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ApolipoproteinE ε4 allelic variant, cognitive decline and psychosis in Alzheimer disease: a review of the literature and suggestions for upcoming studies

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ABSTRACT – Apolipoprotein E (ApoE) ε4 allele represents a well known vascular risk factor for developing Alzheimer disease (AD) and differences in ApoE genotypes may explain a part of the variability in AD phenotypes. In fact, ApoE ε4 allele possession seems to be associated with a more precocious age of onset, greater episodic memory impairment, and psychotic symptoms. The first question we discuss regards the role of ApoE ε4 on cognitive progression of AD. In fact, while a general agreement exists about the role played by ApoE ε4 on the precocious onset of AD, cognitive decline has been differently associated with ApoE ε4 allele possession in AD patients in a continuum of faster decline, no effect, and slower decline. An attemptable interpretation is that the biological processes leading to the onset of AD are different from those involved in determining its clinical course. The second question regards the possible relationship between the presence of the degenerative pathological hallmarks of the disease in specific cerebral areas and different cognitive or behavioural symptoms. In fact, there is evidence that degenerative pathology in hippocampal formation and frontal cortex reflects the progression of cognitive deficits in brain aging and AD and that hypometabolism in right frontal lobe and greater frontal neuropsychological deficits occur in AD patients with psychosis in comparison to those without. The third question regards, specifically, the relationship between ApoE ε4 variant and behavioural symptoms. In fact, there is evidence supporting the link between being carriers of ApoE ε4 allele and severity of delusions, mostly at the early stage of the illness. In an interpretative challenge, we suggest that the link between being carriers of ApoE ε4 allele and suffering from delusions in AD may be explained by frontal

lobe dysfunctions. Finally, we hypothesize that the most precocious onset of AD illness, described in carriers of ApoE ε4 allelic variant, may also be related to the precocious onset of psychotic symptoms, which produces caregiver and patient distress and requires immediate assessment and treatment.

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Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder that typically occurs after age 65, with incidence increasing concurrently with age. AD has a multidimensional clinical expression that manifests in three domains: a) neuropsychological deficits; b) functional impairment and c) behavioural disorders. In the diagnostic assessment process, neuropsychological and functional domains only are taken into consideration. On the contrary, behavioural and psychological symptoms of dementia (BPSD) are not mentioned in both DSM-IV and NINCDS-ARDRA criteria for diagnosis of AD. However, numerous studies demonstrated that BPSD are important components of dementia, contributing to both patient disability and caregiver distress (Cummings *et al.* 1994, Esiri 1996, Burns and Rabins 2000).

During the course of the illness, while cognitive impairment becomes more serious, BPSD seem to fluctuate, appearing either in the early or later phases of dementia (Jost & Grossberg 1995, Jost & Grossberg 1996, Cummings *et al.* 1998, Cummings & Mendez 1997, Cummings 2003, Biswas *et al.* 2005). For example, psychotic symptoms seem to appear most frequently in a later phase of the disease (Schneider & Dagerman 2004), depression is more severe in the precocious phase of the illness (Lyketsos & Olin 2002, Lyketsos & Lee 2004) and tends to improve in the latest stage (Cannon-Spoor *et al.* 2005), and apathy is the only BPSD that tends to worsen in direct correlation with the progression of global cognitive severity (Landes *et al.* 2005, Spalletta *et al.* 2004). These data suggest that cognitive and behavioural features are independent and heterogeneous dimensions, and that some BPSD may be the manifestation of specific dysfunctions, probably in specific cerebral areas. Since BPSD are heterogeneous dimensions that may fluctuate, occurring either in an early or in a late phase of dementia, we believe that it is important to consider the global cognitive level as a clinical index of neuropathological manifestation. In fact, different severity of global cognitive level and stage of AD pathology may be considered as confounding factors in BPSD studies.

