ORIGINAL ARTICLE

APOE3 Christchurch Heterozygosity and Autosomal Dominant Alzheimer's Disease

Y.T. Quiroz, D. Aguillon, D.C. Aguirre-Acevedo, D. Vasquez, Y. Zuluaga, A.Y. Baena, L. Madrigal, L. Hincapié, J.S. Sanchez, S. Langella, R. Posada-Duque, J.L. Littau, N.D. Villalba-Moreno, C. Vila-Castelar, L. Ramirez Gomez, G. Garcia, E. Kaplan, S. Rassi Vargas, J.A. Ossa, P. Valderrama-Carmona, P. Perez-Corredor, S. Krasemann, M. Glatzel, K.S. Kosik, K. Johnson, R.A. Sperling, E.M. Reiman, D. Sepulveda-Falla, F. Lopera, and J.F. Arboleda-Velasquez

ABSTRACT

BACKGROUND

Variants in *APOE* and *PSEN1* (encoding apolipoprotein E and presenilin 1, respectively) alter the risk of Alzheimer's disease. We previously reported a delay of cognitive impairment in a person with autosomal dominant Alzheimer's disease caused by the *PSEN1*^{E280A} variant who also had two copies of the apolipoprotein E3 Christchurch variant (*APOE3*^{Ch}). Heterozygosity for the *APOE3*^{Ch} variant may influence the age at which the onset of cognitive impairment occurs. We assessed this hypothesis in a population in which the *PSEN1*^{E280A} variant is prevalent.

METHODS

We analyzed data from 27 participants with one copy of the *APOE3*^{Ch} variant among 1077 carriers of the *PSEN1*^{E280A} variant in a kindred from Antioquia, Colombia, to estimate the age at the onset of cognitive impairment and dementia in this group as compared with persons without the *APOE3*^{Ch} variant. Two participants underwent brain imaging, and autopsy was performed in four participants.

RESULTS

Among carriers of *PSEN1*^{E280A} who were heterozygous for the *APOE3*^{Ch} variant, the median age at the onset of cognitive impairment was 52 years (95% confidence interval [CI], 51 to 58), in contrast to a matched group of *PSEN1*^{E280A} carriers without the *APOE3*^{Ch} variant, among whom the median age at the onset was 47 years (95% CI, 47 to 49). In two participants with the *APOE3*^{Ch} and *PSEN1*^{E280A} variants who underwent brain imaging, ^{18}F-fluorodeoxyglucose positron-emission tomographic (PET) imaging showed relatively preserved metabolic activity in areas typically involved in Alzheimer's disease. In one of these participants, who underwent ^{18}F-flortaucipir PET imaging, tau findings were limited as compared with persons with *PSEN1*^{E280A} in whom cognitive impairment occurred at the typical age in this kindred. Four studies of autopsy material obtained from persons with the *APOE3*^{Ch} and *PSEN1*^{E280A} variants showed fewer vascular amyloid pathologic features than were seen in material obtained from persons who had the *PSEN1*^{E280A} variant but not the *APOE3*^{Ch} variant.

CONCLUSIONS

Clinical data supported a delayed onset of cognitive impairment in persons who were heterozygous for the *APOE3*^{Ch} variant in a kindred with a high prevalence of autosomal dominant Alzheimer's disease. (Funded by Good Ventures and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Quiroz can be contacted at yquiroz@mgh.harvard.edu. Dr. Lopera can be contacted at francisco.lopera@gna.org.co. Dr. Arboleda-Velasquez can be contacted at joseph_arboleda@meei.harvard.edu or at Schepens Eye Research Institute, Mass Eye and Ear, 20 Staniford St., Boston, MA 02114.

Drs. Quiroz, Aguillon, Aguirre-Acevedo, and Vasquez and Drs. Lopera and Arboleda-Velasquez contributed equally to this article.

This article was updated on June 19, 2024, at NEJM.org.

N Engl J Med 2024;390:2156-64.
DOI: 10.1056/NEJMoa2308583

In Antioquia, Colombia, there is a large family of approximately 6000 blood relatives, including more than 1000 carriers of the E280A variant of the *PSEN1* gene (encoding the protein presenilin 1). Autosomal dominant Alzheimer's disease is destined, with near 100% certainty, to develop in these carriers of *PSEN1*^{E280A}. Most of the carriers in this kindred have mild cognitive impairment in their mid-forties and dementia in their late forties.[1]

