SPECIAL ARTICLE

Deficit schizophrenia: an update

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The criteria for deficit schizophrenia were designed to define a group of patients with enduring, primary (or idiopathic) negative symptoms. In 2001, a review of the literature suggested that deficit schizophrenia constitutes a disease separate from nondeficit forms of schizophrenia. Here we provide a review of new studies, not included in that paper, in which patients with deficit schizophrenia and those with nondeficit schizophrenia were compared on dimensions typically used to distinguish diseases: signs and symptoms, course of illness, pathophysiological correlates, risk and etiological factors, and treatment response. Replicated findings and new evidence of double dissociation supporting the separate disease hypothesis are highlighted. Weaknesses in research and treatment options for these patients are also emphasized.

Key words: Deficit schizophrenia, heterogeneity, negative symptoms, apathy, double dissociation

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Deficit schizophrenia is a syndrome defined by the following criteria: a) presence of at least two out of six negative symptoms: restricted affect (referring to observed behaviours rather than to the patient's subjective experience); diminished emotional range (i.e., reduced range of the patient's subjective emotional experience); poverty of speech; curbing of interests; diminished sense of purpose; diminished social drive; b) some combination of two or more of the above symptoms have been present for the preceding 12 months and were always present during periods of clinical stability; c) the above symptoms are primary or idiopathic, i.e., not secondary to factors such as anxiety, drug effect, psychotic symptoms, mental retardation, depression; d) the patient meets DSM criteria for schizophrenia (1-3).

In 2001, a review of the literature suggested that deficit schizophrenia is a disease separate from other, nondeficit forms of schizophrenia (3). The proposal of a separate disease was based on the evidence that deficit and nondeficit schizophrenia differ on five dimensions typically used to distinguish diseases: signs and symptoms, course of illness, pathophysiological correlates, risk and etiological factors, and treatment response. The deficit group has a poorer quality of life and level of function, so one potential interpretation of the above evidence is that the deficit group simply has a more severe form of the same illness as nondeficit schizophrenia. However, in some studies, the deficit group was closer to healthy controls than the nondeficit group with respect to some variables (e.g., the volume of some brain regions), while in other studies the two groups were simply different from each other, as well as from control subjects (e.g., with respect to season of birth) (3).

In the years following the publication of that review, there have been a number of other studies focused on deficit schizophrenia, as defined by the above criteria. These have advanced our understanding of this group of patients, but have also clarified the remaining weaknesses in this research area (4). Here we will focus on those studies comparing patients with deficit vs. nondeficit schizophrenia.

RISK AND ETIOLOGICAL FACTORS

Family history

Kirkpatrick et al (3) reviewed studies showing that the deficit/nondeficit categorization has a significant concordance within families and that family members of deficit probands, compared with relatives of nondeficit probands, have more severe social withdrawal and an increased risk of schizophrenia.

Since that time, another study found an increased prevalence of subclinical negative symptoms in the relatives of deficit compared to nondeficit probands (5). In an unpublished study, we have also replicated the finding of a significant concordance within families: in families with more than one affected member, the deficit/nondeficit categorization of one member predicted the categorization of the other family member at a rate greater than chance.

Genetics

A few studies have examined the genetics of deficit and nondeficit schizophrenia, but the results have been disappointing. Hong et al (6) reported that the dihydropyrimidinase-related protein 2 (DRP-2) gene was associated with risk for both deficit and nondeficit schizophrenia; however, after correcting for multiple comparisons, the association with nondeficit schizophrenia was not significant, and for deficit schizophrenia the association was present only for Caucasian but not African-American subjects.

Galderisi et al (7), in a sample of 56 deficit and 50 nondeficit patients, found that the Val(158)Met polymorphism of catechol-O-methyl transferase (COMT) influenced neuromotor performance in the deficit but not the nondeficit group. Wonodi et al (8) did not find an association between COMT polymorphism and the deficit/nondeficit categorization, but the total number of deficit and nondeficit subjects

was 86. Limitations in sample size undermine the value of all of these studies, and replications to date are lacking.

Other risk factors

An association between schizophrenia and *winter* birth has been replicated by several studies, especially in the Northern hemisphere. The effect size is small, with a 5% to 8% excess of births (9). This association applies to schizophrenia as a whole, that is, without regard to deficit vs. nondeficit categorization. The 2001 review (3) cited studies that had found an association between deficit (but not nondeficit) schizophrenia and *summer* birth in the Northern hemisphere, with the deficit group differing from both nondeficit schizophrenia and control subjects. Since that time, summer birth has been confirmed as a risk factor for deficit schizophrenia in a combined analysis of 10 datasets from 6 countries (10).

In a study with 88 deficit and 235 nondeficit patients, an association was found between cytomegalovirus seropositivity and deficit schizophrenia (11). The association remained significant after covarying for psychotic symptoms and for demographic features known to be associated with cytomegalovirus seropositivity, and after correcting for multiple comparisons. No association was found with five other human herpesviruses. Goff et al (12) found that serum folate concentration was significantly lower in patients with deficit than nondeficit schizophrenia, a result whose interest increases in view of their finding that the C677T polymorphism of methylenetetrahydrofolate reductase was associated with negative symptoms (13). Replication is needed.