Another issue regards the great pathogenetic variability of clinical characteristics in patients with AD. In fact, research has focused on the identification of cardiovascular, inflammatory, biochemical, genetic and environmental risk factors of AD (Bossù *et al.* 2004, Chong & Sahadevan 2005, Flirski & Sobow 2005, Lee *et al.* 2005, Nowotny *et al.* 2005, Fujino *et al.* 2005, Kolsch *et al.* 2005, Bernardini *et al.* 2005). In particular, several studies focused on the role of vascular factors in the pathogenesis of AD (Derouesne 2005, Newman *et al.* 2005, Vogel *et al.* 2005, Hentschel *et al.* 2005).

Traditionally, AD (with frontotemporal dementia and Lewy body disease) is classified as a neurodegenerative type of demen-

tia whereas other forms may be classified as vascular dementias since they seem to be associated with vascular risk factors. Despite this traditional classification, there is increasing evidence of the common role of haemostatic factors and inflammatory mechanisms in the pathogenesis of both vascular dementia and AD. In fact, many of the risk factors for cerebrovascular disease and vascular dementia, including serum total cholesterol, hypertension, atherosclerosis and Apolipoprotein E (ApoE) genotype, have also been shown to increase the risk of AD (Panza *et al.* 2005, Gupta *et al.*, 2005). Furthermore, longitudinal studies demonstrated a significant increase in the risk of developing AD in cohorts of hypertensive patients compared to normotensive subjects, suggesting that extensive peripheral atherosclerosis is a risk factor for AD (Vogel *et al.* 2005, Newman *et al.* 2005). These findings are interesting but require confirmation. In fact, whereas there are some studies showing beneficial effects of antihypertensive drug use in reducing the risk of developing AD (Yasar *et al.* 2005, Qiu *et al.* 2005) and vascular dementia (in'tVeld *et al.* 2001), the potential benefit of preventive treatment with antihypertensive drugs in decreasing the risk of AD has not been confirmed in clinical trials (Lindsay *et al.* 2002, Morris *et al.* 2001). With the aim to explain these data, the hypothesis of the formation of a cerebrovascular disease that would combine with the neuropathological lesions typical of AD has been evoked, raising doubts on the diagnostic criteria used to define AD (Vogel *et al.* 2005).

Cardiovascular risk factors of AD are also linked to specific genetic polymorphisms, and some of these polymorphisms have been isolated. Papassotiropoulos and colleagues (Papassotiropoulos *et al.* 2005) evaluated whether clusters of cholesterol and lipid-related genetic variations were associated with AD, identifying a cluster of polymorphisms. However, differences in genotypes may explain only a part of the variability in AD phenotypes, such as differences in age of onset, rapidity of cognitive decline and finally heterogeneity of BPSD. In fact, it is well known that AD can appear in sporadic and familial forms (Mayeux *et al.* 1985, Chiu *et al.* 1985, Rossor *et al.* 1984, Rossor *et al.* 1993), and the phenomenology of these two forms can be different in many features. In particular, the familial form of AD accounts for roughly 5-10% of all cases worldwide, whereas the sporadic form of AD represents 90-95% of the remaining cases. The sporadic form is generally believed to be of late onset, occurring after 65 years of age, whereas the familial form is believed to be of early onset. Moreover, familial early onset AD and sporadic late onset AD seem to have differences in clinical and neuropsychological manifestations. Studies found that patients with early onset AD had more aphasia, and a shorter duration of illness than patients with late onset AD (Lampe *et al.* 1994, Haltia *et al.* 1994). Other studies reported that AD patients with familial aggregation compared with sporadic cases had more marked impairment of language, praxia, and graphia (Breitner & Folstein 1984). Finally, some genetic factors, underlying the pathogenesis of early onset AD (Zekanowski *et al.* 2004, Lehtovirta *et al.* 1996, Reiss *et al.* 2005, Mosconi *et al.* 2005) and late onset AD (Olin *et al.* 2005, Bernardini *et al.* 2005, Liang *et al.* 2005, Strittmatter *et al.* 1993, Saunders *et al.* 1993), have been identified.

