SCD and Genetic Propensity for Dementia beyond Apolipoproteinε4

Subjects: Health Care Sciences & Services

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Subjective cognitive decline (SCD) has been described as a probable early stage of dementia, as it has consistently appeared to precede the onset of objective cognitive impairment. SCD is related to many risk factors, including genetic predisposition for dementia. The Apolipoprotein (APOE) ε4 allele, which has been thoroughly studied, seems to explain genetic risk for SCD only partially.

Keywords: subjective cognitive decline ; cognitive complaints ; early dementia stages ; genetic propensity

1. Introduction

Nowadays, awareness of brain health and symptoms of dementia in the general population is growing. Therefore, an increasing number of cognitively unimpaired individuals seek medical help for their cognitive function [1]. A new medical term, subjective cognitive decline (SCD), was conceived in 2014 in order to describe an individual's perception of their own cognitive impairment [2]. At the same time, the SCD initiative (SCD-I), an international working group, established standardized criteria for SCD [2], consisting of a self-experienced persistent decline in cognition, unrelated to an acute event, in comparison to a previously normal cognitive status, along with normal performance on standardized cognitive tests.

Existing data suggest that SCD may precede the onset of objective memory impairment [3], acting as an early dementia stage [4]. Specifically, longitudinal studies have shown that individuals reporting SCD had an increased incidence of dementia [5][6]. Moreover, cognitively normal (CN) individuals with SCD have been related to abnormal Alzheimer's disease (AD) biomarkers, such as low cerebrospinal fluid amyloid-beta [7][8], as well as low hippocampal and medial temporal cortex volume [9][10]. Individuals with SCD have also been associated with peripheral blood biomarkers [11] of AD, such as the peripheral blood transcriptome, which might be considered a pre-disease biomarker.

However, it remains uncertain which factors affect the progression from SCD to dementia. In fact, SCD has been related to many different underlying causes, apart from preclinical dementia, including psychiatric symptoms or disorders [12], medication effects [13], different personality traits [14], poor physical functioning and alcohol abuse [15]. Additionally, the context (community-based or clinical setting) [16] as well as the way SCD is assessed (via a single question or structured questionnaire) [17] have been shown to affect its prevalence. Thus, individuals with SCD appear to be a highly heterogeneous population. Given that, to date, there is no single gold standard instrument which can differentiate individuals with SCD from those without SCD in the clinical setting; SCD is not considered a diagnostic entity in the Diagnostic and Statistical Manual of Mental Disorders [18]. What is of utmost importance, though, is to identify those individuals belonging in the predementia spectrum in whom SCD may yield additional information for future objective cognitive decline [19].

In an effort to determine the factors increasing the risk of an individual with SCD to develop objective cognitive impairment, the SCD-I working group has proposed the SCD-plus criteria [2]. The specific criteria focused on memory rather than other cognitive domains. Moreover, confirmation of perceived cognitive decline by an informant was included, in accordance with previous studies showing that partner reports of memory impairment were more consistent in estimating objective impairment and predicting longitudinal decline [20][21]. Interestingly, Apolipoprotein (APOE) ε4 carriership, which is most commonly associated with late onset AD [22], was also included in the SCD-plus criteria, enhancing the hypothesis of an association between SCD and genetic predisposition for dementia. Thus, genetic risk factors for AD might be helpful in distinguishing individuals with SCD with a higher risk for dementia.

The genetic profile of individuals with SCD, beyond APOE ε4, is relatively unexplored. Family history (FH) of AD has been related to increased worrying about dementia symptoms [23], as well as increased risk of developing dementia [24]. Thus,

family studies investigating siblings or individuals with positive family history (FH) of AD in relation to SCD have been conducted. Furthermore, other genes beyond the APOE ε4 allele have appeared to contribute to SCD, including presenilin-1 (PSEN1) gene mutations [25][26] as well as period circadian clock 2 (PER_2) gene polymorphisms [27]. Nevertheless, only a small proportion of relevant genes has been studied. Additionally, the polygenic risk for AD has recently emerged, with research concerning the polygenic risk for SCD being relatively limited.

