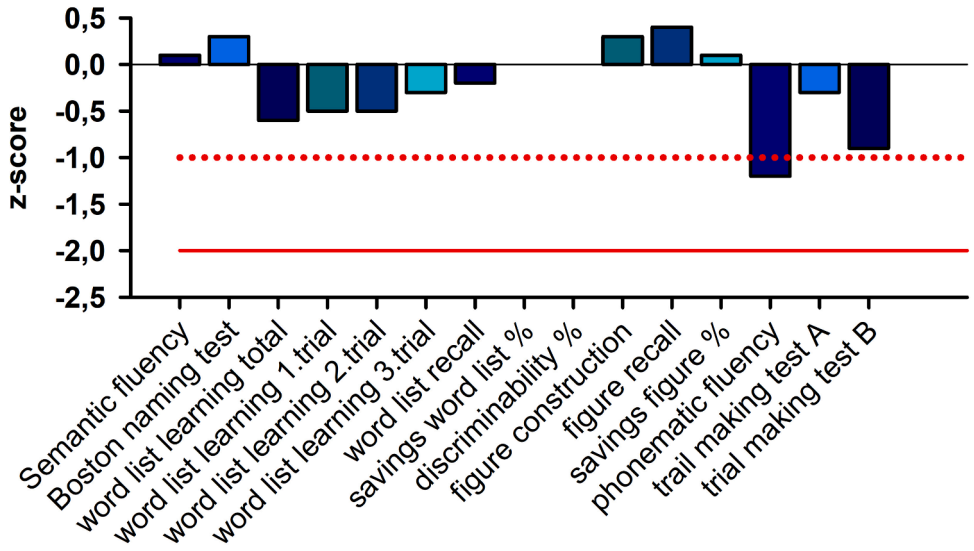

Fig. 1. Neuropsychological profile.

Table 1
Neuropsychological testing.

Testing parameter	First investigation	Follow up after 1 year
MMST, sum score (pathological level <28)	29/30	30/30
BDI, sum score (pathological level >11)	25/63	23/63
CERAD: Boston naming test, percentage rank	62	62
CERAD: semantic word fluency, percentage rank	54	69
CERAD: phonematic word fluency, percentage rank	12*	50
WAIS-IV Number-symbol test, percentage rank	75	75
TMT part A, percentage rank	38	02*
TMT part B, percentage rank	18	31
Division B/A, percentage rank	27	96
RWT, formal lexical categorial change, percentage rank	30	46
RWT, semantic categorial changes, percentage rank	19	84
Visuoconstruction Clock test, percentage rank	02	01
CERAD, constructive praxis, figure copying, percentage rank	62	62
WAIS-IV, mosaic test, percentage rank	84	84
RCFT, figure copying, percentage rank	16	16
WAIS, number span forward, percentage rank	63	84
WAIS, number span backward, percentage rank	75	95
CERAD, word list learning, sum trial 1–3, percentage rank	27	76
CERAD, word list free recall, percentage rank	42	82
CERAD, savings word list (%), percentage rank	50	50
CERAD, word list recognition (%), percentage rank	50	50
WMS-IV logical memory I, percentage rank	50	91
WMS-IV logical memory II, percentage rank	50	91
CERAD, constructive praxis, free recall, percentage rank	66	69
CERAD, saving figures %, percentage rank	54	54

Abbreviations: BDI =Becks Depression Inventory, CERAD = Consortium to Establish A Registry for Alzheimer's Disease, MMST = Mini Mental status examination, RWT =, WAIS-IV = Wechsler Adult Intelligence Scale fourth edition, WMS-IV = Wechlser Memory Scale fourth edition, TMTA and B = Trial Making Test A and B. *refers to abnormal values.

Table 2
Clinical and demographic data of patient.