Thus, neuropathological and genetic findings associated with the different forms of AD may explain different clinical manifestations (Lahiri *et al.* 2004). In particular, in this review we will focalize on an allelic

variant, named ApoE ε4, that seems to influence the risk and age of onset of AD and to have a selective effect on episodic memory decline (Wilson *et al.* 2002; Mayeux *et al.* 2001) and some behavioural symptoms. ApoE ε4 seems to be related with the clinical manifestations of AD through an association with the pathologic hallmarks of disease (neuritic plaques, diffuse plaques, and neurofibrillary tangles) rather than some other mechanisms (e. g., direct effect on neuronal survival) (Bennett *et al.* 2003b). In addition, in transgenic animal studies, ApoE ε4 allelic variant causes neuropathology and behavioral deficits (Holtzman *et al.* 2000).

In order to clarify the status quo of the relationship between ApoE ε4 allelic variant possession, cognitive decline and psychotic manifestations in AD patients, we conducted detailed searches of the published medical literature with a review of the Medline (PubMed) databases. For our searches we used various combinations of the following keywords: "apoe", "Alzheimer", "psychosis", "delusion", "hallucination", "cognitive decline", "onset", "BPSD". The articles highlighted in our searches spanned the years 1992–2005 and include all of the important literature pertaining to the relationship between ApoE ε4 allele possession, psychotic symptoms and cognitive features in Alzheimer's disease. For each citation identified, we scanned titles or abstracts, or both. We searched bibliographies of published articles for relevant titles. We selected English language only. Cross-references and review articles were used for search completion. If such data were available for only a subset of patients, this subset was included. In studies reporting repeatedly on the same study population, only the most recent study was included.

The effect of ApoE ε4 on cognitive impairment

ApoE ε4 allele variant possession represents one well known vascular risk factor for developing AD. ApoE is a plasmatic lipoprotein involved in cholesterol transference, secreted in the central nervous system by astrocytes. ApoE is a polymorphic 299-aminoacid protein, coded by a gene that is allocated on chromosome 19, and has three allelic variants named ε2, ε3, ε4. These isoforms differ from one another at residues 112 and 158. ApoE ε3 has cysteine at position 112 and arginine at position 158, ApoE ε4 has arginine at both positions, and ApoE ε2 has cysteine at both positions. In almost all populations, the ε3-allele accounts for the vast majority of the ApoE gene pool (typically 70-80%) and the ε4 and ε2 alleles account for 10-15% and 5-10% of the population, respectively (Roses 1996). There is evidence that subject carriers of ApoE ε4 allele have higher levels of total and low density lipoprotein cholesterol and a higher risk for myocardial infarction and coronary heart disease than non-carriers of the ε4 allele (Utermann *et al.* 1984, Menzel *et al.* 1983). Several studies suggested that ε4 allele is associated with an increased risk of developing AD in both early onset familial and sporadic forms of the illness (Farrer *et al.* 1997, Bullido *et al.* 1998, Slooter *et al.* 1998, Mayeux *et al.* 1993). In this direction, a study by Hsiung *et al.* (2004) investigated the effect of ApoE ε4 on predicting conversion from normal to "cognitive impairment, no dementia" (CIND) to AD, finding that the ApoE ε4 genotype was a significant risk factor in the conversion from CIND to AD and from normal to AD and vascular dementia. In the same study, ApoE ε4 allele possession was associated with a decrease in age of onset. In fact, in the literature there

