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COMMENTARY

Biomarkers of neurodegeneration among patients with very late-onset schizophrenia-like psychosis: future implications

Commentary on "Characteristics of very late-onset schizophrenia-like psychosis classified with the biomarkers for Alzheimer's disease: a retrospective cross-sectional study" by Satake *et al.*

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Alzheimer's disease (AD) is thought to be complicated by psychosis in one-third of patients (Ropacki and Jeste, 2005). Psychosis in AD is thought to comprise delusions and/or hallucinations that occur in the context of AD and affect function above and beyond that of the neurodegenerative disorder (ND) itself (Jeste and Finkel, 2000). Recently revised research(Fischer *et al.*, 2020) and clinical criteria (Cummings *et al.*, 2020) for dementia-related psychosis reflect an understanding that psychosis may precede onset of AD and that certain symptoms (such as misidentification delusions) may be more pathognomic of AD than late-life psychosis. Prior studies of very late-onset schizophrenia-like psychosis (VLOSLP) have suggested a preponderance of positive symptoms, limited thought disorder, partition delusions, lack of negative symptoms and preservation of functional status when compared to patients with early-onset schizophrenia (Howard *et al.*, 2000).

One question that remains unanswered is the extent to which patients presenting with VLOSLP might manifest markers of neurodegeneration, even in the absence of clinical dementia. As well, would patients who test positive for neurodegenerative (ND) markers manifest phenomenologically different psychotic symptoms relative to patients without ND markers? The paper by Satake and colleagues (Satake *et al.*, 2022) begins to address this question. In the paper, 33 patients followed at the neuropsychology clinic in The Department of Psychiatry, Osaka University Hospital, Osaka, Japan, were further subdivided into eight with VLOSLP AD biomarker-negative, nine with VLOSLP AD biomarker-positive and sixteen amnestic mild cognitive impairment (aMCI) controls. VLOSLP was diagnosed in accordance with the Kanemoto *et al.* criteria (Kanemoto *et al.*, 2022) which specify the presence of delusions and/or hallucinations at age 60 or greater as well as the presence of delusions and/or hallucinations at first visit. There was no requirement to fulfill the existing DSM-V criteria, which are somewhat more rigorous. Biomarkers consisted of cerebrospinal fluid phosphorylated tau and F-Florbetapir (18) positron emission tomography (PET) measures taken within 3 years of symptom onset. In terms of demographics, the biomarker-positive group was significantly older than the negative group, and there were no differences in sex and Mini-Mental Status Examination scores between the subgroups.

Neuropsychologically, the aMCI subgroup performed worse on tests of episodic memory, specifically the Wechsler Memory Scale-Revised Logical Memory scale I (WMS-R LM I), and better on
tests of attention (measured using subtests of the WMS-R) than the VLOSLP group. However, the biomarker-positive subgroup scored intermediate between the aMCI subgroup and the biomarker-negative subgroup in terms of performance on the WMS-R LM II. This is perhaps not surprising given recall deficits are more common in ND and attentional deficits more common in schizophrenia spectrum disorders. Somewhat surprisingly, there were no differences in psychotic symptomatology between the VLOSLP biomarker-positive and biomarker-negative cases. Delusions of theft and partition delusions were common to both AD-positive and AD-negative groups and seemed to correlate with

deficits in episodic memory. Biomarker-negative cases actually had a higher prevalence of other neuropsychiatric symptoms including disinhibition, irritability and nighttime behaviors relative to aMCI participants and biomarker-positive cases.

Perhaps the most crucial element of the study conducted by Satake *et al.* (2022) and colleagues is that approximately half of the patients with VLOSLP exhibited AD biomarkers. Previous studies examining the association between psychiatric symptoms and AD biomarkers have revealed similar conclusions. In a further study, the authors compared AD biomarkers including CSF phosphorylated tau and F-Florbetapir (18) PET in two patients presenting with VLOSLP and found biomarkers in one patient and none in the second (Satake *et al.*, 2021). Paquet *et al.* (2016) in a similar effort examined CSF of 957 patients, 69 of whom had a psychiatric diagnosis (Paquet *et al.*, 2016). Approximately 20% of these patients tested positive for AD biomarkers. Psychiatric symptoms in the AD group tended to occur later, and the interval between psychiatric symptoms and cognitive decline was noted to be shorter (Paquet *et al.*, 2016).

The presence of AD biomarkers in patients with VLOSLP provides further validation for the theory that psychotic symptoms may be an early manifestation of ND disorders such as AD, consistent with the revised clinical (Cummings *et al.*, 2020) and research (Fischer *et al.*, 2020) criteria. Consistent with the construct of mild behavioral impairment (Ismail *et al.*, 2016), there is increasing recognition that the emergence of NPS in otherwise healthy older adults with no prior psychiatric history may be an early manifestation of AD. Studies show in fact that relative to other NPS domains, baseline psychosis in particular in cognitively intact older adults was associated with an increased risk of conversion to AD. Almeida *et al.* (2019) followed patients with late-life psychosis and found an increased risk of developing dementia with a hazard ratio of 2.67 (Almeida *et al.*, 2019). Similarly, Yokoi *et al* followed patients with MBI over 3 years, and only the psychosis subdomain was associated with an increased risk of conversion to dementia (Yokoi *et al.*, 2019).

