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REVIEW ARTICLE

Is that schizophrenia or frontotemporal dementia? Supporting clinicians in making the right diagnosis

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Abstract
Schizophrenia (SCH) and frontotemporal dementia (FTD) are neurobehavioral syndromes characterized by a profound alteration in personal and social conduct. Differential diagnosis between SCH and FTD remains a challenge. In this short narrative review, we summarize evidences regarding similarities and differences between these disorders to support clinicians in making the right diagnosis. Reports of FTD misdiagnosed as schizophrenia or schizophrenia-like psychosis are frequently reported in the literature. The behavioural variant of FTD (bvFTD) along with familial FTD characterized by delusions and hallucinations represent the medical conditions that best illustrate overlaps between psychiatry and neurology. Neuropsychological patterns of core deficits and anatomical and physiological brain alterations primarily concur in differencing such disorders while additional research on genetic alterations and their reflection on clinical phenotypes should be implemented in the near future. In some cases, a correct diagnosis should be made within an interdisciplinary clinical setting by complementary competences and follow-up visits to evaluate pathology evolution.

Historical and clinical framework

Emil Kraepelin (1856–1926) first recognized the similarity of SCH with neurocognitive disorders, describing it as a dementia emerging in young adults (i.e., dementia praecox). It has also been recognized that a proportion of patients with SCH proceed towards a state characterized by lack of productive activity, social withdrawal and occasionally mutism, the so-called "defect state" [1]. SCH is a life-long and devastating disorder associated with reduction in social interactions, reduced rates of employment and impaired ability to live independently [2]. It remains idiopathic, although 5–10% of patients have organic brain disease or clinically significant neuroimaging abnormalities, or both [3]. The SCH affects 1% of the general population, with a reported median incidence of 15.2 per 100,000 persons [4]. It usually occurs from adolescence to early adulthood with no gender predilection. The diagnosis of SCH includes positive and negative symptoms. Within the constellation of positive symptoms, formed or systematized delusions and hallucinations are more common in the earlier stages of the disease whereas thought disorganization, inappropriate affect, and motor symptoms are shared in later stages. Negative symptoms include blunting of affect, poverty of speech and thought, apathy, anhedonia, reduced social activity, loss of motivation, lack of social interest, and inattention to social or cognitive demand [5]. Over the years, the symptom constellations of SCH have gone beyond the simple dichotomy between positive and negative symptoms to include other categories. Indeed, it was proposed that the phenomenology of SCH may be divided into three syndromes: (1) the disorganized type, characterized by disorganization in speech and behaviour; (2) the psychomotor poverty type, with speech quality decrement, lack of spontaneous movement and various aspects of affect blunting; and (3) the reality distorted type, with prominent hallucinations and delusions [6].

The psychiatrist Arnold Pick (1892) provided the original clinical description of FTD in patients with progressive deficit of language, behaviour, and avolition. FTD is a complex disease, accounting for 13% of all cases of young-onset dementia (people < 65 years old) and comprising approximately 3% of all dementia cases [7]. It constitutes a spectrum of progressive neurodegenerative disorder, pathologically

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heterogeneous with abnormal intraneuronal deposits of misfolded proteins. It affects frontal lobes, anterior temporal lobes, or both, with reduced performances on behavioural control, emotion regulation and language [8]. The estimated incidence of FTD is 2.7–4.1 per 100,000 people, and its prevalence is 15–22 per 100,000 [9]. Between 30 and 50% of patients report a family history of the disease [9]. The clinical and pathological variants of FTD may reflect different phenotypes of genetic changes. Mutations in two genes, i.e., microtubule associated protein tau (MAPT) and progranulin (GRN) account for about half of these cases, whereas mutations in four other genes, i.e., valosin-containing protein (VCP), chromatin-modifying protein 2B (CHMP2B), transactive DNA-binding protein (TARDP) and fused-in-sarcoma (FUS), have been identified in a minority of patients [10]. Particularly, familial FTD due to the C9ORF72 mutation is linked with psychiatric disturbance, with up to 50% of patients exhibiting delusions or hallucinations [10]. Onset of FTD is typically in the middle life and life expectancy is about 7–8 years after the onset, even thought the rate of progression significantly varies among patients [11]. Three main subtypes of FTD are described, the so-called "behavioural variant of frontotemporal dementia" (bvFTD), and two language variants. Key features of the language variants are non-fluent effortful speech with grammatical errors, i.e., primary progressive aphasia (PPA) or progressive loss of conceptual knowledge resulting in anomia, impaired comprehension and speech that is fluent but empty of content, i.e., semantic dementia (SD) [12].

The bvFTD is probably one of the conditions that best illustrate the links between psychiatry and neurology. It is characterized by deficits in interpersonal behaviour, disinhibition, stereotypy, personality disturbances, loss of empathy, apathy, gluttony and altered preference for foods, particularly for sweets [13]. Social norms may be infringed and patients may become more irritable and commit antisocial or even criminal acts [14]. Additionally, suicide could be the first manifestation in some cases and patients with SD may show behavioural changes in the course of the disease [15].