is evidence that ApoE ε4 allele possession is associated with a more precocious age of onset (Reiss *et al.* 2005, Mosconi *et al.* 2005, Roses 1994, Lopez *et al.* 1997), and several studies investigated its influence on determining the severity of memory disorder (Bondi *et al.* 1995, O'Hara *et al.* 1998, Mayeux *et al.* 2001). Some research hypothesizes that presence and amount of ApoE ε4 alleles are predictors of impairment in cognitive performances (Nacmias *et al.* 2004). In particular, the presence of ApoE ε4 allele seems to affect the memory in the early stage of dementia, so both normal control and patients with dementia carriers ApoE ε4 allele show a more severe memory impairment and mild verbal involvement (Bondi *et al.* 1995, O'Hara *et al.* 1998, Nagy *et al.* 1995, Wilson *et al.* 2002). In this field, Marra and colleagues (2004) found that AD patient carriers of ApoE ε4 allele were characterized by a different neuropsychological pattern at the onset of the illness compared to AD patient non-carriers of ApoE ε4 allele. However, in the sample with early onset AD (i.e. age of onset under 65) only this effect was significant. Moreover, patients with early onset AD carriers of ApoE ε4 allele showed worse performances in learning, long-term verbal memory and general intelligence tasks compared to late onset AD patients carriers of ApoE ε4 allele. Thus, in patients with late onset AD, the pattern of cognitive impairment at the onset does not seem to be dependent on the possession of an ε4 allele in the genotype. This difference could be due to distinct pathogenic mechanisms between the onset and the course of AD (Marra *et al.* 2004).

While a general agreement seems to exist on the role played by ApoE ε4 allelic variant both at the onset of AD (Slooter *et al.* 1998, Saunders *et al.* 1993) and on the rate of brain atrophy (Wahlund *et al.* 1999), the effect on the cognitive progression of AD during the course of the illness is still controversial. From a mere neuro-pathological point of view, since there is evidence that ApoE ε4 allelic variant works through beta-amyloid deposition in senile plaques and neurofibrillary tangles (Bennett *et al.* 2005, Bennett *et al.* 2003a, Namba *et al.* 1991, Wisniewski & Frangione 1992), which are the neuropathogenetic hallmark of cognitive impairment and seem to be associated with disease progression, ApoE ε4 allele possession should be linked to the rate of cognitive decline (Plassman & Breitner 1996). In reality, in the clinical setting the cognitive decline of AD patients has been differently associated with ApoE ε4 allele possession in a continuum of faster decline (Adak *et al.* 2004, Craft *et al.* 1998, Bondi *et al.* 1999), no effect (Murphy *et al.* 1997, Dal Forno *et al.* 1996, Kurz *et al.* 1996, Growdon *et al.* 1996), and slower decline (Hoyt *et al.* 2005, Frisoni *et al.* 1995, Stern *et al.* 1997).

A hypothesis that may explain these discordant data is that the biological processes that lead to the AD onset are different from those involved in determining its clinical course. In fact, while there is evidence that ApoE ε4 works through beta-amyloid deposition in senile plaques, cognitive impairment has not been found to correlate with plaque density but rather with synaptic and neuronal loss and number of neurofibrillary tangles (Arriagada *et al.* 1992, Terry *et al.* 1991, Terry 2000). Thus, neuronal and synaptic loss are mixed in the AD brain and correlate differently with disease progression (Gomez-Isla *et al.* 1997, West 1993, Kril *et al.* 2002, Davies *et al.* 1987, Masliah *et al.* 1991, Heinonen *et al.* 1995, Hansen *et al.* 1998). A study by Ingelsson *et al.* (2004) confirms that the duration of dementia correlates with the degree of neurofibrillary tangles and synaptic loss, but not with amy-

