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Research article

Longitudinally persisting KCNA2-autoantibodies in mild amnestic dementia with Alzheimer's pathology – Report and literature review

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ABSTRACT

Background: Neural autoantibodies are being increasingly detected in conjunction with neurodegenerative dementias such as Alzheimer's disease dementia (AD), yet their significance is not well clarified. In this case report, we report the previously unreported long-lasting persistence of potassium voltage-gated channel subfamily A member 2 (KCNA2) antibodies in biomarker-supported AD.
Methods: We report on a 77-year-old, male patient evaluated in our outpatient memory clinic of the Department of Psychiatry and Psychotherapy, University Medical Center Göttingen. Neuropsychological test results and autoantibody testing in serum over a period of 4–5 years is provided.
Report: Our patient exhibited mild dementia syndrome and was diagnosed with AD on the basis of a prototypical biomarker profile (reduced Aβ42/40 ratio and elevated p-tau181 protein in cerebrospinal fluid). Within a 5-year follow-up with regular visits to our memory clinic, we observed a nearly stable neuropsychological profile of mild, amnestic variant dementia that did not noticeably progress. KCNA2 autoantibodies were also detectable in serum over 4 years with increasing titers over time. Combined anti-dementia therapy with donepezil, multimodal therapy including non-pharmacological cognitive therapy, and immunotherapy with intravenous methylprednisolone was carried out as an individual treatment approach.
Conclusions: KCNA2 autoantibody persistence in biomarker-supported AD does not necessarily trigger a poor outcome in the long-term, as cognitive impairment did not progress subsequently. At the same time, mild immunotherapy did not result in less immunoreactivity in conjunction with the detection of KCNA2 autoantibodies. This detection of KCNA2 autoantibodies in AD could provide indices of a potentially benign long-term AD course that should be further evaluated in studies.

1. Introduction

Neural autoantibodies have repeatedly been reported to be associated with Alzheimer's disease dementia (AD) [1–4]. So far, a variety of neural autoantibodies were found to be associated with AD, ie, neurochondrin autoantibodies [1], although their significance is unknown. Emerging concepts of autoimmune dementia [5] stand in contrast to classic dementias and are associated with autoantibodies, although the significance of their autoantibodies is still unclear. On the other hand, it is also conceivable that these autoantibodies are an expression of an autoimmune reaction such as increased neuroinflammation, which would be expected in the early stages of AD. The description of such rare individual cases is therefore important to shed more light on this phenomenon. Potassium voltage-gated channel subfamily A member 2 (KCNA2) autoantibodies are neural autoantibodies commonly observed in cognitive disorders [eg, 6], but so far there is no report describing persisting autoimmunity in the form of persistent KCNA2 autoantibodies over several years. We therefore introduce this case of a man with mild dementia in whom KCNA2 autoantibodies were detected over a 4-year period. As this patient also revealed a biomarker-supported AD

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profile, this case also adds up on potential associations between AD pathology in combination with persisting KCNA2 antibodies.