	Patient
CSF	
Cell count per µl	1
Lymphocytes %	68
Monocytes %	26
Granulocytes %	6
Lactat mmol/l	1.5
GEW mg/l	330
Albumin mg/l	229
Albumin quotient	5.6
IgG mg/l	19.5
IgG quotient	2.3
IgA mg/l	2.5
IgA quotient	1.2
IgM mg/l	0.2
IgM quotient	0.1
Measles AI	0.9
Rubella AI	1.2
VZV AI	0.9
HSV AI	1.0
t-tau (<450) pg/ml	313
Ptau181 (<50) pg/ml	37
Aβ1–42 (>570) pg/ml	664
Hybrid ratios	
Ratio Aβ1–42/1–40 (>0.06)	0.058
Aβ1–42/t-tau (>2.006)*	2.12
Aβ1–40	16105
ATP1A3	+1:1
Blood CSF barrier disturbance	Not present
Intrathecal IgG synthesis	Not present
Blood	
Albumin g/l	40.7
IgG g/l	8.6
IgA g/l	2.0
IgM g/l	1.7
ATP1A3	++1: 100

Abbreviations: Aβ1–40 = amyloid beta 1–40, Aβ1–42 = amyloid beta 1–42, ATP1A3 = sodium/potassium transporting ATPase α-3 subunit, CSF = cerebrospinal fluid, GEW = total protein count, HSV = Herpes simplex virus, IgA = immunoglobulin A, IgG = immunoglobulin G, IgM = immunoglobulin M, p-tau181 = phosphorylated tau protein 181, ratio Aβ1–42/1–40 = ratio amyloid beta 1–42/1–40, ratio Aβ1–42/t-tau = ratio amyloid β1–42/ total tau protein, t-tau = total tau protein, VZV = Varizella Zoster virus.

* cut-off value from [22]

the Tau pathology to suggest Alzheimer's disease. We therefore consider this to be biomarker evidence of an Alzheimer's pathologic change in our patient with SCD.

3. Discussion

To our knowledge, our case represents the first report of a patient with ATP1A3 autoantibodies and SCD due to an Alzheimer's pathological change. ATP1A3 antibodies are novel and may be associated with cognitive dysfunction. This assumption is based on further studies: there is also mouse model evidence that its mutation of an ATP1A3 isoform led to cognitive deficits [17]. Another investigation of mice carrying a heterozygous mutation of the ATP1A3 gene causing alternating hemiplegia reported that many of the animals also exhibited cognitive impairment [23] supporting ATP1A3's role in cognitive dysfunction.

3.1. Potential interactions of amyloid-β, ATP1A3 antibodies and neuroinflammation

We do not know the exact mechanism of interaction between amyloid-ß and ATP1A3, however, we do know that amyloid-β positivity in extracellular vesicles more frequently accompanies the transmembrane protein ATP1A3 in AD patients than in MCI patients and controls [24]. This implies that ATP1A3 antibodies may affect vesicle exocytosis, thus influencing the interaction of amyloid-β with synaptic scaffold proteins and vesicle dynamics. In this way, ATP1A3 autoantibodies may have an impact on presynaptic function and thus synaptic plasticity, thus explaining both the onset of cognitive impairment and altered amyloid-β driven effects on synaptic transmission. However, such a molecular mechanism remains speculative. Especially the Aβ-driven synaptic changes occur in the early phase of AD [25] as in our patient, meaning that ATP1A3 autoantibodies could have an influence on the vesicle dynamics by releasing amyloid-β and the resulting synaptic dysfunction. Such an altered release of amyloid-β could also trigger a consecutive change in the concentration of amyloid-β fractions in the CSF and thus AD's typical pathologies. The synaptic vesicles in AD are the primary site for both the production and toxicity of amyloid-β [26]. The ATP1A3 autoantibodies could therefore lead to an initial inflammation with ATP1A3 autoantibodies as a driving force to a change in AD-typical proteins such as amyloid-β and cause synaptic deficits via altered vesicle exocytosis. Such an initial inflammation involving the production of ATP1A3 antibodies would be quite compatible with the hypothesis of a preclinical, early occurring neuroinflammation. However, no data are available on this. Overall, however, these findings are speculative. Our detection of ATP1A3 antibodies in the CSF is noteworthy as it indicates inflammation in the CNS but is by no means AD-specific for. The link to depression symptoms cannot be ruled out, but is less likely. There are only reports that a mutation on the ATP1A3 gene can lead to mood symptoms in gene carriers with motor symptoms [27]. An association with PTSD has not yet been described. Amyloid beta deposition is known to be a risk factor for objective cognitive impairment in patients suffering from SCD [28]. Another study proved that regional amyloid staging is linked to an increased risk of conversion to MCI and later dementia [29]. We therefore assume that our patient with SCD and amyloid pathology carries an increased risk of conversion to MCI. Note that additional evidence from CSF analysis would have supported our hypothesis of CNS inflammation, e.g. intrathecal IgG synthesis or blood-brain barrier disruption. However, our patient exhibited none of these abnormalities, potentially suggesting that the blood-brain barrier had somehow been disrupted and that a significant proportion of autoantibodies may have then entered the brain, as animal models and other NMDAR autoantibody studies have already demonstrated [30–32]. Also, we cannot exclude initial pleocytosis or intrathecal IgG synthesis. We considered other factors to be less important in relation to SCD, i.e. PTSD and sleep apnea after detecting amyloid-β positivity in CSF.