loid plaques in the AD brain. In addition, with the increasing of disease severity, progressive numbers of neurofibrillary tangles occur in hippocampus, enthorinal cortex, and high-order association cortices (Arriagada *et al.* 1992, Gomez-Isla *et al.* 1997, Riley *et al.* 2002, Guillozet *et al.* 2003), frontal lobe among the others (Giannakopoulos *et al.* 2003). On the contrary, amyloid plaques seem to have a more widespread anatomic distribution in the AD brain (Braak & Braak 1991, Arnold *et al.* 1991) and the extent of amyloid deposition tends to correlate poorly with AD symptoms and severity (Braak & Braak 1991, Gomez-Isla *et al.* 1997, Giannakopoulos *et al.* 2003, Guillozet *et al.* 2003). Indeed, amyloid accumulation increases in AD patients irrespective of disease duration. These data seem to suggest that there are distinct processes involved in the initiation and progression of AD pathology. On the other hand, morphologic and biochemical studies have challenged this point of view (Cummings *et al.* 1996, Naslund *et al*. 2000). Thus, this question remains open and one may wonder if these previous mixed results on the course of cognitive deterioration of AD patients were influenced by a different distribution of related genotypes in ApoE ε4 carriers and non-carriers. In addition, a confounding effect of other variables, such as the response to medical treatment, rehabilitation therapy and, most at all, different stages of progression at baseline, could account for the evolution in the later stages.

Another issue regards the relationship between brain pathology of different types and the specific cerebral areas in which this damage occurs, as high-order association cortices or others. An important question is if this damage in specific cerebral areas is linked with different cognitive symptoms or BPSD. For example, there is evidence that pathology in hippocampal formation and frontal cortex (area 9) reflects the progression of cognitive deficits in brain aging and AD (Giannakopoulos *et al.* 2003) and that right frontal hypometabolism (Sultzer *et al.* 1995) and greater frontal neuropsychological deficits (Jeste *et al.* 1992) occur in AD patients with psychosis in comparison to those without.

The effect of ApoE on psychotic symptoms

Several studies explored the relationship between ApoE ε4 allelic variant and BPSD in AD, since there is evidence that this variant may influence the behavioural manifestations of AD. These studies achieved different and controversial conclusions, most of all about the relationship between ApoE ε4 and psychotic symptoms (Scarmeas *et al.* 2002).

A study by Ramachandran *et al.* (1996) examined the relationship between ApoE genotype and depressive/psychotic manifestations in patients with AD, evaluating them as both continuous and categorical variables. Subjects with AD carriers of ApoE ε4 allelic variant had greater severity of depression and psychotic symptoms. An attemptable interpretation is that genotype ApoE ε4, affecting properties of beta-amyloid or neurofibrillary tangles, could create a predisposition to develop behavioural symptoms in patients with AD (Roses 1994). In fact, AD patients with psychotic symptoms have an increased number of senile plaques and neurofibrillary tangles in the encephalon. In particular, the senile plaques are more widespread in the presubiculum, and the neurofibrillary tangles in the medial frontal cortex (Ramachandran *et al.* 1996). These

results have been successively confirmed by Ballard *et al.* (1997) and by Harwood *et al.* (1999). However, there are controversial data. Indeed, Lopez *et al.* (1997) did not find any association between ApoE ε4 and major depression or psychotic symptoms. In addition, Lyketsos *et al.* (1997) did not find any statistical significant association between ApoE ε4 allelic variant and delusions, hallucinations or depression, and concluded that ApoE ε4 cannot be considered a risk factor for developing behavioural symptoms in AD. Hirono *et al.* (1998) found delusions or hallucinations in 51% of their sample in association with advanced age, female gender, longer length of illness, greater cognitive impairment, but not with ApoE ε4 allelic variant. Levy *et al.* (1999) did not find significant differences between patient carriers of ApoE ε4 allele and patient non-carriers of ApoE ε4 allele in any behavioural variable. However, since subjects in this study were affected by different levels of severity of AD, the same authors suggest that the effect of ApoE ε4 could differently contribute to the development of behavioural symptoms in different phases of dementia. Therefore, longitudinal studies may be more valid in this field but only recently this kind of methodology has been applied. Scarmeas *et al.* (2002) conducted a longitudinal study finding a strong association between number of ApoE ε4 alleles and frequency of delusions. On the contrary, the presence of both ApoE ε4 alleles was significantly but weakly associated with a lower risk to develop hallucinations. Finally, there was no association with depressive symptoms or other BPSD. Another longitudinal study, by Chang *et al.* (2004), analyzing the predictive value of ApoE ε4 allele in developing psychiatric symptoms, found that psychotic symptoms were more frequent in AD patients carrying ApoE ε4 allele. They hypothesized that the reason for these results could be linked to a massive decrease in the cholinergic activity (Chang *et al.* 2004, Soininen *et al.* 1995).