2. Case presentation

We report on a male patient with cognitive deficits he had been exhibiting for 5 years who presented to our tertiary memory center for the first time at an age of 77 years. He initially reported to have observed a slow cognitive decline entailing gradually developing memory impairment (eg, with forgetting of appointments and tasks), difficulty finding words and concentration. His medical history includes previous illnesses and operations such as a surgically treated colon and bladder carcinomas, Dupuytren's disease, inguinal hernia surgery, an appendectomy, tonsil surgery, presbycusis and Lyme's disease in 2000 (resolved via antibiotic therapy). According to his family history, he has a brother suffering from depression. He was a professional gardener with an elementary school diploma, took early retirement, is married and has a daughter. He is taking no current medication. The initial psychiatric examination was indicative of temporal orientation, memory, and word-finding difficulties. Lateral plantar hypesthesia became evident in his neurological examination. Further diagnostic examinations carried out soon after his initial presentation revealed no abnormalities in coagulation, blood count, liver values, kidney values and electrolytes, vitamin B12, folic acid, c-reactive protein and thyroid values. His blood count was checked three times in all over a three-year period but revealed no anomalies or pathological values. His hemoglobin value, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets and leukocytes were measured and fell within the normal range. Homocysteine was slightly elevated at 16.5 μmol/l (reference range: 5.5–16.2 μmol/l). In electroencephalography (EEG), no focal slowing, nor any evidence of epilepsy-type potentials were found. Cranial magnetic resonance imaging (MRI) showed a paramedian arachnoid cyst in the posterior fossa. First neuropsychological testing in 01/2018 using the Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery plus (CERAD-NAB- plus; Table 1) revealed cognitive deficits in cognitive domains such as memory (figural memory, word list recognition), attention (information processing speed) and executive functions (cognitive flexibility) to be summarized as amnestic Mild Cognitive Impairment (MCI). However, caregivers reported deficits in instrumental activities of daily living (eg, finances, health care) already suggesting a dementia diagnosis. Within a more comprehensive neuropsychological assessment 6 months later (07/2018), the diagnosis of a mild dementia syndrome was confirmed: On top of the already recorded cognitive impairments in 01/2018, deficits in working and verbal memory as well as in visuoconstructive functions were uncovered. The clinical phenotype was dominated by memory deficits and therefore suspicious of AD. Because of a deficit pattern also including impairments of visuonconstructive functions and processing speed, differential diagnosis of a dementia with Lewy Bodies had to be considered. Subsequent cerebrospinal fluid (CSF) puncture showed no pleocytosis, no immunoglobulin A (IgA), immunoglobulin M (IgM) or immunoglobulin G (IgG) intrathecal synthesis. Specific dementia biomarkers had a prototypical profile compatible with AD pathology (decreased Aβ42/40 ratio at 0.038 and increased p-tau181 at 118 pg/ml, see Table 2). Amyloid peptide measurements were confirmed by analyzing CSF probes via Lumipulse (G600II) platform. S100B in CSF was also elevated (Table 2) as an indication of glial damage, and NSE in CSF (Table 2) also showed pathologically elevated values indicative of non-specific cell damage. Total tau protein was elevated as well, marking axonal cell damage in the CNS. Search for neural autoantibodies resulted in the detection of anti-KCNA2 IgG in the cell-based assay. Antibodies were detected in the BIOCHIP mosaic with brain tissue and recombinant cells. The reference range was less than 1:10. In additional follow-up measurements over 4 years, KCNA2 autoantibody was continuously detectable in serum at an intensity of 1:32–1:1000 (Fig. 1). We detected no other neural autoantibodies in the serum or CSF. We searched for autoantibodies against neural antigens such as glutamic decarboxylase 65 (GAD65), Zic4, Delta/Notch-like Epidermal Growth Factor-Released receptor /Tr (DNER/Tr), SOX1, Ma2, amphiphysin, cronveinten 2/collapse response mediator protein 5 (CV2/ CRMP5), Ri, Yo, HuD, N-methyl-D-aspartate receptor (NMDAR), leucin rich glioma inactivated protein I1 (LGI1), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor 1/ 2 (AMPAR1/2), γ-aminobutyric acid (GABA) type B receptor 1/2 (GABAB1/2), dipeptidyl-peptidase-like protein 6 (DPPX) and contactin-associated protein-like 2 (CASPR2) in serum and CSF

Table 1
Neuropsychological performance over time.

Cognitive domain	Test	11/ 2021	02/ 2020	07/ 2018	01/ 2018
Global cognitive function	MMSE	19/ 30	23/ 30	20/ 30	22/ 30
Learning and memory	WAIS-IV Digit span forward	−1.3	−0.3	−1.3	-
	CERAD-NAB plus Learning trials 1–3 word list	0.9	0.8	−0.9	−0.3
	CERAD-NAB plus Word list free recall	−0.6	−0.7	−1.3	−0.8
	CERAD-NAB plus Savings word list	−1.5	−1.8	−2.0	−0.8
	CERAD-NAB plus Word list recognition	−1.1	1.2	−2.2	−1.2
	WMS-IV Logical memory I	−0.3	−1.0	−1.0	-
	WMS-IV Logical memory II	−2.7	−2.7	−3.0	-
	CERAD-NAB plus Figures free recall	−2.8	-	−3.1	−2.4
	CERAD-NAB plus Figures savings	−2.7	-	−2.8	−2.3
	WMS-IV Visual reproduction I	-	−2.7	-	-
	WMS- IV Visual reproduction II	-	−1.7	-	-
Visuoconstructive functions	CERAD-NAB plus Figure copy	−0.7	−1.4	−1.5	1.0
	WAIS-IV Block design	−0.3	−1.3	−1.3	-
Attention	CERAD-NAB plus TMT A	−2.0	−2.2	−1.8	−1.3
	WAIS-IV Coding	−1.7	−1.7	−2.0	-
Language	CERAD-NAB plus Boston naming test	0.0	0.0	−0.1	−0.1
	CERAD-NAB plus Semantic word fluency (animals)	1.4	0.4	−0.2	0.1
	CERAD-NAB plus Phonematic word fluency (s-words)	−1.2	−0.4	−0.2	0.1
Executive functions	CERAD-NAB plus TMT B	*n.d.*	*n.d.*	*n.d.*	*n.d.*
	RWT Semantic fluency (alternating categories)	−2.1	−0.7	−0.7	-
	RWT Formal lexical fluency (alternating letters)	−0.3	−0.8	−0.7	-
	WAIS-IV Digit span backwards	−2.0	−1.3	−2.0	-

