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Seizures as an early symptom of autosomal dominant Alzheimer's disease

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ABSTRACT

Our objective was to assess the reported history of seizures in cognitively asymptomatic mutation carriers for autosomal dominant Alzheimer's disease (ADAD) and the predictive value of seizures for mutation carrier status in cognitively asymptomatic first-degree relatives of ADAD patients. Seizure occurrence in the Dominantly Inherited Alzheimer Network observational study was correlated with mutation carrier status in cognitively asymptomatic subjects. Of 276 cognitively asymptomatic individuals, 11 (4%) had experienced seizures, and nine of these carried an ADAD mutation. Thus, in the Dominantly Inherited Alzheimer Network population, seizure frequency in mutation carriers was significantly higher than in noncarriers ($p = 0.04$), and the positive predictive value of seizures for the presence of a pathogenic mutation was 81.8%. Among cognitively asymptomatic ADAD family members, the occurrence of seizures increases the a priori risk of 50% mutation-positive status to about 80%. This finding suggests that ADAD mutations increase the risk of seizures.

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1. Introduction

Autosomal dominant Alzheimer's disease (ADAD) is a rare form of Alzheimer's disease (less than one percent of all AD cases) (Bird, 1998) that usually has an earlier symptomatic onset (35–55 years) relative to sporadic AD (Ryman et al., 2014). First-degree relatives of persons with ADAD are at 50% risk for carrying a disease-causing mutation in one of the 3 known ADAD genes: *PSEN1*, *PSEN2*, and *APP*, coding for presenilin 1, presenilin 2, and amyloid precursor protein, respectively. Such mutations cause ADAD with almost complete penetrance (Jayadev et al., 2010). The Dominantly Inherited Alzheimer Network (DIAN) observational study aims to reveal the pathological changes in the course of ADAD, particularly in the period before cognitive decline (Bateman et al., 2012).

Interictal epileptiform discharges measured by electroencephalography (EEG) and overt seizures have been reported in transgenic mouse models of AD (Born, 2015; Palop and Mucke, 2010). Persons with AD are at an increased risk for seizures (Horvath et al., 2016; Nicastro et al., 2016), in particular those with an early age of onset (Amatniek et al., 2006) and in advanced stages (Romanelli et al., 1990). Pathogenic ADAD mutations or *APP* duplications may confer an even higher risk of seizures than in sporadic AD (Born, 2015). In accordance with the 2012 classification scheme of the International League Against Epilepsy (Panayiotopoulos, 2012), ADAD due to *PSEN1* mutations was even proposed as a genetic epilepsy syndrome (Larner, 2011). Recently, the DIAN observational study has reported seizures in 2.8% of symptomatic ADAD mutations carriers (Tang et al., 2016). Based on evidence that AD starts much earlier than its cognitive manifestation (Bateman et al., 2012), we hypothesized that asymptomatic (i.e., Clinical Dementia Rating [CDR] [Morris, 1993] score of 0) ADAD mutation carriers show a higher frequency of seizures than noncarriers.

2. Methods

2.1. Study population

Data from the DIAN observational study, collected using the Uniform Data Set of the National Alzheimer's Coordinating Center (NACC-UDS2) (Morris et al., 2006) with examiners blinded to and participants mostly unaware of mutation status at 15 sites in the USA, Australia, the UK, and Germany from January 2009 to January 2015 (data freeze 9) formed the basis for our analysis. The data set included extensive information about 144 participants with *PSEN1*, *PSEN2*, and *APP* mutations and nonmutation carrying ADAD family members ($n = 132$) who served as controls. The protocol for the study received approval by the institutional review boards at all participating sites. The study was performed in accordance with the declaration of Helsinki. Written informed consent was obtained from each subject.

2.2. Seizure assessment

Seizure occurrence is assessed by a single item in the NACC-UDS (question 4a on form A5). We analyzed the occurrence of seizures by evaluating this item along with the adverse event forms for all visits included in data freeze 9 in all cognitively asymptomatic participants (defined by a CDR score of 0). NACC-UDS asks for characterization of seizures in 4 mutually exclusive categories: "recent/active" (happened within the last year or still requiring active management), "remote/inactive" (existing or occurring in the past, i.e., more than one year ago, having been resolved or without current treatment), "absent" and "unknown," respectively. Evaluation is based on report of the subject and the accompanying informant, medical records, and/or observation (Fig. 1).