The article by Satake and colleagues (Satake *et al.*, 2022) further elaborates topics raised in a recent theme issue entitled "Serious Mental Illnesses in Older adults" featured by International Psychogeriatrics. For example, in a recent paper by Nagendra and colleagues based out of Australia, among 55 patients with delusional disorder followed prospectively over time, arguably a much more benign disorder than schizophrenia, four patients developed dementia and two patients developed cognitive decline (Nagendra and Snowdon, 2020). Had the patients been followed over a longer time frame, one could speculate that rates of dementia would be even higher. Patients with VLOSLP, similar to patients with typical onset schizophrenia, may have a number of reasons that would make them more vulnerable to cognitive decline. As recently highlighted in a paper by Schuster and colleagues, patients with schizophrenia are more likely to take benzodiazepines which have proven to have deleterious effects on cognition and memory (Schuster *et al.*, 2020). In their paper, they emphasize the subpopulation on benzodiazepines are typically more ill with more frequent hospitalizations and greater medical co-morbidity (Schuster *et al.*, 2020). Patients with schizophrenia may also have a higher burden of cardiovascular morbidity and decreased socioeconomic status, factors linked independently to dementia. Schizophrenia, whether diagnosed in early or late life, is associated with an increased risk of dementia according to a recent meta-analyses (Cai and Huang, 2018).

Another issue requiring addressing relates to clinical relevance. In the absence of a therapeutic that could meaningfully impact the course of AD, what might be the relevance of detecting AD biomarkers? Would such knowledge influence whether or not antipsychotic medication could be prescribed, whether or not a cognitive enhancer would be suggested? All antipsychotic medications are associated with increased mortality in dementia (Kales *et al.*, 2007) so would detecting AD biomarkers make clinicians more reluctant to prescribe these medications? With the approval of the first anti-amyloid therapy, and the promise of others to follow, this question has become more prescient. In addition, new blood-based biomarkers may make it easier and less costly to detect in vivo levels of AD biomarkers, thus making it easier to distinguish VLOSLP patients from those with NDs. In a recent paper, an argument is made that psychosis, perhaps similar to apathy, should be considered a treatment target in dementia in particular given its association with more rapid cognitive decline and adverse prognosis (Agüera-Ortiz *et al.*, 2022). In the paper, they comment on the need to develop methods of distinguishing VLOSLP from ND, whether clinically or based on biomarker evidence (Agüera-Ortiz *et al.*, 2022).

A more remote possibility is that psychotic symptoms, even in the context of ND, may share mechanisms with other psychotic disorders across the age spectrum. Even younger patients with schizophrenia develop neurocognitive deficits that are quite disabling and lead to functional impairment (Tripathi *et al.*, 2018). Is it possible that these symptoms share a common neurobiology across the age spectrum that is distinct from ND? Could the presence of ND in a person who is

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genetically vulnerable lead to increased expression of psychosis? Is it possible that the presence of ND markers is an incidental finding and has nothing to do with the causation of psychotic symptoms?

The question of phenomenology is an interesting one and requires further thought. Few studies in psychiatry have linked phenomenology to pathological markers of ND. For example, C9orf72 repeats among patients with frontal–temporal dementia (FTD) have been found to be associated with psychosis. In a recent study by Nassan *et al.* (2021), visual hallucinations and misperceptions were found to be more indicative of AD/Lewdy body dementia (LBD) pathology while misidentification delusions were more common among FTD-TDP (TAR DNA-binding protein 43) patients and paranoia more common in LBD. Recent studies have also pointed to differential effects of Apolipoprotein E 4 (APOE4) on psychosis linked to sex, Lewy body pathology and zygosity, making the situation even more complex (Valcic *et al.*, 2022).

What remains unclear is why some patients presenting with psychotic symptoms have no ND course or biomarkers suggestive of ND while others do. The inability to separate out phenomenologically similar patients as postulated by Satake and colleagues (Satake *et al.*, 2022) may suggest that psychotic symptoms, though associated with ND and ND markers, have a separate mechanism or that unique mechanisms underlying psychosis may give rise to similar symptoms. While the findings of their paper are compelling, some limitations mitigate the conclusions drawn from this paper. A factor associated with AD biomarkers independent of VLOSLP is age, and it is possible that the positive observed markers would reflect older age. As the authors report, AD biomarkers were conducted mostly in younger adults while there was no age restriction put on patients with VLOSLP. Additionally, the sample size utilized was quite small, and there was no control for multiple comparisons, thereby limiting the conclusions that can be drawn with respect to phenomenology, etc. As the authors state, further large-scale longitudinal studies with more precise definitions of psychosis are needed to further uncover these associations. This paper is a crucial first step in the process.

Conflict of interest

None.

Description of authors' roles

Corinne E Fischer wrote, revised and approved this manuscript.

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