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Delusions in Alzheimer's disease: What researchers should not forget

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Importance of delusions in AD

Emerging data show that psychotic symptoms, particularly delusions, that manifest in about one-third to one-half of patients with Alzheimer's disease (AD) are associated with decreased quality of life, increased rates of aggression, higher frequency of hospitalization, poorer prognosis for patients and increased short-term mortality while also increasing the burden of care and decreased quality of life for caregivers. Accelerated cognitive decline even before the onset of psychotic symptoms, greater reduction in selected gray matter regions, reduced blood flow and reduced regional glucose metabolism with accelerated accumulation of tau protein are also reported. For these reasons, AD with psychotic symptoms appear to demonstrate a more aggressive course and is considered a distinct phenotype within AD demanding greater attention to neurobiological underpinnings.

AD with psychotic symptoms poses challenges in clinical management as well. Accurately identifying delusions in the context of cognitive decline and associated behavioral manifestations requires astute clinical skills to carefully select patients for antipsychotic treatment. This is because antipsychotics are less effective in treating delusions in AD patients and are likely to be more toxic in this group due to serious side effects compared to schizophrenia patients. While conventional antipsychotics may cause extrapyramidal symptoms, tardive dyskinesia akathisia, second generation antipsychotics are associated with higher incidence of cerebrovascular events and higher mortality.

These data clearly argue for greater attention to this sub-phenotype within AD. Manuscript by Qian et al in this issue of this Journal is significant in this regard.

Neurobiological substrates of delusions in AD

Current consensus is that the neuropsychiatric symptoms related to AD develop early in the course of cognitive decline although precise etiological pathways leading up to the clinical manifestation is still debated¹. This observation provides an opportunity to investigate individuals at elevated risk for developing delusions and other psychotic symptoms before

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the clinical manifestation with an eventual goal of early treatment to reduce its impact on the course of the illness and caregiver burden, and, also to develop strategies for prevention. A clearer understanding of the neurobiology of psychotic symptoms including delusions provides an added advantage of gaining deeper understanding of the pathophysiology of AD and its course.

Replicated evidence suggests that AD with psychosis is familial. However, convincing evidence for specific genetic variants that elevate the risk for psychosis in AD are not reported. Neuroimaging studies using MRI have reported decreased volumes in the frontal, temporal and subcortical regions. FDG PET showed greater hypometabolism in frontal regions and increased metabolism in the somatosensory regions. PET studies showed increased striatal D2/D3 availability². Neuroimaging findings do not consistently localize to the same regions. There are several reasons for such inconsistency, namely stage of AD at which the imaging data is acquired, severity of delusions, associated psychotic symptoms, field strength of the magnet, sample size, comorbid medical illnesses and processing methods. Different modalities of imaging also do not show consistency. A strategy to connect this series of data to develop an integrated biological model of delusions in AD is an urgent need.

A recent study demonstrates the potential of localizing the regions within a connectivity map. This is an interesting approach consisting of identifying networks of brain regions that show alterations in morphometry and functional differences since different regions that show differences across studies may all be within a network. This study showed that a network comprising of mesial temporal lobes, temporo-parietal lobes and precuneus was relatively specific to AD, and the network that was specific to AD with delusions included right frontal cortex³. Identifying such consistency in regions could elucidate interconnected network with more intuitive functional implications related to delusions.

In addition to these efforts, more longitudinal data are needed to identify brain regions that change with the onset of delusions. In this context, Qian et al's study⁴ in this *Journal* is unique in that it examines AD patients before and after developing delusions. Using voxel-based morphometry, they find increased fronto-temporal region gray matter volume prior to delusions that declined as they developed delusion over a mean duration of 2.8 years of follow up. Findings of these studies are important because other studies that followed patients before and after manifestation of delusions included patients with AD and minimally cognitively impaired. A similar study from Japan that was published earlier showed reductions in parahippocampal gyrus, posterior cingulate cortex, orbitofrontal cortex and inferior frontal cortex in patients with AD and psychotic symptoms at baseline in those who developed delusions after a mean follow up duration of 2 years⁵ suggesting that volume reductions may exist even before the onset of delusions making them vulnerable to develop delusions. The same study noted distinctly different set of regions showed decreased gray matter in AD without delusions suggest that reductions in certain regions may be critical for delusions compared to others. Such reductions may make some individuals with AD more susceptible to develop psychotic symptoms. Thus, there are some important differences in the findings that requires more carefully designed studies with larger samples.

Neurobiological substrates of delusions in non-AD subjects

There are some similarities in findings among younger schizophrenia patients with delusions and hallucinations who show changes in the temporo-limbic and frontal regions⁶. We showed that the volumes of entorhinal⁷ and parahippocampal⁸ cortices were associated with delusions and discussed the possibility of “corrupt memory” to be underlying the process of delusion formation. Dopaminergic dysfunctions associated with abnormal salience and attribution⁹, and jumping-to-conclusion biases¹⁰ that are described by others appear to support our prior hypothesis on delusions in schizophrenia. There are similarities in the regions affected in AD with psychosis; therefore, the mechanisms underlying delusion formation in AD patients may be similar but has not been formally tested. However, such investigations could be challenging among patients with AD. Since it is unclear how cognitive deficits observed in AD affects such psychological process, understanding such processes is critical to link how the observed volumetric changes are related to these functions.

Life span approach to neurobiology of delusions

Since delusions are observed among individuals with psychotic disorders in all age groups, a “lifespan approach” to examining this phenomenon can shed more light on the similarities and differences in the biology of delusions in AD, schizophrenia and other psychotic disorders across the entire developmental spectrum. Qualitative differences in delusional phenomenology observed in different age groups may be related to underlying status of cognitive development or impairment. AD patients experience poorly constructed delusions possibly owing to underlying cognitive impairments. Delusional content may differ depending on the regional pathology, e.g. fronto-striatal pathology is associated with paranoid content whereas more global cerebral changes related to misidentification delusions¹¹. Comparative studies of AD with psychosis and late-onset schizophrenia where nature of delusional manifestations may be different compared to younger adult onset schizophrenia¹² is likely to be more fruitful. Previous studies also show an age-related systematization in the construction of delusions¹³— older adults showing more systematized delusions compared to younger adults with psychosis. Thus, there are tremendous opportunities for examining delusions that could elucidate certain aspects of neurobiology of psychosis in different disease contexts across different age groups.

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