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

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†Deceased 26 July 2017.

Word count paper: 2932
Word count abstract: 149
Number of references: 254
Number of figures: 24
Number of tables: 2
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Acknowledgements:

This project was supported by The Dominantly Inherited Alzheimer’s Network (DIAN, UF1 AG032438) funded by the National Institute on Aging (NIA), the German Center for Neurodegenerative Diseases (DZNE), the NIHR Queen Square Dementia Biomedical Research Centre and the MRC Dementias Platform UK (MR/L023784/1 and MR/009076/1).

This manuscript has been reviewed by DIAN Study investigators for scientific content and consistency of data interpretation with previous DIAN Study publications. We acknowledge the altruism of the participants and their families and contributions of the DIAN research and support staff at each of the participating sites for their contributions to this study. The authors thank Ingrid Ricard (Institute for Medical Informatics, Biometry & Epidemiology, Ludwig-Maximilians-Universität München, Munich, Germany) for statistical consulting.
Abstract

Our objective was to assess the reported history prevalence 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 (DIAN) observational study was correlated with mutation carrier status in cognitively asymptomatic subjects. Of 276 cognitively asymptomatic individuals, 11 (4%) had experienced seizures, and nine out of these carried an ADAD mutation. Thus, in the DIAN population seizure frequency in mutation carriers was significantly higher than in non–carriers ($P = .04$) 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.

Keywords: Alzheimer’s disease; Autosomal dominant; Seizures; Positive Predictive Value; Dementia; Genetics
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 TD. Alzheimer Disease Overview. 1998 Oct 23 [Updated 2015 Sep 24]. In: Pagon RA] that usually has an earlier symptomatic onset (35 to 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 three 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].

Intercital epileptiform discharges measured by electroencephalography 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 non-carriers.
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 non-mutation 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 nine in all cognitively asymptomatic participants (defined by a CDR score of 0). NACC-UDS asks for characterization of seizures in four 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 (Figure 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 three individuals with TBI in the study population and assessed their FLAIR MR 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 one year interval between the TBI and the MRI. We compared the prevalence of TBI in subjects with seizures between mutation carriers and non-carriers 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 non-carriers 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 non-carriers.

Sensitivity, specificity, and the positive predictive value of seizure occurrence with respect to mutation carrier status were calculated using a two-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, utilizing a two-sided t-test.

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 two-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 non-mutation carrying ADAD family members. Mutation carriers were significantly younger than non-carriers and had a longer time to the expected age of onset (EAO) of their family mutations. Otherwise, no significant baseline differences between the two groups were found (Table 1).

3.2. Reported history of seizures prevalence

Among these 276 individuals, seizures were reported in 11 participants (4%) and of these, 9 participants (81.8%) were ADAD mutation carriers (Figure 2). Fisher’s exact test showed a significantly higher frequency of seizures in mutation carriers compared to non-carriers (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 unaffected ADAD mutation carriers and non-carriers 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,
since 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 above was 14 years prior to 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”. Further, the TBI occurred not necessarily before the appearance of seizures. FLAIR MR
images in these three 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 non-
carriers was found (p = 1.0). No other possibly contributing factors were evident in
individuals affected by seizures (Table 2). In the 2 non-carriers with seizures, no specific
reasons could be identified from the dataset.
4. Discussion

Our data suggest an increased lifetime prevalence of seizures in cognitively unaffected carriers of mutations in three genes underlying autosomal dominant Alzheimer’s disease (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 two 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 four 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 members were not part of that recent analysis (Zarea, et al., 2016). Our analysis of the DIAN data set with its non-mutation carrying family members as controls strengthens the French findings: we found a statistically significant group difference in the prevalence of a reported seizure history between ADAD mutation carriers and non-carriers. 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% (three 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 prior to 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 one 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.
(Tang, et al., 2016) had seizures, whereas in our sample 2 out of the 24 asymptomatic APP
mutation carriers were affected. Taking into account the study of Ryan et al. (Ryan, et al.,
2016) that found 9 out 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 non-genetic 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