Notes and abbreviations: Z-values presented as age- (for CERAD-NAB plus subtests also education- and gender) specific reference values with z-values ≥ -1.0 denoting normal performance. Abbreviations: MMSE = Mini Mental State Examination; WAIS-IV = Wechsler Adult Intelligence Scale – 4th edition, CERAD-NAB plus = Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Assessment Battery plus, WMS-IV = Wechsler Memory Scale – 4th edition, TMT = Trail making test, RWT = Regensburger Wortflüssigkeitskeit (Regensburg word fluency test), n.d. = not determined (infeasible due to cognitive impairment).

Table 2
Dementia biomarker in cerebrospinal fluid.

Parameter	Result
NSE ng/ml (> 30 ng/ml)	35.0
S100B μg/ml (> 2.7 ng/ml)	4.1
Total tau protein pg/ml (> 450 pg/ml)	505
P-tau181 pg/ml (> 61 pg/ml)	118
Aβ1–40 pg/ml	18662
Aβ1–42 pg/ml (< 450 pg/ml)	716
Ratio Aβ1–40/1–42 (< 0.05)	0.038

Abbreviations: Aβ = Amyloid-beta, NSE = neuron specific enolase, P-tau181 = phosphorylated tau protein 181. Pathological reference values in brackets.

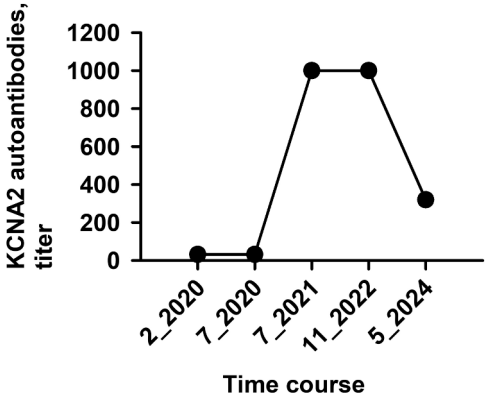

Fig. 1. Long-term follow-up of the KCNA2 autoantibody titer in serum. The follow-up measurements of KCNA2 autoantibodies in serum showed a continuous detection in serum with an intensity of 1:32–1:1000 over a period of 4 years. Abbreviations: KCNA2 = potassium voltage-gated channel subfamily A member 2.

samples. After the AD diagnosis was made based on a prototypical biomarker profile and an amnestic variant as clinical phenotype, we started drug therapy with donepezil 10 mg/d after the patient proved unable to tolerate rivastigmine. Non-drug treatment involving occupational therapy and physiotherapy was also provided. Parallel to the anti-dementia therapy, we initiated immunotherapy involving 6 cycles of methylprednisolone therapy of 1 g each over 5 days as an individualized treatment approach after having clarified that this is a case of additional KCNA2 autoantibody-associated dementia. The patient reported a subjective benefit after the first cycles of immunotherapy with methylprednisolone, however caregivers was unable to confirm his subjective improvement, so that immunotherapy was discontinued after shared decision making with the patient and his family. MMSE values remained stable within a range of mild dementia during follow-up (Fig. 2).

3. Discussion

This report is fascinating for two reasons: (1) the continuous detection of KCNA2 autoantibodies over several years is remarkable, and it is interesting how this seems to modulate the mild dementia outcome over the long-term. (2) although there is biochemical CSF evidence of AD pathology with a clinical phenotype of an amnestic variant, such a stable long-term course is atypical for AD and therefore makes the diagnosis of typical AD questionable.