2. Family Studies

To begin with, FH of AD was studied using first-degree relatives of patients with AD as a composite risk factor for dementia, as shown previously [28]. FH studies have yielded conflicting results regarding the association of FH of AD and SMC. On the one hand, the longitudinal study of Nicholas et al. [29] as well as the case–control study of Heun et al. [30] showed that SMC were not associated with FH of AD. On the other hand, Tsai et al. [31] as well as Haussman et al. [32] found that SMC were related to FH of AD in all participants and in the CN group, respectively. The most recent multicenter study of Heser et al. [33] showed a strong association between SMC and FH of AD (p = 0.008), as well as increased all-type dementia risk (p = 0.002). In that study, the authors considered a negative participant's answer valid regarding FH only if the respective maternal age or age of death was at least 75 years (or paternal age at least 70 years), resulting in a very high missing data rating for FH (approximately 60%). Additionally, the mean age of participants was approximately 80 years old; hence, the results may not apply to younger cohorts.

Selection bias is the most important limitation of FH studies, as some participants were excluded due to absence of living relatives [33], while self-selection may have resulted in a healthier sample with fewer memory complaints than the general population [31]. In any case, the generalizability of results is limited. Moreover, SCD estimation in most family studies was made using simple questions, either via in-person or telephone interviews, except for one study [29], in which a structured SMC questionnaire was used. Thus, the SMC assessment raises questions concerning the reliability of the results, as simple questions are likely to be vague and, therefore, hide useful information, leading to an increased risk of misclassification. Last but not least, an important concern regarding FH studies, compared to single genetic variants such as APOE ε4, is the possible contribution of the psychological distress caused by the knowledge of being at increased risk of SCD. There is an ongoing debate about whether disclosing genetic dementia risk information has negative psychological consequences on relatives of patients with AD [34].

All twin studies [35][36][37] concluded that there was no association between SCD and genetic background. However, questions arise regarding the generalizability of these results in different populations, as the ethnic background of participants was limited, and all studies included community-dwelling populations, while one study included only male individuals [36]. The twin study design itself offers an advantage, allowing researchers to differentiate between the contributions of genetic and environmental factors [35]; thus, the conduction of multi-ethnic, larger twin studies in the future is essential.

3. Other Genes beyond APOE ε4

As far as other alleles beyond APOE ε4 are concerned, only PSEN1 280A mutation carriers were cross-sectionally related to SCD [25]. PSEN1 280A mutation, which is recognized as the most common cause of familial early-onset AD with complete penetrance, meaning that eventually all carriers will develop AD until their fifth decade of age, appears to be associated with SCD as well. Prospectively, KIBRA T allele [38], which is involved in cell migration and synaptogenesis, as well as PER2 G carriership [27], which is involved in sleep–wake cycle alterations and neurodegeneration, were related to increased longitudinal cognitive decline in subjects with SCD; however, the number of events was relatively small. Among the rest of the gene variants studied [26][39], neither the APOE ε7 allele nor the PSEN-1 Glu318Gly mutation were directly associated with SCD and longitudinal cognitive decline, even though these were found only in the SMC groups. The 50 genes related to vascular damage [40] were not associated with cognitive decline in subjects with SMC receiving anti-hypertensive treatment, similarly to inflammatory genes studied in the past [41].

The aforementioned studies offered indications rather than conclusions concerning the genetic profile of individuals with SMC, presenting remarkable limitations, such as the generalizability of the findings due to the specific features and characteristics of the population samples and the statistical power being limited by the relatively short sample sizes. Additionally, each study used a different questionnaire to evaluate SMC, enhancing the heterogeneity of participants' answers. A recent study aimed to link questionnaire data from international aging studies and was able to differentiate items that made the greatest contribution to measurement precision, opening new perspectives of developing new self-perceived cognitive functioning questionnaires [42]. In any case, many more genes need to be investigated, such as the bridging integrator 1 (BIN_1), clusterin (CLU), and phosphatidylinositol-binding clathrin assembly protein (PICALM), which

have been previously shown to be associated with increased risk for late onset AD [43] and also predict objective verbal memory ($p < 0.05$) [44].

4. Polygenic Risk

To date, polygenic risk in subjects with SCD has not been studied in depth. Only in one study [45] higher PRS for AD was associated with increased amyloid positivity as well as progression to AD in a population with SCD (an association which was no longer significant after adjusting for APOE), while the other two studies [36][46] which used a different PRS for AD did not show an association. Another study, not included in the results due to the unavailability of the full text, examined the application of a PRS algorithm (genoSCORE), including over 100.000 genetic variations related to AD, in subjects with SCD and MCI in a London Memory Clinic [47], with promising results, as individuals with SCD who were most likely to decline cognitively towards AD had higher PRS values. Taking the above-mentioned results [36][45][46] into consideration, it appears that a variety of different genes is implicated in SCD, just like AD [48]; thus, the PRS method can be helpful in future studies in revealing the genetic underpinnings of SCD.

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