3.2. ATP1A3 antibodies and memory dysfunction

We investigated this autoantibody for the first time because of its potential role in memory formation and because our research group had not investigated it before [2]. This antibody had already been detected in a woman with cerebellum and brainstem syndrome [33] being in agreement with a slight dizziness in our patient. Recently published cohort studies of patients with an ATP1A3 mutation suggest that cognitive dysfunction is always part of the phenotype [34–36]. The observation that this target antigen's mutation frequently causes cognitive dysfunction, which supports our hypothesis that autoantibody-induced disruption of the target antigen would potentially cause similar functional cognitive deficits. These are additional reasons why we investigated ATP1A3 autoantibodies in this patient. Interestingly, ATP1A3 antibodies were detected in both her serum and CSF in the time course of her first clinical manifestation with SCD. Therefore, it is interesting to consider whether an autoantibody-related process could trigger the clinical manifestation of the disease in our patient presenting an Alzheimer's pathologic change. ATP1A3 is involved in ion flow across the membrane and is thus a part of neuronal synaptic transmission. Autoantibodies against ATP1A3 mean that the transport of sodium ions out of the cell and potassium ions into the cell cannot take place. This in turn means that the nerve cells' resting membrane potential cannot be maintained. Such an alteration in resting membrane potential can explain anomalies in transmitting synaptic electrical excitation and thus cause impaired memory formation. Blockade could lead to a disruption of synaptic transmission resulting in subjective cognitive dysfunction – even at a subsyndromal level – as seen in our patient. Our patient's slightly decreased phonematic fluency may be attributable to impaired functional connectivity caused by synaptic disturbances in information processing because of ATP1A3 autoantibodies. Word production is essentially based in the left frontal area in conjunction with subcortical regions and some left frontal pathways [37]. Reduced phonemic fluency may also be associated with damage to the posterior segment of the middle and superior frontal gyrus, the left dorsal anterior cingulate gyrus, and caudate nucleus [37]. Because we detected no anomalies on either her MRI or FDG-PET, such structural changes in the frontal and cingulate areas might be considered only in functional-connectivity terms.

3.3. Alzheimer disease stage and ATP1A3 autoantibodies

It is completely unclear whether an Alzheimer's pathologic change within the AD continuum is exacerbated by the accumulation of amyloid beta peptides through this ATP1A3 antibody, or whether a preexisting Alzheimer's pathologic change is accompanied by an epiphenomenon unrelated to the disease process. Ultimately, however, we conducted no amyloid PET to further confirm the amyloid pathology, as it can be negative at the SCD stage and thus would offer no additional value. Furthermore, a recently published study demonstrated that CSF at the SCD stage exhibits 10 % more amyloid abnormality than amyloid PET [38]. There is ample evidence that inflammation plays a role in AD at various stages [39] but also at the beginning of its preclinical stages in the form of increased microglial activation [40]. Neuroinflammatory processes [39,41,42] and especially autoantibody-associated processes in AD [42,43] can lead to the initiation and amplification of neurodegenerative processes. There is recent evidence that 7 specific autoantibodies can predict CSF tau levels and cognitive decline in AD [43]. This study suggests that in the future serum autoantibodies may take on a whole new meaning by improving the prediction of AD by serum autoantibodies. The Aβ42/40 ratio is a good predictor of conversion to mild cognitive impairment in SCD patients, and of brain structure loss and amyloid deposition [44]. It is therefore likely that our patient might convert to MCI within years due to her amyloid-β positivity. The probability of progressive cognitive decline in a patient with SCD presenting amyloid-β pathology is high [45–47]. However, it remains unclear when