Common variants of the apolipoprotein E gene (*APOE*) influence the risk of Alzheimer's disease: *APOE4* is linked to high risk, *APOE3* is considered to confer a neutral risk, and *APOE2* is associated with relative protection.[2-5] In addition to *APOE*, several other genes, when variant, cause susceptibility to Alzheimer's disease; one of these is *PSEN1*.[6] We previously reported the case of a person with the *PSEN1*^{E280A} variant who also had two copies of the rare Christchurch variant (R136S) in *APOE3* (*APOE3*^{Ch}); in this person, mild cognitive impairment developed during her seventies — almost three decades after the expected age at onset.[7] In vivo and postmortem analyses showed that the *APOE3*^{Ch} variant was linked to reduced tau accumulation and reduced neuroinflammation, which led to less neurodegeneration and less cerebral amyloid angiopathy within the context of higher cortical amyloid burden than is observed in persons with the *PSEN1*^{E280A} variant and without the *APOE3*^{Ch} variant.[7,8] We aimed to ascertain whether heterozygosity for the *APOE3*^{Ch} variant (*APOE3*$^{Ch/e3}$, *APOE3*$^{Ch/e2}$, or *APOE3*$^{Ch/e4}$) would delay the age at onset of mild cognitive impairment or dementia in 27 persons with this genotype among members of the Colombian kindred with the *PSEN1*^{E280A} variant, which is associated with autosomal dominant Alzheimer's disease.

METHODS

STUDY DESIGN

In this retrospective study, we investigated data from a cohort of 1077 descendants in a family with the *PSEN1*^{E280A} variant,[9] which was assessed by our group from 1995 to 2022 (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The study was approved by the institutional review boards of the University of Antioquia, Colombia, and the Mass General Brigham integrated health care system. All the participants (or their representatives) provided written informed consent before the initiation of study procedures. (The document was read to participants who were unable to read, and they were asked to sign, if possible, or to provide a fingerprint.) Enrolled participants were 18 years of age or older and had at least one parent with the *PSEN1*^{E280A} variant, and therefore, mild cognitive impairment followed by autosomal dominant Alzheimer's disease was destined to occur. During data collection, investigators were unaware of the genetic status of the participants.

Participants underwent regular clinical and neuropsychological assessments. The intervals between testing have been analyzed previously and were homogeneous across *APOE3*^{Ch} carriers and noncarriers.[1,10] In one report involving this kindred,[1] testing in a group of 309 persons with the *PSEN1*^{E280} variant took place at a mean interval of 2 years (range, 1 to 11), and in another report,[10] at a median interval of 2 years (interquartile range, 1 to 3).

Neuropsychological assessments were conducted in Spanish with the use of a battery that has been adapted and validated for the detection of Alzheimer's disease–related cognitive impairment in this kindred, which included the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), the Trail Making Test, and the Rey–Osterrieth complex figure, among other assessments.[10-12] Using these data, neurologists and neuropsychologists, who were unaware of the genetic variants in the specific participants, retrospectively classified participants as having normal cognitive status, mild cognitive impairment, or dementia, according to the National Institute on Aging and the Alzheimer's Association Workgroup criteria for mild cognitive impairment due to Alzheimer's disease[13] and the related Workgroup criteria for dementia due to Alzheimer's disease.[14]

We also used the Functional Assessment Staging (FAST) system, which is a scale to assess the level of functional impairment in patients with dementia (scores range from 1 [no impairment] to 7 [total dependence]), and the Mini-Mental State Examination (MMSE; scores range from 0 to 30, with lower scores indicating greater cognitive impairment). The criteria for mild cognitive impairment were as follows: for persons with less than 9 years of education, a FAST score

of at least 3 and an MMSE score of no more than 24; and for persons with 9 or more years of education, an MMSE score of no more than 26. The criteria for mild dementia were as follows: for persons with less than 9 years of education, a FAST score of at least 4 and an MMSE score of no more than 22; and for persons with 9 or more years of education, an MMSE score of no more than 24.

PARTICIPANTS

In an extended family of 1077 *PSEN1*^{E280A} carriers in whom autosomal dominant Alzheimer's disease was destined to develop, we identified 121 carriers of the *APOE3*^{Ch} variant (Fig. S2), among whom 1 had the previously reported *PSEN1*^{E280A} variant and was homozygous for *APOE3*^{Ch} and 27 were carriers of *PSEN1*^{E280A} and were heterozygous for the *APOE3*^{Ch} variant. Of these 27 persons who were heterozygous for *PSEN1*^{E280A} and *APOE3*^{Ch}, 1 died at 57 years of age without cognitive symptoms (last examination at 2 years before death), 13 had mild cognitive impairment or dementia, and 13 did not meet the criteria for mild cognitive impairment or dementia (and are not identified in the family tree in order to protect privacy) (see the Supplementary Appendix).

