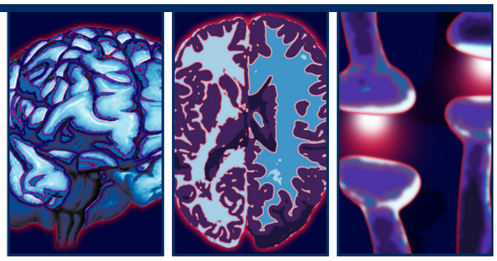

Is schizophrenia a frontotemporal dementia?

Dennis Velakoulis[†]: Dr Dennis Velakoulis is a consultant neuropsychiatrist and Director of the Neuropsychiatry Unit, Royal Melbourne Hospital and Clinical Director of the Melbourne Neuropsychiatry Centre, University of Melbourne and Melbourne Health. Following graduation from the University of Melbourne in Medicine in 1985, Dr Velakoulis completed a Diploma of Criminology (University of Melbourne) in 1988, gained fellowship for the Royal Australian and New Zealand College of Psychiatrists in 1994 and a Masters of Medicine in Neuroscience (University of Melbourne) in 1998. He was appointed an NHMRC Fellow at the Mental Health Research Institute of Victoria between 1994 and 1997 and began ongoing research into the structural brain changes in schizophrenia. Dr Velakoulis has been the Director of the Neuropsychiatry Unit at the Royal Melbourne Hospital since 2001 and has developed clinical and research interests in younger onset dementia, including conditions such as frontotemporal dementia, Alzheimer's disease, Huntington's disease, as well as rarer disorders such as Creutzfeldt–Jakob disease, choreoacanthocytosis and Niemann–Pick Type C. Dr Velakoulis has published over 160 Medline-indexed scientific papers and book chapters. Dr Velakoulis' recent work has been particularly aimed at understanding the association between neurodegenerative disorders in younger persons and the presentation of such disorders with psychiatric syndromes.

Q How has the understanding of frontotemporal dementia neurobiology evolved over the last 5–10 years?

Until 2006 the main protein known to be involved in frontotemporal dementia (FTD) was the tau protein. Since then a series of discoveries have dramatically altered our understanding of FTD, including the identification of the protein TAR DNA-binding protein (TDP)-43 as the link between FTD and motor neuron disease, the identification of mutations in the progranulin gene as a cause of autosomal dominant FTD and the identification of abnormalities in the fused in sarcoma protein as a cause of FTD. Abnormalities of tau and TDP-43 are thought to account for approximately 90% of FTD.

Q What is the relationship between schizophrenia & dementia?

Approximately 25% of patients with schizophrenia will exhibit a chronic course of illness and a proportion of these patients will show progressive functional and cognitive decline together with structural temporal and frontal brain changes. Such patients will satisfy criteria for a dementia but do not readily fit into current dementia diagnoses

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given the relatively slow rate of decline (i.e., over decades). It is not uncommon for such patients to be diagnosed with 'the dementia of chronic schizophrenia'. This patient group has been termed 'Kraepelinian schizophrenia' [1], an acknowledgement of Emil Kraepelin's initial concept of 'dementia praecox' as a neurodegenerative process. Studies in the modern era have shown that patients with Kraepelinian schizophrenia exhibit a greater degree of psychosocial decline, structural brain changes and cognitive impairment [2–5] compared with 'non-Kraepelinian schizophrenia' patients.

"With respect to patients with Kraepelinian schizophrenia, it cannot be excluded that the observed ... structural and cognitive changes are related to long-term institutionalization and/or the long-term effects of psychotropic medications."

Despite this body of clinical, neuroimaging and neuropsychological evidence for frontotemporal dysfunction in patients with Kraepelinian schizophrenia, few studies had sought to examine the relationship between FTD and schizophrenia. In the 2009 study from our group, we undertook a literature review of FTD cases and a clinicopathological study of 17 patients with a young onset of FTD [6]. The literature review revealed that patients who developed FTD at a very young age were highly likely to have presented with a schizophrenia-like illness and to have been diagnosed and treated as having schizophrenia on the basis of both positive and negative symptoms of schizophrenia. In the clinicopathological arm of this study we found that young FTD patients presenting with a schizophrenia-like illness had a TDP-43-related FTD. In a follow-up neuropathological study of patients diagnosed during life with schizophrenia or bipolar disorder we identified three out of 12 patients with abnormalities in TDP-43 [7]. These three patients had presented after the age of 50 years and been diagnosed with schizophrenia or bipolar disorder. All three patients had adult children with the same psychiatric diagnosis as themselves.