A limitation of our study is the ascertainment of seizure history. EEG examinations, that
would be very useful to corroborate a potential epileptic cause of an event that has been
reported as a seizure, are not part of the work-up of the DIAN observational study. EEG
examinations would further yield the opportunity to detect subclinical seizures that can occur
in AD (Lam et al, Nature Medicine, 2016). Data regarding potential provoking factors or
seizure types are not assessed in a standardized manner. As the term “seizures” is not defined
in detail in the UDS that is used for assessment of clinical data in the DIAN observational
study, it can only be considered a rough surrogate for actual epileptic events. The knowledge
of having a mutation or not could have influenced the willingness to report a symptom that occurred earlier in the history of a participant. Due to the small number of participants with seizures in this study, our results need to be validated in the future. For an optimized assessment of epileptic seizures long-term overnight EEG examinations and a standardized seizures work-up in ADAD cohorts like the DIAN observational study are needed.

A proportion of subclinical epileptiform activity ascertained with overnight long-term video-electroencephalography of greater than 40% in patients with sporadic AD was reported in a recent study (Vossel, et al., 2016). Given this high percentage, analyzing the value of the occurrence of seizures 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 found in this study would be of worth.

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 non-recurring 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). Further, 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 post-mortem 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. Further, 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 three ADAD genes, *PSEN1*, *PSEN2*, or *APP*, even if rare, appears to be a reasonable differential diagnosis in the work-up of seizures in adults, particularly with a family history suggesting early onset dementia.
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Figure 1: Excerpt from the coding guidebook version 2 for the Uniform Data Set version 2 of the National Alzheimer’s Coordinating Center 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.
Figure 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 non-carriers.
Table 1: Title: Study population characteristics. Legend: 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 non-carriers were found. Abbreviations: EAO, expected age of onset of family mutations.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mutation carriers (n = 144)</th>
<th>Non-carriers (n = 132)</th>
<th>Total (n = 276)</th>
<th>p Value</th>
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<td>Mean age ± SD, y</td>
<td>35 ± 9.2</td>
<td>38.3 ± 10.2</td>
<td>36.5 ± 9.8</td>
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<td>58 : 74</td>
<td>119 : 157</td>
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</tr>
<tr>
<td>Mean EAO ± SD, y</td>
<td>47.5 ± 7.1</td>
<td>46.9 ± 6.7</td>
<td>47.2 ± 6.9</td>
<td>0.47</td>
</tr>
<tr>
<td>Mean time to EAO ± SD, y</td>
<td>12.5 ± 7.9</td>
<td>8.6 ± 11.5</td>
<td>10.6 ± 10.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Seizures, n (%)</td>
<td>9 (6.3)</td>
<td>2 (1.5)</td>
<td>11 (4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Family mutation type, PSEN1 : PSEN2 : APP, n</td>
<td>105 : 15 : 24</td>
<td>84 : 12 : 36</td>
<td>189 : 27 : 60</td>
<td>0.1</td>
</tr>
<tr>
<td>Seizures, n (%) of mutation type</td>
<td>5 (4.8) : 2 (13.3) : 2 (8.3)</td>
<td>2 : 0 : 0</td>
<td>7 : 2 : 2</td>
<td>1.0</td>
</tr>
<tr>
<td>No seizures, n of mutation type</td>
<td>100 : 13 : 22</td>
<td>82 : 12 : 36</td>
<td>182 : 25 : 58</td>
<td>0.08</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Subjects with seizures (n = 11)</td>
<td>Subjects without seizures (n = 265)</td>
<td>Total (n = 276)</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------</td>
<td>-------------------------------------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse, n</td>
<td>0</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Substance abuse, n</td>
<td>0</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Stroke, n</td>
<td>1*</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Traumatic brain injury, n</td>
<td>3</td>
<td>47</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Title: Relevant comorbidities in the histories of the 276 cognitively asymptomatic DIAN study participants analyzed, separated into groups with and without seizures, respectively. Legend: The 3 individuals with seizures and traumatic brain injury (loss of consciousness less than 5 minutes in all cases) in their histories showed no related lesions on brain MRI FLAIR images. *Stroke occurred after seizures had developed.