These 27 persons who were heterozygous for the *APOE3*^{Ch} and *PSEN1*^{E280A} variants (i.e., the group of interest) had extensive clinical data and underwent neuropsychological testing. Two participants also had neuroimaging data, and 4 also underwent postmortem brain examinations. Genotyping was performed for the *PSEN1*^{E280A} and *APOE* variants, as previously described.[7]

NEUROIMAGING METHODS

One participant underwent amyloid (^{11}C-Pittsburgh compound B) and tau (^{18}F-flortaucipir) positron-emission tomographic (PET) imaging at Massachusetts General Hospital in Boston. Two participants (Participants 1 and 2) underwent structural magnetic resonance imaging and ^{18}F-fluorodeoxyglucose (FDG) PET imaging at the Hospital Pablo Tobón Uribe in Medellín, Colombia.

NEUROPATHOLOGICAL METHODS

Neuropathological material, which was obtained with the use of previously described techniques,[8] was available from four persons who were heterozygous for the *PSEN1*^{E280A} and *APOE3*^{Ch} variants (Participants 3 through 6), from five carriers of *PSEN1*^{E280A} and *APOE3* (Participants 7 through 11), and from one person who was a *PSEN1*^{E280A} carrier and was homozygous for *APOE3*^{Ch} (Participant 12). Immunohistochemical staining was performed uniformly for pathological markers of Alzheimer's disease in cortical areas, followed by quantitative morphologic evaluation of vascular pathologic features in all the participants. ImageJ software, version 1.52p (National Institutes of Health), was used for image analysis for all findings. A description of these methods is provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We retrospectively estimated the cumulative incidence function, which represents the probability of mild cognitive impairment or dementia over time, considering the time from the date of birth to the onset of mild cognitive impairment or dementia in all the participants available from the cohort described above. We calculated the restricted mean and median survival times (i.e., the time to mild cognitive impairment or dementia) with the standard error and 95% confidence intervals, respectively, with categorization according to *APOE3*^{Ch} genotype. For participants with censored data, the times to these end points were calculated to the date of the last medical evaluation. We considered death to be a competing event for the analyses because death could occur before the onset of mild cognitive impairment or dementia.

To control for potential confounding factors of sex, *APOE* genotype, and years of formal education, we established a matched sample between carriers and noncarriers of the *APOE3*^{Ch} variant. For this matching, we used the nearest-neighbor method with the propensity score as a measure of similarity,[15] resulting in a ratio of approximately 12 noncarriers to 1 *APOE3*^{Ch} carrier, which was determined by the MatchIt package in R software, after the maximum ratio was initially set at 20:1. To examine the balance of the groups before and after matching, we used a standard mean (or proportion) difference (Fig. S3). A subhazard ratio[16] was calculated in an exploratory analysis to estimate the association between *APOE3*^{Ch} status and the time to mild cognitive impairment or dementia (Table S1 and Fig. S4). Statistical analyses were performed with the use of R software, version 4.3.1.[17]

RESULTS

CLINICAL AND NEUROIMAGING FINDINGS IN TWO LIVING PERSONS HETEROZYGOUS FOR *APOE3*^{CH}

The first participant was a man with the genotype *PSEN1*^{E280A}–*APOE3*$^{Ch/\varepsilon 3}$ and 11 years of formal education. At 47 years of age, he had no subjective or objective cognitive problems or changes in daily functioning, and neurologic examinations and testing were normal (FAST score, 1; MMSE score, 28). At 49 years of age, his cognitive test performance was within normal limits for his age and educational level, and he reported having mild subjective memory concerns (FAST score, 2; MMSE score, 27). At 51 years of age, he received a diagnosis of mild cognitive impairment (FAST score, 3; MMSE score, 25) and had a decline in semantic fluency (decline in the CERAD Animal Fluency score from the 79th to 53rd percentile [range in normal populations, 25th to 75th]), executive functioning (decline in the Trail Making Test score from the 45th to 42nd percentile [range in normal populations, 25th to 75th]) and memory recall (decline in the CERAD Word List Recall score from the 23rd to 1st percentile [range in normal populations, 25th to 75th]). At 54 years of age, he received a diagnosis of mild dementia (FAST score, 4; MMSE score, 21).