conversion to MCI and dementia can be precisely predicted. Furthermore, we cannot exclude that sleep apnea syndrome might have contributed to her cognitive impairment. However, that is quite unlikely as her sleep apnea is already being alleviated via a continuous positive airway pressure mask. In addition, note that as a differential diagnosis, Hashimoto's thyroiditis can also lead to encephalopathy. However, she has suffered no stroke-like episodes, and her biomarker findings are incompatible with this.

3.4. Subjective cognitive decline and neural autoantibodies

In this section, we discuss the evidence in the literature found so far that neuronal autoantibodies may be involved in triggering SCD. Antibodies against the NR2 subunit of the N-methyl-D-aspartate receptor (NR2a) serum levels were determined in 70 patients in a single cohort presenting varying degrees of cognitive impairment and MRI evidence of small vessel disease [48]. They also detected increased levels of NR2a and mild cognitive impairment in conjunction with SCD. The autoantibodies were probably caused by endothelial dysfunction in the context of small vessel disease [48]. However, the serum concentration of NR2a antibodies with SCD is particularly interesting. Another study demonstrated conclusively that the existence of neuronal autoantibodies is associated with more probable cognitive impairment in patients with small cell lung cancer [49]. A relationship is likely between the presence of autoantibodies and the extent of cognitive impairment. In addition, a study of MCI ($n = 55$) and dementia patients ($n = 22$) showed that specific autoantibodies (e.g., anti- Outer Dense Fiber of Sperm Tails 3 protein and Rho GDP Dissociation Inhibitor Gamma protein) correlated negatively with the extent of cognitive impairment in the MoCA questionnaire [50]. It is therefore conceivable that neural autoantibodies such as ATP1A3 autoantibodies might be related to the degree of cognitive impairment like the SCD in our case. Relying on the role played by ATP1A3 in cognition in animal and human studies, we propose that ATP1A3 autoantibodies may play a role in the perception of cognitive impairment, although we cannot prove this. This is only speculation, and we do not yet know whether the autoantibodies per se are pathogenic for cognitive dysfunction. Note that in this case we have only observed an association between SCD and ATP1A3 antibodies together with amyloid positivity, and we cannot draw any conclusions about the causal role of ATP1A3 autoantibodies in SCD with amyloid positivity in the CSF.

3.5. Autoantibodies in dementia

It is important to distinguish whether neural autoantibodies such as ATP1A3 autoantibodies are present in the context of neurodegenerative dementias, or as a feature of pure autoimmune dementias without neurodegeneration. Various neurodegenerative dementias can be associated with neural autoantibodies, such as AD or dementia with Lewy bodies. For example, there is recent study evidence [51] that prolonged exposure to GluA3 antibody IgG changes the location of AMPA receptors containing GluA3, resulting in altered dendrite organization and numbers, thus causing anomalies in synaptic connectivity. GluA3 autoantibodies have been described in up to 25 % of frontotemporal dementia [52]. There is evidence that anti-GluA3 in an animal model led to an accumulation of phosphorylated tau at the postsynapse in the frontal cortex after transfer [52]. Another important autoantibody-mediated disease is IgLON5 autoantibody disease, which leads to tau deposits in structures similar to tauopathies and also reveals concomitant TDP43 pathology [53], resulting in patterns resembling FTD or tauopathies, but it is not common with neurodegenerative dementias. However, neural autoantibodies can also exert neuroprotective effects in AD, as a recently published study showed: high levels of NMDAR were found in AD patients with better cognitive performance than in AD patients with low NMDAR levels [14]. That evidence could therefore mean that autoantibodies may be pathogenically significant in the development of cognitive dysfunction at the synaptic level, but but also have a cognitively protective function. The significance of autoantibodies is therefore unclear, and each underlying autoantibody should always be examined individually. Autoantibodies are more common than we had assumed; IgG and IgA autoantibodies against brain proteins were found in 21 % of patients with dementia but in only 2.9 % of controls [13]. This work shows that autoantibodies are much more frequent in neurodegenerative dementia than previously thought. They may also reflect the initial neuroinflammation that triggers the gradual progression of neurodegenerative dementia.