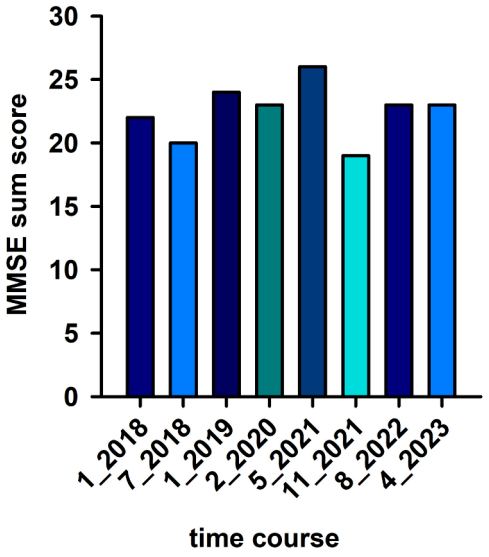

Fig. 2. Long-term cognitive function. The MMSE score is shown here over a period of 5 years, and no relevant progression is observed within this period. Legend to the figure: MMSE = Mini Mental Status Examination.

3.1. KCNA2 autoantibodies and slowly progressing semantic dementia

The detection of KCNA2 autoantibodies in subjects with cognitive disorders is not surprising and has been recently published [6,7]. A case series [6] revealed cognitive disorders present in about 29 % of all neuropsychiatric phenotypes accompanied by KCNA2 antibody detection; these in fact accounted for the most frequent clinical presentation [6]. The significance of KCNA2 antibodies in our patient is unclear, but it is worth noting that his autoantibody titers even increased after six months of immunotherapy. It is unclear that KCNA2 antibodies are pathogenic, as they possess two major intracellularly localized epitopes [8] and are therefore according to current opinion, are less pathogenic than antibodies directed against membrane surfaces. According to the Arlt case series, there are associated tumors in only about 10 % of KCNA2 autoantibody-associated neuropsychiatric diseases [6], but the predominantly intracellular location of the epitope suggests that these antibodies have little pathogenic significance. Nevertheless, histological sections have yielded evidence that KCNA2 antibodies bind to memory-forming structures such as the hippocampus [6] and can therefore play a role in the pathogenesis of cognitive disorders. Arlt et al. also demonstrated that KCNA2 antibodies were no longer detectable after immunotherapy [6], in contrast to the persistence in our patient. This may indicate that immunotherapy in this case might not have been strong enough to exert an effect. Nonetheless, our patient refused renewal of immunotherapy after failing to perceive an obvious benefit such as for instance, a strong improvement in his cognitive capacities, meaning that we cannot know whether a continuation of immunotherapy or escalation of immunotherapy would have led to a better clinical outcome in cognition terms.

3.2. Neural autoantibodies associated with Alzheimer's disease

Another interesting aspect of this case is that the prototypical AD profile entailing a clinically typical presentation with an amnestic variant suggests a diagnosis of AD. The presence of KCNA2 antibodies does not rule out an AD diagnosis, as there are several reports of neural autoantibodies associated with AD [1–4]. In a large cohort, for example, autoantibodies against brain proteins of the IgG or IgA type were identified in 30 % of patients with AD [2]. Specific autoantibodies such as N-methyl-D-aspartate-receptor (NMDAR) IgG, IgM and IgA antibodies had been detected in 16 % of patients with atypical dementia compared

to healthy controls (4 %) [9]. Studies have also identified certain autoantibody panels that distinguish between AD and controls with high diagnostic accuracy [4] amongst others. Neural autoantibodies have long been reported in conjunction with progressive dementias that do not follow the clinical course of relapse-remitting autoimmune encephalitis. Various neural autoantibodies have been reported such as Rho GTPase activating protein 26 (ARGHAP26) [10], glycine [11], recoverin [12], Leucin rich glioma inactivated protein 1 (LGI1), NMDAR or IgLON family member 5 (IgLON5) [13], to just name a few. IgLON5 represents a potentially important hybrid between pure autoimmunity and neurodegeneration, as there is evidence that IgLON5 antibody disease often also leads to tauopathy. There are proposals such as those of Prüss et al. [14] postulating that autoantibodies can induce changes in brain function. Autoantibodies in dementia are not described as being well-established, but rather as "emerging autoantibodies" due to their relatively recent discovery [15]. Another consideration here is that detecting persistent KCNA2 autoantibodies may serve as evidence of neuroinflammation, which is particularly suspected in AD's pathogenesis [16].