PET imaging in this participant at 51 years of age showed slightly higher levels of brain cortical amyloid plaque (Aβ) burden than was seen in *PSEN1*^{E280A} carriers in whom Alzheimer's disease had developed at the expected age in this kindred (distribution volume ratio [DVR], 1.68 vs. a mean [±SD] of 1.50±0.12 among *PSEN1*^{E280A} carriers with cognitive impairment) but a more limited tau burden in brain regions related to Alzheimer's disease, including the entorhinal cortex (standardized uptake value ratio [SUVR], 1.33 vs. a mean of 1.60±0.29) (Fig. 1 and Fig. S5). When this participant was 53 years of age, ^{18}F-FDG PET imaging showed a cerebral metabolic rate for glucose in the precuneus within the range of younger *PSEN1* variant carriers in whom mild cognitive impairment had developed at a typical age in this kindred (SUVR, 1.15 vs. a mean of 1.23±0.17) (Fig. 1).

The second participant was a man with genotype *PSEN1*^{E280A}–*APOE3*$^{Ch/\varepsilon 2}$ who was illiterate and had received no formal education. His evaluation at 38 years of age showed slow processing speed and low verbal memory recall, although the scores were within the normal limits for his educational level (FAST score, 2; MMSE score, 27). He reported subjective cognitive concerns at 42 years of age, and his performance on the MMSE was reduced as compared with previous scores (FAST score, 2; MMSE score, 22) in the context of depression (Geriatric Depression Scale-15 score, 6; on a scale from 0 to 15, with a score above 5 indicating depression). His overall objective performance, however, was within the normal limits for his age and educational level. His scores were similar to those on previous verbal and nonverbal memory tests, and he did not have functional decline, so he did not meet the criteria for mild cognitive impairment at that time.

At 52 years of age, with no intervening testing after the previous battery, this participant had a decline in verbal memory, and his family reported having increased concerns about his cognitive condition despite preserved functional independence. At that time, he met the criteria for mild cognitive impairment (FAST score, 3; MMSE score, 25). (When the numerical results on the MMSE and FAST diverged, the clinical study team placed more emphasis on the FAST score because it reflects functional capabilities; the study team retrospectively classified this person as having mild cognitive impairment at this time point.) When this participant was 57 years of age, functional decline led to a diagnosis of mild dementia (FAST score, 4; MMSE score, not available). At 62 years of age, his memory skills declined further, although his naming and semantic fluency skills remained similar to the results on previous tests. He required more support to complete instrumental activities of daily living and had progression to moderate dementia (FAST score, 5; MMSE score, 18). When this participant was 64 years of age, FDG PET imaging showed a relatively preserved cerebral metabolic rate for glucose in the precuneus (SUVR, 1.35) (Fig. 1) as compared with *PSEN1*^{E280A} carriers in whom mild cognitive impairment had developed at the expected age. Imaging for Aβ and tau was not conducted owing to a lack of local availability and travel restrictions to the United States.

AGE AT ONSET IN PERSONS WITH *PSEN1*^{E280A} HETEROZYGOUS FOR *APOE3*^{CH}

To evaluate the time to mild cognitive impairment or dementia, with accounting for known

influencing factors, we matched *APOE3*^{Ch} carriers with noncarriers on the basis of sex, educational level, and *APOE* genotype, as described above. This matching process yielded a subgroup of 353 participants for this part of the study (Table S2). Figures 2A and 2B show the time to mild cognitive impairment or dementia among the 1077 *PSEN1*^{E280A} carriers, including 27 carriers of the