Neuroimaging findings

Ventriculomegaly and cortical atrophy are common in SCH [16]. Johnston et al. [17] first demonstrated brain abnormalities on computed tomography (CT) scans in patients with SCH whereas neuroanatomical abnormalities (i.e., volume reduction) have been demonstrated in multiple brain regions using magnetic resonance imaging (MRI) including frontal and temporal lobes, superior temporal gyrus, hippocampi, amygdalae, and thalamus, in addition to cerebellar asymmetry [18]. Functional imaging investigations have indicated that SCH is particularly associated with altered functions in the prefrontal, cingulate and temporal cortices [19] and that specific symptoms, such as auditory hallucinations and thought disorder, are mediated by these brain regions [16]. Other investigations using positron emission tomography (PET) revealed that patients with SCH show increased dopamine content and excessive D_2/D_3 receptor density [20], as well.

Seelaar et al. [21] showed atrophy in the ventromedial frontal cortex, bilateral posterior orbital frontal regions, bilateral insula, anterior cingulate cortex, dorsolateral frontal cortex and premotor cortex of patients with FTD by using the T1-weighted MRI scan. ^{18}F-FDG PET images of patients with FTD revealed hypometabolism in extensive cortical regions, such as frontal and anterior temporal areas, cingulate gyri, uncus, insula and subcortical areas, including basal ganglia and medial thalamic regions. It has been suggested that brain alterations in the appearance of psychotic symptoms in FTD involved thalamus and the cerebellum [22]. Moreover, some investigations found a strong correlation between psychotic symptoms and predominant right hemisphere pathology [23, 24].

Onset and progression

The major clinical differences between SCH and FTD are about onset and progression. FTD typically begins in people above 45 years of age whereas in SCH the onset is below such a period. FTD progresses in a constant way towards a severe decline while the course is different for patients with SCH [25]. FTD evolves into profound dementia and even death whereas the likelihood that patients with SCH show clinical worsening appears to be correlated with the duration and number of positive symptoms. They could also reach a relatively stable plateau [26, 27].

Positive and negative symptoms

Psychotic phenomena, the so-called "positive symptoms", are usually considered to be the hallmark of SCH and are often more prominent in early stages. Patients with young-onset FTD may be diagnosed with psychotic illness years before the diagnosis of dementia [28]. An outstanding review of the literature concluded that an approximate prevalence of psychotic symptoms in FTD is equal to 10% [29]. Some studies have suggested that particular subgroups of patients with FTD have a higher rate of psychotic symptoms. In particular, hallucinations have been described in patients with ubiquitin-positive and transactive response-DNA-binding protein-43 (TDP-43)-positive pathologies (FTLD-U-TDP) and with progranulin gene mutations [30,

31]. Among patients with C9ORF72 mutation, a relatively high proportion have late-onset positive symptoms [22].

What we today call 'negative symptoms' actually represent a loss or reduction of certain normal functions or behaviours about social interaction, purpose and motivation. It may be difficult for a psychiatrist who meets the patient infrequently to recognize the presence of negative symptoms, especially if they are not so prominent. Friends and family members are able to recognize some changes occurring over time in patient's behaviour, so information from reliable informants should be very useful in clinical practice. Their prevalence in first-episode psychosis is high as 50–90%, and 20–40% of patients with SCH have persisting negative symptoms [32]. There are several descriptions in bvFTD literature about emotional blunting, loss of empathy and complete lack of emotional display as well as reports of patients described as "flat" or "robotic", showing little warmth and often seeming indifferent to the feelings of the others. Particularly, the association between negative symptoms and impaired medial prefrontal functions in bvFTD could support the hypothesis that they may be framed within the frontal lobe syndrome, as primarily hypothesized for negative symptoms in patients with SCH [33].

Cognitive decline

The inability of patients with SCH to live independently and to gain competitive employment is largely due to cognitive dysfunction. Schizophrenic patients show deficits across a large number of neurocognitive domains such as speed of processing, attention, working memory, verbal/visual learning and memory, reasoning, problem solving, and verbal comprehension [34]. It is unclear if patients with SCH show stable cognitive dysfunction versus progressive or late cognitive decline. One perspective suggests that cognitive deficits become progressively worse throughout the duration of the illness; after an insidious onset, patients' cognitive functions become weaker and social skills become coarser. Another perspective suggests that cognitive deficits—once they arise—remain relatively stable over time.

Cognitive dysfunction, although usually overshadowed by prominent behavioural disturbances, is still an important feature in bvFTD. Impairment of executive functions including planning, judgement, problem-solving and mental flexibility is characteristic of FTD, whereas memory, visual perception, and spatial skills are relatively preserved [10].