"While the question 'Is this schizophrenia or is this FTD?' is an important one, just as important is the need to ensure that these deficits are acknowledged as equally deserving of services and management, as would be the case if the patient was diagnosed with FTD."

Several recent papers provide further support for a link between FTD and schizophrenia. In a genetic linkage study of a large cohort of Latin–American patients, linkage was identified to chromosome 17q21 (lod score: 3.3), the region of the progranulin and tau genes [8]. This region has previously been identified in genome-wide scans of patients with schizophrenia [9,10]. A second study described a family in which two siblings had a diagnosis of schizophrenia and one sibling a diagnosis of FTD. The sibling with FTD and one of the siblings with schizophrenia were found to have a progranulin mutation. The third sibling was not tested [11]. Finally, a study of the first-degree relatives of patients with FTD and patients with Alzheimer's disease found a greater morbid risk of schizophrenia in the relatives of patients with FTD than in relatives of patients with Alzheimer's disease [12]. The authors suggest that in some families the co-occurrence of schizophrenia and FTD may reflect a common underlying cause.

Q What is the most likely explanation for this relationship?

There are several possible explanations for the relationships identified earlier between schizophrenia and FTD. With respect to patients with Kraepelinian schizophrenia, it cannot be excluded that the observed frontal and temporal structural and cognitive changes are related to long-term institutionalization and/or the long-term effects of psychotropic medications. Second, the development of a dementia in patients with chronic schizophrenia may be unrelated to the illness or a consequence of the higher prevalence of risk factors for dementia (e.g., cigarette use, hypertension, diabetes and hypercholesterolemia) [13]. Finally, it may be that, as concluded in a recent review of Kraepelinian schizophrenia, some patients with schizophrenia have a variant of an as yet undetermined progressive dementing illness [14].

The finding that young patients with FTD are very likely to have been diagnosed with a schizophrenia-like illness could be understood in several ways [7]. First, schizophrenia is frequently diagnosed in young patients who are developing neurodegenerative disorders such as Niemann–Pick Type C [15] or metachromatic leukodystrophy [16]. Our findings that young patients with FTD present with schizophrenia could be a nonspecific phenotypic expression of a neurodegenerative insult in a young developing brain. Second, the relationship could be a 'frontotemporal coincidence', in that both disorders involve the same brain regions and will present in similar ways in younger adults.

Identifying the most likely explanation is problematic given that it is very likely that each of these explanations may be the correct one in different patients. The possibility that a subgroup of patients with schizophrenia may have an insidious, 'slow burning', variant of a FTD that develops over decades is, however, an intriguing one and one that opens up new avenues of research in the neurobiology of schizophrenia.

Q Should diagnostic criteria for FTD include psychotic symptoms?

Based on our findings, the prevalence of psychotic symptoms is very high in younger patients with FTD (those <40 years of age) but reduces with the age of onset of FTD, such that by the sixth and seventh decades, psychotic symptoms are more common in Alzheimer's disease than in FTD. Given that FTD in patients below 40 years of age is very rare, it would not be of any diagnostic value to include psychotic symptoms in diagnostic criteria for FTD.

Q What are the clinical implications of recent findings?

In day-to-day clinical practice, these findings are more relevant to the clinical management of patients diagnosed with chronic schizophrenia. A proportion of patients with chronic schizophrenia will develop clinical, functional and structural brain imaging findings that are not dissimilar to those found in patients with FTD. While the question 'Is this schizophrenia or is this FTD?' is an important one, just as important is the need to ensure that these deficits are acknowledged as equally deserving of services and management, as would be the case if the patient was diagnosed with FTD.

These findings also serve to alert clinicians to the possibility that in rare situations, patients presenting with schizophrenia between the age of 20 and 40 years may be in the early stages of a FTD. Clinical clues to such a presentation include a family history of a dementia or motor neuron disease, neurological hard signs, the presence of frontotemporal atrophy on structural brain imaging and the presence of neuropsychological deficits beyond what would be expected in a person with schizophrenia. While such presentations are rare, the early diagnosis of FTD in a young person is important in terms of determining prognosis, the genetic implications for family members and the planning of appropriate services and care for patient and family.

"These findings also serve to alert clinicians to the possibility that in rare situations, patients presenting with schizophrenia between the age of 20 and 40 years may be in the early stages of a FTD."

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