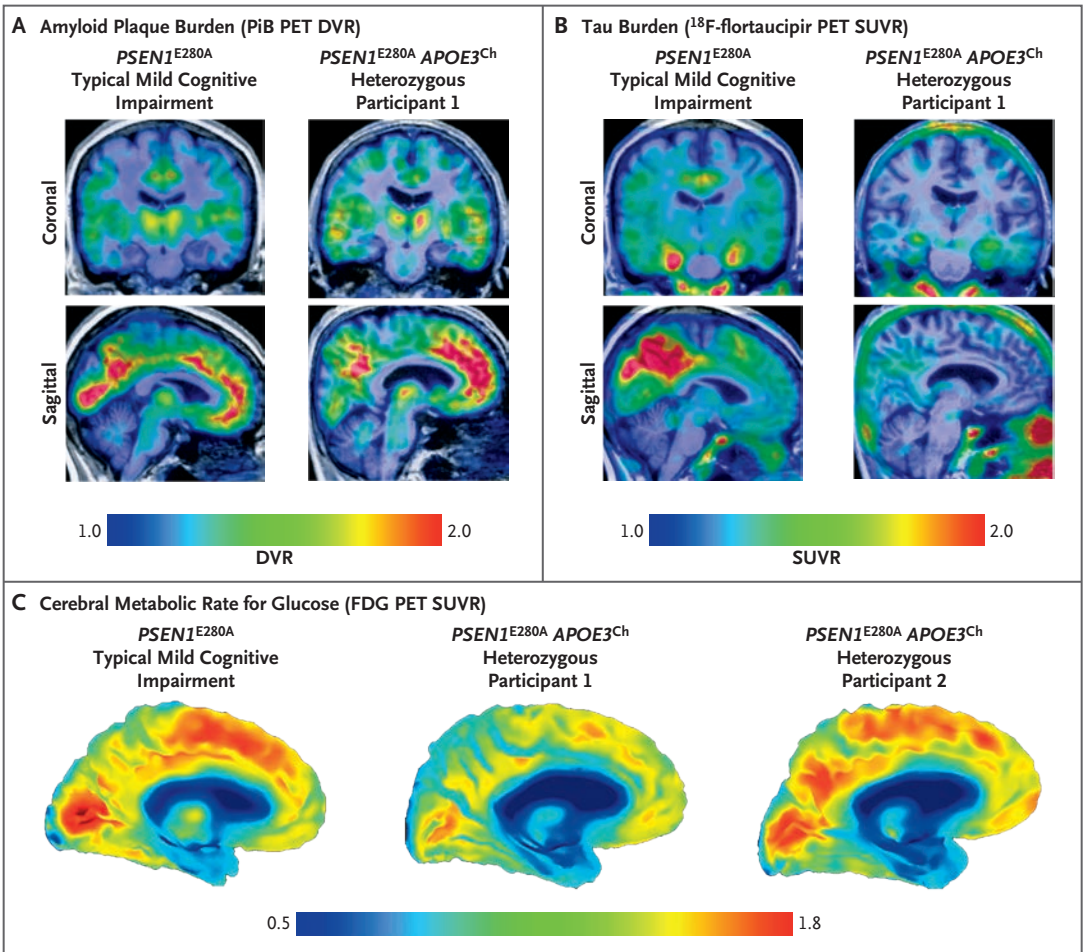

Figure 1. Limited Tau Pathological Findings and Relatively Preserved Regional Cerebral Metabolic Activity in Persons Heterozygous for the *PSEN1*^{E280A} and *APOE3*^{Ch} Variants.

Shown are baseline amyloid-β positron-emission tomographic (PET) images (Panel A; ^{11}C-Pittsburgh compound B [PiB]) and tau PET images (Panel B; ^{18}F-flortaucipir). Sample coronal views (upper images) and sagittal views (lower images) are shown for each. For visual comparison, samples that were obtained from two participants are shown: from a typical person with the E280A variant of presenilin 1 (*PSEN1*^{E280A}) who had mild cognitive impairment (Panels A and B, left images), and from a person with the *PSEN1*^{E280A} variant who was also heterozygous for the *APOE3*^{Ch} variant (right images). The color-coded scale bar indicates the PiB distribution volume ratio (DVR) or flortaucipir standardized uptake value ratio (SUVR) values; blue represents the lowest binding and red represents the highest binding, with values ranging from 1.0 to 2.0. The person who was heterozygous for the *APOE3*^{Ch} variant had greater amyloid-β plaque burden and a relatively limited tau burden as compared with persons with the *PSEN1*^{E280A} variant in whom the onset of mild cognitive impairment occurred at the typical age in this kindred, as exemplified by the person whose images are shown here. Panel C shows ^{18}F-fludeoxyglucose (FDG) PET images indicating the precuneus cerebral metabolic rate for glucose. In all three panels, the sample was obtained from a person with the *PSEN1*^{E280A} variant. The leftmost image in Panel C shows the sample of a person in whom the onset of mild cognitive impairment occurred at a typical age in this kindred, the middle image a sample from a person heterozygous for the *APOE3*^{Ch} variant, and the rightmost image a sample from a second person heterozygous for the *APOE3*^{Ch} variant. The color-coded scale bar indicates FDG SUVR values; blue represents lowest values and red represents highest values, with values ranging from 0.5 to 1.8. SUVR values represent the regional cerebral metabolic rate for glucose.

APOE3^{Ch} variant. Figures 2C and 2D show the data for the matched samples that had been obtained from 326 persons who did not have the *APOE3*^{Ch} variant and from 27 carriers of the *APOE3*^{Ch} variant.