A meta-analysis has confirmed that male gender is a risk factor for deficit (but not for nondeficit) schizophrenia (14).

COURSE OF ILLNESS

Premorbid functioning

Evidence of worse psychosocial functioning in patients with deficit than in those with nondeficit schizophrenia, both before the appearance of positive symptoms and later in the course of the illness, was reviewed in Kirkpatrick et al (3). The higher degree of impairment could not be attributed to more severe positive symptoms, depressive mood or other dysphoric affect, or substance abuse.

Since that review, Galderisi et al (15) have replicated the finding of poorer premorbid adjustment during childhood and adolescence, but not in adulthood, in patients with deficit schizophrenia than in those with nondeficit schizophrenia. They also showed that the association between the deficit state and poor premorbid adjustment was not due to the presence of more severe negative symptoms in the deficit group.

Long-term prognosis

Recent studies confirmed that the diagnosis of deficit schizophrenia is associated with a worse long-term prognosis, as compared with nondeficit schizophrenia. Tek et al (16), in a prospective study including 46 patients with deficit and 174 with nondeficit schizophrenia, found that after an average of five years, the deficit patients had a poorer quality of life, poorer social and occupational functioning, and more severe negative symptoms, but were less distressed and did not show more severe positive symptoms. In a study by Chemerinski et al (17), 111 chronic patients with deficit schizophrenia and 96 with nondeficit schizophrenia were followed up for 6 years. The nondeficit group was further subdivided into delusional and disorganized types. Functional impairment was greatest in delusional, lowest in disorganized and intermediate in the deficit group.

RESPONSE TO TREATMENT

Convincing evidence is available that both old and new-generation antipsychotics may act on secondary negative symptoms by removing, in part or completely, some of their causes, such as positive symptoms, depression or extrapyramidal symptoms. However, the efficacy of these drugs on primary and persistent negative symptoms has not been proven (18).

A meta-analysis by Leucht et al (19) showed that amisulpride was significantly superior to placebo, but not to conventional antipsychotics, in patients suffering predominantly from persistent negative symptoms. A study of Buchanan et al (20) found no efficacy for clozapine on negative symptoms among deficit patients. No other evidence supports the efficacy of clozapine on primary and enduring negative symptoms (see 17 for a systematic review). Kopelowicz et al (21) investigated the efficacy of olanzapine in 39 patients with deficit or nondeficit schizophrenia: an improvement of positive, negative and extrapyramidal symptoms was observed among nondeficit patients, while in the deficit group only extrapyramidal symptoms improved, strongly suggesting that olanzapine is efficacious for secondary but not for primary negative symptoms of schizophrenia. Lindenmayer et al (22) tested the efficacy of olanzapine on primary negative symptoms in 35 patients with deficit schizophrenia. They reported a significantly higher decrease of the negative symptoms score of the Positive and Negative Syndrome Scale (PANSS) in the olanzapine than in the haloperidol group, in the absence of significant changes of positive symptoms, general psychopathology and depression, and considered these findings as an evidence of olanzapine efficacy in the treatment of primary negative symptoms. However, in the absence of data on a nondeficit group, these findings are difficult to interpret and do not rule out the possibility that olanzapine reduces secondary but not primary negative symptoms.

Based on the hypoglutamatergic hypothesis, several studies investigated the possibility that primary negative symptoms would improve following treatment with compounds that increase NMDA receptor transmission. Full agonists of the glycine site, such as glycine and D-serine, as well as a partial agonist of the glycine site, D-cycloserine, when used as adjuncts to antipsychotic drugs, have shown a favorable effect in the treatment of negative symptoms, including deficit or primary negative symptoms (23-26). However, in a large multicenter, double-blind study, 157 patients with schizophrenia or schizoaffective disorder who had substantial negative symptoms but at most mild positive, depressive, or extrapyramidal symptoms, were randomly assigned to adjunctive treatment with glycine, D-cycloserine or placebo for 16 weeks (27). Neither glycine nor D-cycloserine was superior to placebo for negative symptoms; no evidence was found that treatment effects differed in deficit versus nondeficit subjects. According to the authors, the discrepancy between their findings and those from previous studies might be due to the high percentage of patients treated with new-generation antipsychotics in their trial; in fact, evidence has been provided that the efficacy of compounds increasing the NMDA transmission on negative symptoms is more robust in subjects treated with conventional antipsychotics than in those treated with new-generation antipsychotics (28).

A need for effective pharmacological treatment is one of the most important research issues in the area of deficit schizophrenia.

NEUROCOGNITIVE AND NEUROLOGICAL FINDINGS

Early neurocognitive studies reported a greater impairment on tests sensitive to fronto-parietal dysfunction in deficit compared with nondeficit schizophrenia patients (29-31). With one exception (32), more recent investigations failed to confirm these results (15,33-38).