2.3. Other variables

Additional DIAN study data that were included in our analysis of cognitively asymptomatic participants are age and gender, apolipoprotein E (*APOE*) genotype (allele combinations ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4 or ε4/ε4, respectively) and, if applicable, gene affected and expected age of onset (EAO). EAO is defined as the age of ADAD symptom onset in the index patient in the family of a DIAN participant and has been shown to be a predictor of the age of onset of ADAD symptoms in the respective family (Bateman et al., 2012; Ryman et al., 2014). Time to EAO is the difference in years (whole numbers) between EAO and the current age of the participant at the time of the visit.

2.4. Comorbidities

The data set was also screened for additional factors that might cause or mimic seizures such as alcohol and substance abuse, syncope, diabetes, and other medical comorbidities, as well as for a history of stroke and other neurologic and psychiatric comorbidities such as traumatic brain injury (TBI). Three degrees of TBI are distinguished in NACC-UDS: (1) TBI with brief loss of consciousness of less than 5 minutes, (2) TBI with extended loss of consciousness (greater than or equal to 5 minutes), and (3) TBI with chronic deficit or dysfunction, with each classified as either "absent" or "recent/active" or "remote/inactive" or "unknown." We identified 3 individuals with TBI in the study population and assessed their fluid-attenuated inversion recovery magnetic resonance images with specific emphasis on epileptogenic brain lesions. These MR images were performed during the DIAN study visit at which a history of TBI was recorded and all of the TBI were stated "remote/inactive." There was therefore at least a 1-year interval between the TBI and the MRI. We compared the prevalence of TBI in subjects with seizures between mutation carriers and noncarriers using Fisher's exact test.

2.5. Data and statistical analysis

For comparison of subjects' baseline age, EAO, and time to EAO between mutation carriers and noncarriers, Student's t-test was used. Gender, affected gene (*PSEN1*, *PSEN2*, or *APP*), and *APOE* genotype were compared using Fisher's exact test.

Due to the small number of individuals with seizures, a right-sided one-tailed Fisher's exact test was performed to test the hypothesis of a higher frequency of seizures in mutation carriers compared to noncarriers.

Sensitivity, specificity, and the positive predictive value of seizure occurrence with respect to mutation carrier status were calculated using a 2-dimensional contingency table.

To analyze the timing of seizures in the cognitively asymptomatic stage of ADAD mutation carriers, we assumed that the seizure had occurred at the latest possible time point for each individual participant: we posited that if seizures were stated as "recent/active," they happened on the day of the study visit. If seizures were stated as "remote/inactive" (occurred more than a year ago), it was assumed that they had happened exactly one year before the study visit. We used the first study visit at which presence of seizures was mentioned (i.e., as "recent/active" or "remote/inactive," in contrast to "absent" or "unknown") for subsequent calculations. For group comparisons, we put the latest possible time point of seizure occurrence in relation to EAO. Because of repeated claims of an increased seizure risk particularly of *PSEN1* mutations, the latest possible time point of seizure occurrence in relation to EAO was studied in individuals with *PSEN1* mutations in comparison to those with *PSEN2* or *APP* mutations, using a 2-sided *t*-test.

A

The purpose of this form is to record a history of conditions at the current visit as determined by the clinician's best judgment. The form should be completed by the clinician, based on subject/informant report, medical records, and/or observation.

- A condition should be considered "Absent" if it is not indicated by information obtained from informant report, medical records and/or observation.
- A condition should be considered "Recent/Active" if it happened within the last year or still requires active management, and is consistent with information obtained from informant report, medical records and/or observation.
- A condition should be considered "Remote/Inactive" if it existed or occurred in the past (greater than one year ago) but was resolved or there is no current treatment underway.
- A condition should be considered "Unknown" if there is insufficient information available from informant report, medical records and/or observation.

B

	Absent	Recent/Active	Remote/Inactive	Unknown
4. Other neurologic conditions				
a. Seizures	☐ 0	☐ 1	☐ 2	☐ 9
b. Traumatic brain injury				
1) with brief loss of consciousness (< 5 minutes)	☐ 0	☐ 1	☐ 2	☐ 9
2) with extended loss of consciousness (≥ 5 minutes)	☐ 0	☐ 1	☐ 2	☐ 9
3) with chronic deficit or dysfunction	☐ 0	☐ 1	☐ 2	☐ 9
c. Other (*specify*): _____	☐ 0	☐ 1	☐ 2	☐ 9

Self-explanatory. For item 4b3, check number 1 or 2 if sustained neurological impairment resulted from the head injury.