Survival analyses of the matched samples showed that the median age at the onset of mild cognitive impairment was 52 years (95% CI, 51 to 58) among *APOE3*^{Ch} carriers, as compared with approximately 47 years (95% CI, 47 to 49) in the matched sample of noncarriers. The median age at the onset of dementia among *APOE3*^{Ch} carriers was 54 years (95% CI, 49 to 57), which indicated an apparent delay as compared with the noncarriers, among whom the median age at onset was 50 years (95% CI, 48 to 51) (Table S3). Some imprecision in the ages at the onset of mild cognitive impairment and dementia in both groups may have been introduced by gaps in testing that could have been as long as 5 years.

PATHOLOGICAL FINDINGS IN PERSONS WITH *APOE3*^{CH}

The four participants who were heterozygous for *APOE3*^{Ch} and had available autopsy material had a greater amyloid-β plaque burden and a relatively limited tau burden as compared with *PSEN1*^{E280A} variant carriers in whom mild cognitive impairment had occurred at the kindred's typical age as determined by qualitative visual inspection, but this observation was not quantified. The regional distribution patterns of amyloid and tau in the participants were typical of those in persons with Alzheimer's disease. In our previous article, we reported that the participant, who was homozygous for the *APOE3*^{Ch} variant, had a distribution of tau deposition in the cortex that largely spared the frontal lobe and was prominent in the occipital lobe.[7,8] In contrast, the brains of the *APOE3*^{Ch} heterozygous carriers in the current study did not show this pattern of tau deposition. Findings were within the expected range of tau deposition variation and without visible association between the extent of tau pathological findings and the age at onset of dementia (Table S4 and Fig. S6).

Pathological findings of cerebral amyloid angiopathy were less prominent in the frontal cortex in *APOE3*^{Ch} carriers (Fig. S7A) than in noncarriers. In addition, *APOE3*^{Ch} carriers had a numerically lower percentage of partial involvement of vessel walls (present only in a portion the annular circumferences of walls) than noncarriers, with pathological findings of cerebral amyloid angiopathy in frontal and occipital cortexes (Figs. S7B and S7C). The participant in the earlier study, who was homozygous for the *APOE3*^{Ch} variant, was less affected in all these measurements of cerebral amyloid angiopathy than the current cohort of participants who were heterozygous for the variant. However, direct comparisons between homozygous and heterozygous participants cannot be made because the homozygous participant in the earlier case report was much older than the participants in the current cohort. Furthermore, vessels that were analyzed in participants who were heterozygous or homozygous for *APOE3*^{Ch} showed greater similarity to controls in terms of length, branching pattern, and spacing between them than those obtained from *PSEN1*^{E280A} carriers without the *APOE3*^{Ch} variant (Fig. S8).

DISCUSSION

We report clinical, cognitive testing, neuroimaging, and neuropathological data from heterozygous *APOE3*^{Ch} variant carriers among participants with familial Alzheimer's disease due to *PSEN1*^{E280A} from an extensively studied group of persons in Colombia. Within the limits of confidence that could be extracted from the data obtained from 27 participants who were heterozygous for the *APOE3*^{Ch} variant, as compared with 1050 participants who did not have this variant, we found that they had an onset of mild cognitive impairment and dementia, analyzed retrospectively, that was approximately 5 years later for mild cognitive impairment and 4 years later for dementia; we also found that they had different patterns on PET imaging. The precision of these estimates was probably not affected by irregular intervals between testing for the reasons noted above, including homogeneity of intervals across the entire group of persons with the *PSEN1*^{E280A} variant. The apparent delay in the onset of clinical features that were attributable to autosomal dominant Alzheimer's disease in participants who were heterozygous for the *APOE3*^{Ch} variant was less than that observed in a previously reported case of *APOE3*^{Ch} homozygosity.

Our original report about one person in this population who was homozygous for *APOE3*^{Ch}[7]

Figure 2 (facing page). Cumulative Incidence of Mild Cognitive Impairment and Dementia among Persons with the *PSEN1*^{E280A} Variant.

Shown are the cumulative incidence functions of mild cognitive impairment and dementia among persons with the *PSEN1*^{E280A} variant, 27 of whom had the *APOE3*^{Ch} variant and 1050 of whom did not. The analyses of mild cognitive impairment shown in Panel A and of dementia shown in Panel B included all the participants. The analyses of mild cognitive impairment shown in Panel C and of dementia shown in Panel D included matched samples from 27 persons with the *APOE3*^{Ch} variant and 326 persons without this variant. Participants were matched for sex, *APOE* genotype, and years of formal education. Death without a diagnosis of mild cognitive impairment or dementia was a competing risk. Shading indicates the 95% confidence interval.

also discussed four persons with the *PSEN1*^{E280A} variant who were heterozygous for *APOE3*^{Ch}, and we did not describe a delay in the age at onset of cognitive impairment. This finding led us[7] and others[18] to initially conclude that *APOE3*^{Ch} heterozygosity was not protective. The analyses that we present here encompassed a larger cohort with *APOE3*^{Ch} and *PSEN1*^{E280A} variants, with more comprehensive longitudinal clinical characterization, and indicated that *APOE3*^{Ch} heterozygosity is apparently linked to delay in the expected cognitive impairment.