An interpretative challenge

How we can explain the inconsistent and contrasting results on the relationship between being carriers of ApoE ε4 allelic variant and psychotic symptoms? As we have seen, they may probably be attributed to methodological flaws. Indeed, studies on this issue used different methods and samples are not comparable by phase of illness, so a further variability is linked to the different length and severity of dementia. The principal limitation of these studies is that they examine the frequency of symptoms without considering how a patient is situated in the course of dementia (Scarmeas *et al.* 2002). Moreover, 1) some of these studies are based on small samples, having low statistic power; 2) they use different criteria or guidelines for the diagnosis of AD and, in particular, dissimilar definitions of psychotic symptoms or syndromes; 3) most of the studies do not consider interactions between factors (Hirono *et al.* 1998) and there is no control for confounding factors; 4) all the studies on the relationship between ApoE ε4 and psychotic symptoms published until 2002 have a cross-sectional experimental design, and this strongly limits the possibility of an interpretation of causal relationships between factors (Chang *et al.* 2004); and finally 5) another issue regards the distinction between hallucinations and delusions. In fact, almost all the studies consider psychosis as a whole and undifferentiated phenomenon.

In a recent study, Spalletta *et al.* (2005) analysed the relationship between the entire

range of BPSD, cognitive deficit, sociodemographic characteristics, and ApoE ε4 allele possession in AD patients with late onset. They found that the ApoE ε4 allele possession was associated with an increased level of delusions within the month preceding the first examination, and with the presence of categorical delusions at the early stage until the first examination. Furthermore, at the early stage of the illness, the relationship between ApoE ε4 allele and behavioural symptoms was confirmed for delusions only. These results confirm data of the longitudinal study of Scarmeas *et al.* (2002). It is important to underline that in the Spalletta *et al.* (2005) study the level of delusions in AD patients carrying ApoE ε4 allele within the month of the first examination was exactly twice as much as the level found in patients who did not carry the ApoE ε4 allele. In addition, frequency of patients with clinically significant categorical delusions having the ApoE ε4 allele was more than twice as much as the frequency of patients who did not carry the ApoE ε4 allele.

Considering that patients with delusions have different cerebral functional abnormalities in comparison to patients with hallucinations (Kotrla *et al.* 1995, Lopez *et al.* 2001), that patients with hallucinations may have specific cerebral atrophy (Holroyd *et al.* 2000), and that patients with delusions have, among the others, frontal lobe dysfunction (Staff *et al.* 1999, Lopez *et al.* 2001, Sultzer *et al.* 2003), in a challenge to interpret these above-mentioned results we suggest that the link between being carriers of ApoE ε4 allele and suffering from delusions in AD is related to frontal lobe dysfunction. In addition, cerebral functional abnormalities (Hogh *et al.* 2001, Sakamoto *et al.* 2003, Mosconi *et al.* 2004) and abnormalities in cholinergic neurons (Soininen *et al.* 1995, Soininen & Riekkinen 1996) in the frontal areas have been described in association with ApoE ε4 allele possession. In fact, some neuroimaging studies found that psychotic symptoms in AD correlated with hypometabolic abnormalities in the right frontal cortex (Sultzer *et al.* 1995) and an association between psychosis in AD and hypoperfusion in frontal lobes was reported using SPECT (Mega *et al.* 2000). Another study found that delusions were related to hypometabolism, particulary in the right superior dorsal lateral cortex and anterior cingulate, and that hypometabolism in the right inferior frontal pole and orbital frontal areas correlated with clinical severity of delusions (Sultzer *et al.* 2003). In addition, patients with psychotic symptoms have greater frontal lobe and executive function neuropsychological deficits than AD patients with psychosis. A study by Jeste *et al.* (1992) found that delusional AD patients had more impairment in conceptualisation and verbal fluency tasks, that require frontal function, than non delusional patients. Thus, our hypothesis seems to be supported by convergent data indicating frontal lobe dysfunctions in delusional AD patients.