Fig. 1. Excerpt from the coding guidebook version 2 for the Uniform Data Set version 2 of the National Alzheimer's Coordinating Center (NACC-UDS2) that has been used for assessment of seizures. (A) General instructions and criteria for assessment of the participant's health history. (B) Single Item question for the assessment of seizures.

To compare seizure frequency of asymptomatic carriers of ADAD mutations (i.e., CDR = 0) with that in carriers already affected by cognitive symptoms of ADAD (CDR of 0.5 and above), we drew on data obtained in another analysis of the DIAN data set (Tang et al., 2016) and used 2-sided Fisher's exact test for the comparison of the cognitively asymptomatic and symptomatic states.

3. Results

3.1. Population characteristics

The DIAN data set under analysis contained data from 276 cognitively asymptomatic participants (CDR = 0), 144 of which were carriers of mutations in *PSEN1*, *PSEN2*, or *APP* and 132 were nonmutation carrying ADAD family members. Mutation carriers were significantly younger than noncarriers and had a longer time to the EAO of their family mutations. Otherwise, no significant baseline differences between the 2 groups were found (Table 1).

3.2. Reported history of seizures

Among these 276 individuals, seizures were reported in 11 participants (4%), and of these, 9 participants (81.8%) were ADAD mutation carriers (Fig. 2). Fisher's exact test showed a significantly higher frequency of seizures in mutation carriers compared to noncarriers (6.3% vs. 1.5%, $p = 0.04$).

3.3. Predictive value

Occurrence of seizures corresponds to a sensitivity of 6.3%, a specificity of 98.5%, and a positive predictive value of 81.8% for the presence of an ADAD mutation within the population of cognitively

Table 1
Study population characteristics

Variable	Mutation carriers (n = 144)	Noncarriers (n = 132)	Total (n = 276)	*p* value
Mean age ± SD, y	35 ± 9.2	38.3 ± 10.2	36.5 ± 9.8	**0.01**
Female: male, n	61: 83	58: 74	119: 157	0.81
Mean EAO ± SD, y	47.5 ± 7.1	46.9 ± 6.7	47.2 ± 6.9	0.47
Mean time to EAO ± SD, y	12.5 ± 7.9	8.6 ± 11.5	10.6 ± 10.0	**0.001**
Seizures, n (%)	9 (6.3)	2 (1.5)	11 (4)	**0.04**
Family mutation type, *PSEN1*: *PSEN2*: *APP*, n	105: 15: 24	84: 12: 36	189: 27: 60	0.1
Seizures, n (%) of mutation type	5 (4.8): 2 (13.3): 2 (8.3)	2: 0: 0	7: 2: 2	1.0
No seizures, n of mutation type	100: 13: 22	82: 12: 36	182: 25: 58	0.08
APOE genotype, ε2/ε2: ε2/ε3: ε2/ε4: ε3/ε3: ε3/ε4: ε4/ε4, n	1: 10: 6: 96: 29: 2	1: 15: 2: 78: 34: 2	2: 25: 8: 174: 63: 4	0.41

For group comparisons concerning age, EAO and time to EAO t-tests and for the other items, Fisher's exact tests were performed. No statistically significant difference in distribution of *APOE* genotypes between mutation carriers and noncarriers were found.
p-values < 0.05 are presented in bold.
Key: EAO, expected age of onset of family mutations.