The PET imaging findings in two participants heterozygous for the *APOE3*^{Ch} variant, which showed limited tau pathological findings and relatively preserved glucose metabolism, suggest that the delayed clinical onset that is associated with the *APOE3*^{Ch} variant may involve mechanisms that limit tau pathologic conditions and neurodegeneration, even in the presence of a high burden of Aβ amyloid plaque. These findings are consistent with our observations in the previously reported case of a person who was homozygous for the *APOE3*^{Ch} variant, but these are speculations and were not systematically studied owing to the small sample.

Limitations of this study arise from the relatively small number of persons who have both the *APOE3*^{Ch} and *PSEN1*^{E280A} variants, as well as the homogeneity of the population belonging to a genetic isolate.[19] These limitations increase uncertainty around differences in the point estimates for the ages at the onset of mild cognitive impairment and dementia. Further studies involving larger and more ethnically diverse samples of persons with Alzheimer's disease may shed light on any apparent protective effect of the *APOE3*^{Ch} variant. Furthermore, the biologic insight that the *APOE3*^{Ch} variant is protective in this group of persons from the Antioquia, Colombia, cohort may not translate to sporadic Alzheimer's disease or to other groups.

The clinical, cognitive, neuroimaging, and neuropathological data that we present here provide evidence that *APOE3*^{Ch} heterozygosity delayed the onset of cognitive impairment in a form of autosomal dominant Alzheimer's disease and may have a protective effect against Alzheimer's disease and neurodegeneration in this population.

Supported by grants from Good Ventures (to Drs. Krasemann and Sepulveda-Falla and to Dr. Arboleda-Velasquez), by the Remondi Family Foundation (to Dr. Arboleda-Velasquez), by grants (R01AG054671, to Dr. Quiroz; RF1AG077627, to Drs. Quiroz and Lopera; K99AG073452, to Dr. Vila-Castelar; and P30AG072980, to Dr. Reiman) from the National Institute on Aging (NIA), by the Massachusetts General Hospital (MGH) Executive Committee on Research (MGH Research Scholar Award, to Dr. Quiroz), by the Alzheimer's Association (to Dr. Quiroz), by a grant (RM1NS132996, to Drs. Quiroz, Lopera, and Arboleda-Velasquez) from the National Institute of Neurological Disorders and Stroke (NINDS), by the National Institutes of Health (to Dr. Lopera), by Roche (to Dr. Lopera), by the Banner Alzheimer's Foundation for the Alzheimer's Prevention Initiative Colombia Registry and the Alzheimer's Prevention Initiative (API) and the API ADAD Colombia Trial (to Drs. Reiman and Lopera), by a joint grant (RF1NS110048, to Dr. Sepulveda-Falla) from NINDS and NIA, by a grant from the Werner Otto Foundation (to Drs. Krasemann and Sepulveda-Falla), by the German Federal Ministry of Education and Research (UndoAD-Project, to Drs. Glatzel and Sepulveda-Falla), by grants (KR 1737/2-1, to Dr. Krasemann; and SFB877, to Dr. Glatzel) from the German Research Foundation, by an Alzheimer's Association Research Fellowship (to Dr. Langella), and by the NOMIS Foundation (to Dr. Reiman).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.

APPENDIX

The authors' full names and academic degrees are as follows: Yakeel T. Quiroz, Ph.D., David Aguillon, M.D., Ph.D., Daniel C. Aguirre-Acevedo, Ph.D., Daniel Vasquez, M.D., Yesica Zuluaga, M.A., Ana Y. Baena, M.A., Lucia Madrigal, Ph.D., Liliana Hincapié, B.S., Justin S. Sanchez, B.A., Stephanie Langella, Ph.D., Rafael Posada-Duque, Ph.D., Jessica L. Littau, M.Sc., Nelson D. Villalba-Moreno, M.Sc., Clara Vila-Castelar, Ph.D., Liliana Ramirez Gomez, M.D., Gloria Garcia, M.S., Elizabeth Kaplan, B.S., Sofia Rassi Vargas, M.D., J. Alejandro Ossa, B.S., Pablo Valderrama-Carmona, B.S., Paula Perez-Corredor, M.S., Susanne Krasemann, Ph.D., Markus Glatzel, M.D., Kenneth S. Kosik, M.D., Keith Johnson, M.D., Reisa A. Sperling, M.D., Eric M. Reiman, M.D., Diego Sepulveda-Falla, M.D., Francisco Lopera, M.D., and Joseph F. Arboleda-Velasquez, M.D., Ph.D.