3.6. Limitations

The fact that what we report here is a case that could also be an incidental finding without further significance, and it is as such a limitation. However, neuroinflammation is known to occur in AD's early disease processes, and ATP1A3 autoantibodies may be an early sign of the neuroinflammatory process. It is unclear whether the interaction between Alzheimer's pathology and ATP1A3 autoantibodies could trigger faster cognitive decline. This is worthy of investigation in a follow-up study, as ATP1A3 autoantibodies could lead to more rapid cognitive decline. Such a possibility is consistent with the importance of co-pathologies in AD pathology, which can also lead to more rapidly progressing cognitive dysfunction. This should be addressed in a follow-up study. Another limitation is the fact that we cannot completely rule out that our patient's subjective cognitive decline represents cognitive dysfunction associated with posttraumatic stress disorder. However, if it were PTSD, we would expect to observe more deficits in explicit memory, which she did not have. Moreover, her PTSD symptoms appeared much earlier than her SCD. Sleep apnea is another factor potentially contributing to cognitive dysfunction. However, the patient has a mask, so the risk factor of sleep apnea is rather negligible in this case. In addition, the involvement of RLS must be discussed, but the onset of the RLS symptoms was 3 years earlier than the cognitive symptoms, and the RLS symptoms decreased with pregabalin. Note also that depressive symptoms were present according to the BDI scores (Table 1), which were recorded twice a year and revealed considerable depressive symptoms. However, the affective symptoms are more likely PTSD-related, as they have existed for years and are not part of the cognitive symptoms that began only recently. Depressive symptoms in the context of dementia, for example, are also more likely after the manifestation of SCD [54]. This also supports the assumption that depressive symptoms are more likely to be considered as affective involvement in PTSD, which was diagnosed long ago and is not part of the recently-onset cognitive symptoms. Depressive symptoms in a dementia context for example, tend to occur after the manifestation of SCD [54]. This also supports the assumption that depressive symptoms are more likely to be considered as affective involvement in PTSD, something we have known for a long time. However, we assume that SCD and depressive symptoms are associated with the high probability of evolving cognitive decline [54].

4. Conclusions

Our case concerns a patient with SCD and an Alzheimer's pathologic change associated with ATP1A3 serum and CSF autoantibodies, which have not been reported previously. The biological significance of ATP1A3 autoantibodies is unclear, we suggest that there is a role that synaptic transmission failure plays in triggering cognitive dysfunction. As we also detected evidence of amyloid beta pathology, her p-tau181 level in the CSF is not yet pathological. Follow-up investigations will demonstrate whether she develops AD and a manifest cognitive disorder.

Ethics approval and consent to participate

The patient consented to participation by using their data for

publication. Furthermore, an ethical approval has been obtained from the University Medical Center Göttingen.

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CRediT authorship contribution statement

Rentzsch Kristin: Methodology, Investigation. **Hansen Niels:** Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bartels Claudia:** Writing – review & editing. **Wiltfang Jens:** Writing – review & editing. **Fitzner Dirk:** Writing – review & editing. **Schott Björn Hendrik:** Writing – review & editing. **Hirschel Sina:** Methodology. **Sagebiel Anne Elisa:** Investigation.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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Consent for publication

A written informed consent was obtained from the participant.

Author Contributions

NH and CB wrote the manuscript. KR, AES, SH, JW, BHS, and DF authors have read, edited and agreed to the submitted version of the manuscript.

Data availability

Data will be made available on request.

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