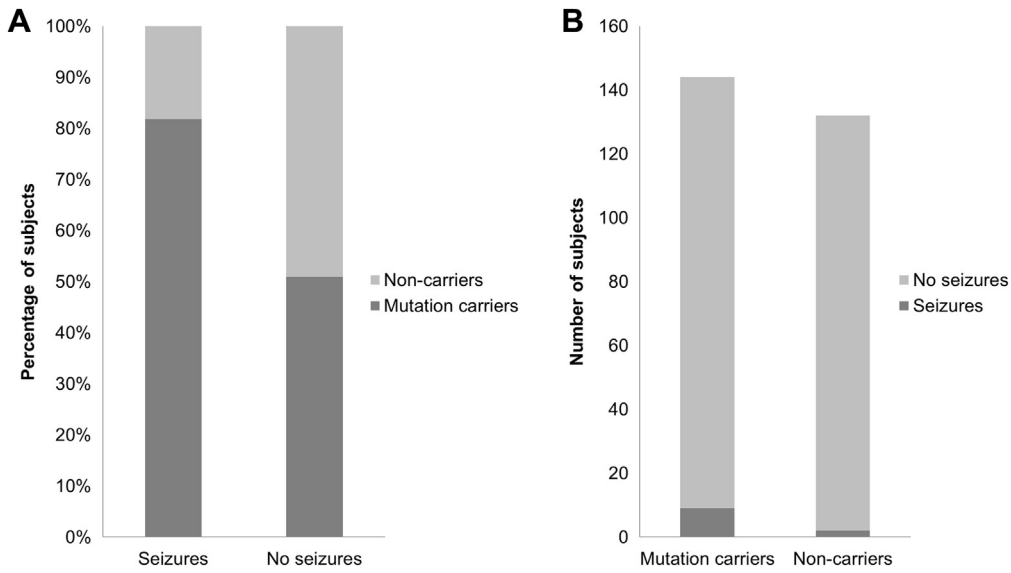

Fig. 2. Relation of mutation status and seizures. (A) Proportion of mutation carriers in subjects with and without seizures. (B) Number of subjects with seizures among mutation carriers and noncarriers.

unaffected ADAD mutation carriers and noncarriers in the DIAN observational study.

3.4. Seizures and mutation types

No significant correlation between seizure occurrence and mutation types (number of mutation carriers with seizures: *PSEN1* = 5, *PSEN2* = 2, *APP* = 2) was found (Table 1). The well-known preponderance of *PSEN1* mutations in ADAD is reflected in our study population, with a ratio of 100 to 35 of *PSEN1* versus *PSEN2* and *APP* mutations in the mutation carriers without seizures. However, it appears shifted in favor of *PSEN2* and *APP* mutations to a ratio of 5 to 4, if seizures occur. Although this suggests that seizures may be more common in association with *PSEN2* and *APP* mutations, the difference was not significant ($p = 0.25$). It is possible that a larger sample size would verify this association because a theoretical calculation in an assumed sample with unaltered gene mutation distributions but threefold size would result in a more suggestive p value of 0.04.

3.5. Seizures in the time course of ADAD

Among the 9 ADAD mutation carriers with seizures, they were stated as "remote/inactive" in 8 and as "recent/active" in one. On average, the latest possible time point of seizure occurrence determined with the method described previously was 14 years before EAO (standard deviation 10.4 years). Although not significant ($p = 0.06$), seizures in *PSEN1* mutations appeared earlier than in *PSEN2* and *APP* mutations (mean −19.6 and −7 years to EAO, respectively) with respect to EAO.

3.6. Comorbidities

In 3 individuals with seizures, one episode each of TBI was reported in their histories, all with brief loss of consciousness of less than 5 minutes, and all stated "remote/inactive." Furthermore, the TBI occurred not necessarily before the appearance of seizures. Fluid-attenuated inversion recovery magnetic resonance images in these 3 cases did not reveal any apparent epileptogenic brain lesions related to TBI, such as temporobasal or other cortical contusions. In subjects with seizures, no statistically significant difference in frequency of TBI between mutation carriers and noncarriers was found ($p = 1.0$). No other possibly contributing factors were evident in individuals affected by seizures (Table 2). In the 2 noncarriers with seizures, no specific reasons could be identified from the data set.

4. Discussion

Our data suggest an increased lifetime prevalence of seizures in cognitively unaffected carriers of mutations in 3 genes underlying ADAD (*PSEN1*, *PSEN2*, *APP*). French authors initially had suggested that seizures that occurred several years before cognitive onset in their ADAD family SAL510 might be related to the L235P *PSEN1* mutation, yet 2 children of a mutation-unaffected family member had seizures similar to the childhood-onset epilepsy of their L235P-carrying grandfather and parental sibling, respectively (Campion et al., 1996). The cohort of the French *PHRC GMAJ* (*Programme Hospitalier de Recherche Clinique-Génétique Malades Alzheimer Jeunes*) collaborators was reported to include 4 subjects with seizures as the very first symptom among 132 mutation carriers from 77 ADAD families (i.e., in 3% of the *PHRC GMAJ* subjects) and, according to the supplemental data provided, the SAL510 family