The authors' affiliations are as follows: Massachusetts General Hospital (Y.T.Q., J.S.S., S.L., C.V.-C., L.R.G., E.K., K.J., R.A.S.), the Departments of Neurology (Y.T.Q., J.S.S., L.R.G., K.J., R.A.S.), Psychiatry (Y.T.Q., S.L., C.V.-C., E.K.), and Ophthalmology (P.P.-C., J.F.A.-V.), Harvard Medical School, Brigham and Women's Hospital (K.J., R.A.S.), and Schepens Eye Research Institute, Mass Eye and Ear (P.P.-C., J.F.A.-V.) — all in Boston; Grupo de Neurociencias de Antioquia, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia (Y.T.Q., D.A., D.C.A-A., D.V., Y.Z., A.Y.B., L.M., L.H., R.P.-D., G.G., S.R.V., J.A.O., P.V.-C., F.L.); the Institute of Neuropathology, University Medical Center Hamburg–Eppendorf, Hamburg, Germany (J.L.L., N.D.V.-M., S.K., M.G., D.S-F.); the Neuroscience Research Institute, Department of Molecular Cellular Developmental Biology, University of California, Santa Barbara, Santa Barbara (K.S.K.); and the Banner Alzheimer's Institute, Phoenix, the University of Arizona, Tucson, and Arizona State University, Tempe — all in Arizona (E.M.R.).

REFERENCES

1. Acosta-Baena N, Sepulveda-Falla D, Lopera-Gómez CM, et al. Pre-dementia clinical stages in presenilin 1 E280A familial early-onset Alzheimer's disease: a retrospective cohort study. Lancet Neurol 2011;10:213-20.

2. Strittmatter WJ, Saunders AM, Schmechel D, et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A 1993;90:1977-81.

3. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 1993;261:921-3.

4. Reiman EM, Arboleda-Velasquez JF, Quiroz YT, et al. Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study. Nat Commun 2020;11:667.

5. Corder EH, Saunders AM, Risch NJ, et al. Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. Nat Genet 1994;7:180-4.

6. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature 1995;375:754-60.

7. Arboleda-Velasquez JF, Lopera F, O'Hare M, et al. Resistance to autosomal dominant Alzheimer's disease in an APOE3 Christchurch homozygote: a case report. Nat Med 2019;25:1680-3.

8. Sepulveda-Falla D, Sanchez JS, Almeida MC, et al. Distinct tau neuropathology and cellular profiles of an APOE3 Christchurch homozygote protected against autosomal dominant Alzheimer's dementia. Acta Neuropathol 2022;144:589-601.

9. Lopera F, Ardilla A, Martínez A, et al. Clinical features of early-onset Alzheimer disease in a large kindred with an E280A presenilin-1 mutation. JAMA 1997;277:793-9.

10. Aguirre-Acevedo DC, Lopera F, Henao E, et al. Cognitive decline in a Colombian kindred with autosomal dominant Alzheimer disease: a retrospective cohort study. JAMA Neurol 2016;73:431-8.

11. Aguirre-Acevedo DC, Jaimes-Barragán F, Henao E, et al. Diagnostic accuracy of CERAD total score in a Colombian cohort with mild cognitive impairment and Alzheimer's disease affected by E280A mutation on presenilin-1 gene. Int Psychogeriatr 2016;28:503-10.

12. Torres VL, Vila-Castelar C, Bocanegra Y, et al. Normative data stratified by age and education for a Spanish neuropsychological test battery: results from the Colombian Alzheimer's prevention initiative registry. Appl Neuropsychol Adult 2021;28:230-44.

13. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270-9.

14. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263-9.

15. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083-107.

16. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med 2017;36:4391-400.

17. R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2023.

18. Cochran JN, Acosta-Uribe J, Esposito BT, et al. Genetic associations with age at dementia onset in the PSEN1 E280A Colombian kindred. Alzheimers Dement 2023;19:3835-47.

19. Bedoya G, Montoya P, García J, et al. Admixture dynamics in Hispanics: a shift in the nuclear genetic ancestry of a South American population isolate. Proc Natl Acad Sci U S A 2006;103:7234-9.