Suggestions for upcoming studies

After a review of the literature about the issue of the relationship between ApoE genotypes, cognitive features and psychotic symptoms in AD patients, the main question that arises regards the methodological flaws affecting most of the studies we report. A suggestion for the upcoming research is to consider how patients are situated in the course of dementia, so that different studies could be comparable, having eliminated the

variability linked to the different phase of illness and different severity of global cognitive decline and possibly neuropathology. The question of the relationship between ApoE ε4 allele possession and psychotic symptoms requires a longitudinal experimental design, that permits to follow patients during time and extend the possibility of interpretations of casual relationships between factors. Since some of the studies we report are based on small samples, another methodological guideline regards the importance of using more numerous samples with the aim to increase statistical power. The third methodological issue regards the necessity to standardize criteria used for the diagnosis of psychotic symptoms. In order to resolve this important limit, we suggest using criteria that have been elaborated by Jeste & Finkel (Biswas *et al.* 2005). On the basis of these specific guidelines, to diagnose psychosis in AD the following criteria must be fulfilled: presence of one (or more) of the visual or auditory hallucinations or delusions (criterion A); DSM-IV and NINCDS-ARDRA criteria for the diagnosis of AD (criterion B); evidence from the history that symptoms in criterion A have not been present continuously prior to the onset of dementia (criterion C); symptoms in criterion A must be present, at least intermittently, for 1 month or longer during the course of the illness and be severe enough to cause some disruption in patients' and/or others' functioning (criterion D); mood disorder with psychotic features that have never been met (criterion E); the disturbance does not occur exclusively during the course of a delirium (criterion F); the disturbance is not better accounted for by another general-medical condition or direct physiological effects of a substance (e.g., a drug of abuse, a medication) (criterion G). In addition, it is possible to specify if there are associated features such as agitation (when there is evidence, from history or examination, of prominent agitation with or without physical or verbal aggression); negative symptoms (when prominent negative symptoms, such as apathy, affective flattening, avolition, or motor retardation, are present); depression (when prominent depressive symptoms, such as depressed mood, insomnia or hypersomnia, feelings of worthlessness or excessive or inappropriate guilt, or recurrent thoughts of death, are present).

Since recent studies have demonstrated the presence of a specific association between ApoE ε4 allele possession and delusions (Spalletta *et al.* 2005, Scarmeas *et al.* 2002) the last methodological suggestion regards the importance of operating a distinction between hallucinations and delusions and between misidentification and paranoid delusions, and not to consider psychosis as a whole and undifferentiated phenomenon. Neuroimaging (Spalletta *et al.* 2005) and phenomenological (Perez-Madrinan *et al.* 2004) data confirm this idea.

The upcoming research will probably be focused on the relationship between ApoE ε4 and psychotic symptoms also in the precocious phase of dementia.

Conclusions

We believe that the issue of the relationship between ApoE ε4 allelic variant and behavioural symptoms in AD is very interesting and needs to be accurately investigated, because it can be useful, in conjunction with other clinical and pathogenetic characteristics, for an early detection of dementia even before the onset of cognitive impairment.

Finally, we hypothesize that the most precocious onset of AD illness, described in carriers of ApoE ε4 allelic variant, may also be related to the precocious onset of psychotic symptoms, which produces caregiver and patient distress, requires immediate assessment and treatment, and facilitate early diagnosis.

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