Table 2
Relevant comorbidities in the histories of the 276 cognitively asymptomatic DIAN study participants analyzed, separated into groups with and without seizures, respectively

Comorbidity	Subjects with seizures (n = 11)	Subjects without seizures (n = 265)	Total (n = 276)
Alcohol abuse, n	0	14	14
Substance abuse, n	0	16	16
Stroke, n	1[a]	1	2
Diabetes, n	0	3	3
Traumatic brain injury, n	3	47	50

The 3 individuals with seizures and traumatic brain injury (loss of consciousness less than 5 min in all cases) in their histories showed no related lesions on brain MRI FLAIR images.
Key: DIAN, Dominantly Inherited Alzheimer Network.
[a] Stroke occurred after seizures had developed.

members were not part of that recent analysis (Zarea et al., 2016). Our analysis of the DIAN data set with its nonmutation carrying family members as controls strengthens the French findings: we found a statistically significant group difference in the lifetime prevalence of a reported seizure between ADAD mutation carriers and noncarriers. In the entire DIAN cohort with its 251 mutation carriers, emerging from 144 cognitively asymptomatic mutation carriers of our analysis and 107 symptomatic mutation carriers of the work of Tang et al., 9 individuals suffered from seizures as the initial ADAD symptom. This leads to a proportion of 3.6% of mutation carriers with seizures as the first symptom of ADAD matching the French result of 3%. For comparison, estimates in epidemiological studies with respect to prevalence of epilepsy are reaching from 0.4% to 1% in different populations (Sander, 2003).

Another detailed evaluation of ADAD patients caused by mutations in *PSEN1* (n = 85) and *APP* (n = 36) described seizures in 20 *PSEN1* and in 9 *APP* mutation carriers. Hence, throughout their entire lives, around 25% of mutation carriers with either gene had a seizure (Ryan et al., 2016). Notably, in 9 of the 29 patients with seizures, the seizures had occurred at least 5 years before symptom onset. These figures can be recalculated into a seizure incidence of 7.4% (9/121) in cognitively asymptomatic mutation carriers which is close to the 6.3% obtained in the present analysis.

The recent evaluation of 107 DIAN subjects already symptomatic with ADAD only analyzed "recent/active" seizures according to NACC-UDS (Tang et al., 2016). The reported proportion of 2.8% (3 individuals) is lower than the 6.3% of cognitively unaffected mutation carriers from our analysis, which also considered seizures that had occurred more than a year before the study visit ("remote/inactive"). In any case, there is no statistically significant difference with respect to seizure frequency in the cognitively symptomatic and asymptomatic groups ($p = 0.2$).

In the majority (89%) of asymptomatic mutation carriers studied, seizures occurred at least 1 year before the respective study visit and were classified as resolved or untreated. These data might indicate that seizures in asymptomatic ADAD are of a benign nature. The early appearance in relation to EAO and the apparent lack of difference in seizure frequency between asymptomatic and symptomatic ADAD mutation carriers supports the assumption that the pathomechanism underlying the seizures, although present early, remains stable from the asymptomatic stage through to the manifestation of ADAD. This might be taken as an argument against instituting antiepileptic pharmacotherapy after a first seizure in cognitively asymptomatic subjects at risk for ADAD beyond consideration of current guidelines (Fisher et al., 2014) and sociocultural consequences (i.e., regarding employment, driving license) of a seizure relapse for treatment decisions.

Despite repeated reports of a particular association of *PSEN1* mutations with epilepsy, culminating in the bold proposal to acknowledge *PSEN1*-related ADAD as a genetic epilepsy syndrome (Larner, 2011), our data do not support a specific association of seizures with *PSEN1* mutations. In fact, we found *PSEN1* mutation carriers might be less commonly affected by seizures than *PSEN2* and *APP* mutation carriers. Firm conclusions as to the specific influence of distinct mutations would be premature due to the lack of sufficient data. As an example, none of the 19 symptomatic *APP* mutation carriers reported in Tang et al., 2016 had seizures, whereas in our sample, 2 of the 24 asymptomatic *APP* mutation carriers were affected. Taking into account the study of Ryan et al., 2016 that found 9 of 36 carriers affected, seizures are a feature in about 14% of *APP* mutation carriers.