3.3. Long-term persistence of neural autoantibodies

Overall, the most interesting aspect of this case report is the persistent detection of the KCNA2 autoantibodies over four years. There is a paucity of data on the long-term course of neural autoantibodies and cognitive disorders. In general, only few case reports and case series have been published on this matter. One case report described a 15-year persistence of NMDAR antibodies entailing remission of the initial symptoms (such as psychoses, seizures and dyskinesias) and white matter abnormalities in the context of a demyelinating disorder that ultimately characterized this patient's course [17]; these authors thus wondered whether years of NMDAR autoimmunity had contributed to demyelination. This is obviously highly speculative, but it must be considered that another report demonstrated that NMDAR antibodies detected in the CSF after 1 year were associated with a poor outcome [18]. A report on as many as 28 patients with antibody-mediated autoimmune encephalitis showed that there was no difference in long-term clinical outcome between antibody-positive ($n = 16$) and antibody-negative patients at six months of follow-up [19]. It thus remains controversial whether the persistence of neural autoantibodies, as in our case, leads or leads not to a significant deterioration over time. Further research is warranted to clarify whether the neural autoantibodies found in AD patients and subsequent treatment or treatment response of immunotherapy have an impact on their clinical long-term outcome differing from those of AD patients without neural autoantibodies.

3.4. Blood-brain barrier disturbance and KCNA2 autoantibodies

There is evidence from animal models [20,21] that in animals with a disrupted blood-brain barrier, neural autoantibodies are pathogenic because they can access the brain. It is assumed that autoantibodies, for example NMDAR autoantibodies, enter the brain through a disturbed blood-brain barrier [22], where they bind to brain structures and thus trigger cognitive symptoms. There is evidence from a small cohort of surgery patients [23] that the levels of NMDAR autoantibodies in the blood are decreased in post-anesthesia NMDAR autoantibody-positive patients, as these presumably bind to brain structures after the blood-brain barrier has been compromised. It is therefore conceivable that KCNA2 may have initially entered the brain through the blood-brain barrier's opening. Our patient has a history of several operations involving anesthesia which could have led to an opening of the blood-brain barrier. Although such operations may have taken place a long time ago, they may have caused a long-lasting dysfunction of the blood-brain barrier, as anesthetics can lead to impaired recovery of the blood-brain barrier dysfunction with increasing age and through a long period of exposure to anesthetics [24]. It is therefore conceivable that our patient also experienced a disruption of the blood-brain barrier at least temporarily, which could have permitted KCNA2 autoantibodies to enter the brain. However, it is also conceivable that recovery from a blood-brain barrier dysfunction prevented the KCNA2 autoantibodies from entering the brain during the disease course. However, to assume an effect on progressing cognitive impairment via KCNA2 autoantibodies, a disruption of the blood-brain barrier must be proven, as a study with NMDAR autoantibodies has demonstrated [25]. However, the blood-brain barrier disorder may worsen and coincide with cognitive impairment over the disease course, which a study in the hippocampus region already showed [26]. However, this factor does not explain the minor effect of the persisting KCNA2 autoantibodies on cognitive function over the disease course, it is thus possible that the initial corticosteroid therapy had a beneficial effect on the blood-brain barrier's integrity, as one study has shown [27]. The pathogenicity of KCNA2 antibodies would therefore become irrelevant for the brain over the disease course.

3.5. Limitations

Some limitations should be mentioned, namely that a case report on single patient obviously does not constitute strong evidence, and that a case series should be examined to learn more about the outcome and significance of these antibodies in AD. In addition, our patient's AD diagnosis may also be questionable in a differential diagnosis context. Other rare clinical manifestations such as limbic-predominant amnestic neurodegenerative syndrome (LANS) [28] are also out of the question, because although our patient is over 75 years old, he revealed no hippocampal atrophy on MRI. It remains speculative whether KCNA2 autoantibodies have contributed at all to a change in cognition over his disease course.

3.6. Conclusions

KCNA2 autoantibodies persisting for more than four years may indicate an inflammatory component in biochemically confirmed AD. It is therefore important to initiate an autoantibody search during diagnosis and, due to a possible immunotherapeutic response, also in patients with neurodegenerative cognitive impairment or dementia. There is a shortage of large-scale studies to learn more about these autoantibodies in AD.

Author contributions

NH and CB wrote the article, all authors have revised and edited the article.

Consent for publication

Written informed consent was obtained from this study participant.

CRediT authorship contribution statement

Bartels Claudia: Writing – review & editing, Writing – original draft. **Fitzner Dirk:** Writing – review & editing. **Wiltfang Jens:** Writing – review & editing. **Hirschel Sina:** Writing – review & editing. **Fox Janosch:** Writing – review & editing. **Hansen Niels:** Writing – original draft, Visualization, Validation, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Teegen Bianca:** Writing – review & editing, Methodology, Investigation.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Data availability

Data will be made available on request.

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