A recent meta-analysis (37) including 13 neuropsychological studies concluded that patients with the deficit syndrome were globally more neuropsychologically impaired than nondeficit patients. Most effect sizes were small, but those for tests of olfaction (1.11), social cognition (0.56), global cognition (0.52), and language (0.51) were moderate or large. According to Cohen et al (37), the neuropsychological profile of deficit patients does not support the hypothesis that deficit schizophrenia is the more severe end of a continuum: if it were so, the greatest effect sizes should be found for memory, attention and working memory, i.e. the domains most significantly involved in schizophrenia (39).

Studies including a structured neurological examination confirmed the previously reported greater neurological impairment in patients with deficit than in those with nondeficit schizophrenia (15,34,40), supporting the hypothesis that the former is related to non-progressive, non-localized brain damage. However, two out of these three studies did not confirm the previously reported association between the deficit syndrome and an impairment of sensory integration (40), and found instead an association with an impaired sequencing of complex motor acts (15,34). The most recent study reporting an association between deficit schizophrenia and sensory integration deficits included a small sample of patients with the syndrome (n=12) and did not assess the simultaneous effect of negative symptoms and deficit/nondeficit categorization on neurological impairment (41).

Brain imaging findings

Four studies found no enlargement of the lateral ventricles in patients with the deficit syndrome (42-45). The negative finding is surprising: the enlargement of the lateral ventricles is one of the most replicated brain imaging findings in schizophrenia, and has been – although not consistently – reported to be associated with negative symptoms and poor outcome. Except for the study by Sigmundsson et al (43), all the others included a group of patients with nondeficit schizophrenia, in which lateral ventricles were larger than in healthy controls.

An involvement of fronto-parietal brain circuits in deficit schizophrenia was suggested by early functional brain imaging studies (46-49), in agreement with early cognitive findings. More recent investigations confirmed metabolism/cerebral blood flow abnormalities in the frontal and/or parietal regions in patients with deficit compared to nondeficit schizophrenia (50-52). Neuronal loss in prefrontal cortex is suggested by a proton magnetic resonance spectroscopy study reporting lower *N*-acetylaspartate/creatine ratio in this region in a small sample of deficit patients compared to nondeficit patients and healthy controls (53).

Electrophysiological findings

Recent event-related potential (ERP) studies do not support the severity continuum hypothesis. Turetsky et al (54) investigated a putative endophenotype of schizophrenia, the left lateralized amplitude reduction of the P3 component of the event-related potentials (ERPs). This abnormality was found in nondeficit schizophrenia, while a right parietal reduction of the component was observed in the deficit group.

Bucci et al (55) investigated evoked and induced 40-Hz gamma power, fronto-parietal and fronto-temporal event-related coherence in patients with deficit or nondeficit schizophrenia and in matched healthy controls. A reduction of both induced gamma power and event-related coherence was observed only in nondeficit patients with respect to controls. As these measures reflect cortical functional connectivity, it might be speculated that the fronto-temporal and fronto-parietal dysconnection hypothesis only applies to nondeficit schizophrenia. In a partially overlapping sample, Mucci et al (56) found evidence of a double dissociation of ERP abnormalities: compared to healthy subjects, only patients with

deficit schizophrenia showed an amplitude reduction of the N1 component over the scalp central leads, and a reduced activity of its cortical generators in the cingulate and parahippocampal gyrus, whereas only patients with nondeficit schizophrenia showed a left-sided reduction of the P3 component and of its generators' activity, that was also reduced in bilateral frontal, cingulate and parietal areas.

Other findings

A factor analysis of the Schedule for the Deficit Syndrome (SDS), used to assign patients to deficit or nondeficit subgroups, suggested that the six negative symptoms of the SDS loaded onto two factors (57). The first, which the authors of the study called the avolition factor, consisted of curbing of interest, diminished sense of purpose, and diminished social drive; the second one, named emotional expression, included restricted affect, diminished emotional range, and poverty of speech. A review of the literature suggested a fairly similar pattern in studies of schizophrenia as a whole (58). These findings raise the interesting possibility that there are somewhat separate circuits or mechanisms for these two broad groups of negative symptoms, a possibility that could be explored with imaging and other studies.

DISCUSSION

Since the time of the 2001 review, additional studies have provided evidence for the separate disease hypothesis of deficit schizophrenia. Most notably, the findings that deficit subjects have increased summer births and more normal regional brain volume, compared to nondeficit subjects, have received further support.

Other intriguing findings have also emerged. The most important is the double dissociation of the deficit and nondeficit groups with event-related potentials (56), as a double dissociation supports the separate disease hypothesis. The association with cytomegalovirus seropositivity is also potentially important, as this marker could be used in studies of gene/environment interaction. Both findings, however, await replication.

There are also disappointments in the research to date. As noted above, earlier evidence had suggested that glycine agonists might be effective treatments for the negative symptoms of deficit patients, but a large multicenter trial did not confirm these preliminary studies. Thus there remains no proven treatment for primary negative symptoms (59). Drugs with innovative mechanisms of action will probably be required.

There has also been a lack of progress in the area of genetics. The most appropriate strategy at this juncture may be a genome-wide association study, in which deficit subjects are considered as if they were a separate disease. The existing family studies, as well as the replicated difference with regard to an environmental risk factor – summer birth – suggest that there may be genetic differences between deficit and nondeficit schizophrenia.

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