With a positive predictive value of 81.8% for the presence of an ADAD mutation, the occurrence of seizures signals a shift from the a priori value of 50% genetic risk for members of affected families. Despite an increased risk on the order of 80% for having a pathogenic mutation, it is important to note that the risk is not absolute. That is, 2 of the 11 asymptomatic individuals experiencing seizures did not carry a pathogenic mutation, which indicates the occurrence of seizure in cognitively normal members of these families should not be considered as evidence of mutation status. Moreover, our findings represent an association of seizures with mutation status, but we do not have the data to consider causality. It is possible that nongenetic factors were responsible for the seizure history in at least some of the 9 mutation carriers. In all cases, appropriate clinical evaluation after seizure occurrence is strongly recommended.

A clear limitation of our analysis lies in the method used to ascertain seizure history. Electroencephalography (EEG) examinations, which would be helpful to corroborate an epileptic cause of an event reported as seizure, are not part of the DIAN observational study protocol. EEG might further yield the opportunity to detect subclinical seizures known to occur in AD (Lam et al., 2017). Potentially provoking factors or types of seizures are not assessed in a standardized manner with the NACC-UDS2. As this tool of the DIAN study does not define the term "seizure" in detail, it can only be considered a rough surrogate for actual epileptic events. Furthermore, knowledge about carrying a mutation or not might have influenced a participant's willingness to report symptoms from his or her history. Owed to the small number of participants with seizures in this study, these results must be further validated. Optimized assessment in ADAD cohorts such as followed in the DIAN studies could include long-term overnight EEG in addition to standardized, routine seizure workup.

A recent study reported subclinical epileptiform activity, as ascertained with overnight long-term video-electroencephalography, in more than 40% of patients with sporadic AD (Vossel et al., 2016). Given this percentage, analyzing the value of seizure occurrence in a cognitively healthy population to predict the occurrence of cognitively symptomatic sporadic Alzheimer's disease and a comparison to the 82% positive predictive value in ADAD described here could be worthwhile.

These clinical findings do suggest a relationship between presymptomatic seizures and the effects of ADAD mutations, which deserves further study. A potential explanation for this relationship could be a lowering of the seizure threshold through ADAD mutations that may account for the relatively rare and nonrecurring seizures in the asymptomatic stage of the disease. An association of ADAD causing mutations and seizures is experimentally supported by data from various transgenic mouse models that display early amyloid β–associated neuronal hyperactivity and epileptiform activity (Busche and Konnerth, 2016; Palop and Mucke, 2010). Furthermore, a connection was shown in the Colombian E280A *PSEN1* family: 5 affected persons who had epileptic seizures and came to autopsy showed neuronal loss in the CA1 field of the hippocampus similar to the typical finding in epilepsy patients with hippocampal sclerosis (Velez-Pardo et al., 2004). Another possible link is provided through the case of a *PSEN1* S169L mutation carrier who suffered from seizures and showed ectopic white matter neurons in the postmortem neuropathological examination (Takao et al., 2001).

The occurrence of seizures might help to identify cognitively as yet unaffected mutation carriers in ADAD families, which is of particular interest with respect to possible inclusion of such individuals in the asymptomatic treatment studies that are currently under way such as the DIAN Trials Unit (NCT01760005) or the Alzheimer Prevention Initiative (NCT01998841) (Rohrer, 2015. http://www.neurodegenerationresearch.eu/wp-content/uploads/2015/10/JPND-Report-Rohrer.pdf). Hereby, these persons with a significantly increased mutation positive risk could be provided the opportunity to receive a potentially effective treatment. Furthermore, new ADAD pedigrees could be identified based on a family history of early-onset dementia and seizures.

Antiepileptic treatment decisions after seizures in individuals at risk for ADAD may consider the low risk of ongoing seizures in cognitively asymptomatic mutation carriers. This suggests that genetic testing may not be warranted solely for seizure management of ADAD family members. However, the increased risk of being a mutation carrier may prompt interest in appropriate genetic counseling and testing.

Finally, carrier status of a mutation in one of the 3 ADAD genes, *PSEN1*, *PSEN2*, or *APP*, even if rare, appears to be a reasonable differential diagnosis in the workup of seizures in adults, particularly with a family history suggesting early-onset dementia.

Disclosure

The authors report no conflicts of interest.

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