An impairment of verbal communication is one diagnostic feature of SCH. The phenomena include "derailment", a pattern of spontaneous speech that tends to slip off track and in which the ideas expressed are either obliquely related or completely unrelated, and tangentiality when a patient replies to a question in an irrelevant manner. Neologism as well as echolalia and verbigeration are often observed in language performance of schizophrenic patients. Language disturbance is quite common in FTD, as well. Expressive and receptive language deficits both characterize PPA and SD in a different way. On one hand, PPA is denoted by isolated speech and language impairment during the first 2 years of the disease course and language deficits encompass non-specific anomia and word finding difficulties. Subsequently, speech becomes agrammatic and difficult to be comprehended often due to a significant shortage of verbs and phonological errors in conversation. On the other hand, SD patients typically present with comprehension and naming deficits, semantic paraphasias and circumlocutory responses in the context of normal fluency, syntax, and episodic memory. Language in bvFTD is initially spared, with behavioural and personality changes being the core diagnostic features. Later, as the disease progresses, decreased speech or logopenia, reduced conversational initiation, stereotyped utterances, repetitive responses, unelaborated sentences, echolalia, and changes in pragmatic aspects of conversation are observed [35].

Social cognition

Social cognition—as the ability of processing social stimuli—is a rapidly emerging area of study in SCH. Patients often display marked impairments in such a cognitive and emotional skill resulting in misinterpretations of social intent of other persons, withdrawal and impaired daily interpersonal functioning [36]. It is unclear whether the impairment is present at the beginning and if the degree of the impairment progressively increases or decreases [36]. Studies have provided empirical support for social cognitive deficits in bvFTD, as well, including impaired ability to process facial emotions, detect socially inappropriate speech, adopt perspective of another person, solve social dilemmas, and perceive sarcasm or react to fearful or sad stimuli [37]. An interesting research perspective [38] suggested that while current deficits in social and interpersonal functioning in patients with FTD may reflect a decrement in previously acquired skills, similar deficits in patients with SCH may reflect an overall inadequately learned process.

Implications for clinical practice in psychiatry

A summary of the main differences between SCH and FTD for all the subheadings considered is reported in Table 1. There is a great overlap of clinical features between SCH and FTD sometimes making it difficult to distinguish between these two conditions. It is laborious to establish for

Table 1 Summary of the main findings differencing SCH and FTD

	SCH	FTD
Neuroimaging findings	Structural: atrophy in frontal and temporal lobe, superior temporal gyrus, hippocampi, amygdale, thalamus; cerebellar asymmetry Functional: altered functioning of prefrontal, cingulate and temporal cortices; increased dopamine content and excessive D_2/D_3 receptor density	Structural: atrophy in ventromedial prefrontal cortex, bilateral posterior orbitofrontal regions, bilateral insula, anterior cingulate cortex, dorsolateral prefrontal cortex and temporal cortices Functional: hypometabolism of frontal and anterior temporal areas, cingulate gyri, uncus, insula and subcortical area
Onset and progression	Onset: from late adolescence Progression: in relation to the acute phase, it it possible to have a partial remission, a complete remission or a chronic course	Onset: insidious on people above 45 years of age Progression: slow but more constant towards dementia
Positive and negative symptoms	Positive symptoms: distinctive features of the psychiatric condition Negative symptoms: present in 20–40% of the patients as persistent	Positive symptoms: presentation in young-onset *FTD* and associated with genetic mutations Negative symptoms: manly associated to frontal lobe involvement
Cognitive decline	A wider neurocognitive damage including processing speed, attention, working memory, verbal/visual learning, reasoning, problem solving, verbal comprehension Language dysfunctions is represented by derailment and tangentially, neologism, echolalia and verbigeration	A more limited range of cognitive deterioration, mainly including executive abilities (i.e., planning, judgement, problem-solving, mental flexibility) is present in the *bvFTD* PPA: expressive and receptive language deficits with different progression over the illness course SD: comprehension and naming deficits, semantic paraphasias and circumlocutory responses bvFTD: language deficits are present in the course of the illness
Social cognition	Misinterpretations of social intent and impaired models of relationships	bvFTD: impaired ability to process facial emotion and solve social dilemmas, socially inappropriate speech, and reduced empathy

SCH schizophrenia, *FTD* frontotemporal dementia, *bvFTD* behavioural variant of FTD, *PPA* primary progressive aphasia, *SD* semantic dementia

a clinician whether a patient has late-onset SCH or FTD. Identifying bvFTD is also challenging because symptoms features traditionally fall within the realm of psychiatry. One study showed that as many as 21% of autopsy-verified FTD patients were misdiagnosed with psychosis or SCH [39]. Recently, some researchers also introduced the hypothesis that SCH and FTD could be manifestations of the abnormalities involving the same genes at different life stages, early in SCH and later in FTD while other researchers support the interpretation that some specific aspects of the pathology of Pick's disease resemble disturbed brain functions in a manner that reproduces certain fundamental aspects of SCH pathophysiology [40].

Differentiating between SCH and FTD represents a serious clinical problem with respect to diagnosis and treatment. There is need to implement neuropsychological assessment that seems promising in differentiating between these two conditions by detecting specific patterns of neurocognitive deficits as well as neuroimaging. Follow-up visits are also required to better discriminate between SCH and FTD. Genetic counselling and testing are useful in individuals with family history of frontotemporal degeneration, as well. Finally, due to the complexity of the specific condition, patients with young-onset bvFTD should be evaluated in the context of an interdisciplinary clinical setting in order to support clinicians in making the right diagnosis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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