Schizophrenia: a multisystem disease?

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A multisystem disease is one that usually affects a number of organs and tissues during the course of the illness (Dorland, 2008). It has long been observed that some individuals with schizophrenia have levels of general physical illnesses in excess of that seen in the general population, but recent studies suggest that *most* people with schizophrenia have co-morbid physical disease and multiple related risk factors. Jones et al. (2004) reported that 74% of patients with schizophrenia had at least one chronic co-morbid medical condition. Bell et al. (2009) found that 90% of Medicaid recipients with schizophrenia had at least one major metabolic risk factor. Using a higher standard of at least three major risk factors (NCEP-ATP-III guidelines: abdominal obesity, hypertriglyceridemia, dyslipidemia, hypertension and hyperglycemia) approximately 40% of European patients and up to 51.6% patients with schizophrenia in the United States satisfy criteria for the metabolic syndrome (De Hert et al., 2009; Meyer et al., 2005). In the METEOR study, the largest analysis of risk factors in schizophrenia and related disorders reported that 69.9% had lipid disorders and 43.4% had hypertension (De Hert et al., 2008). Together this evidence suggests that most people with schizophrenia have a significant co-morbid physical illness and further the great majority have metabolic risk factors (Mitchell and Malone, 2006).

Rates of co-morbidity appear to be influenced by the severity of psychiatric symptoms, the setting of study and nature of prescribed medication. Physical co-morbidity in turn has an impact upon quality of life, suicide attempts and mortality, even when suicide is eliminated (Heila et al., 2005; Hennekens et al., 2005; Joukamaa et al., 2006; Kolotkin et al., 2008). While core symptoms of schizophrenia usually first emerge in the late teens and early twenties, peripheral physical disease gradually increases with age (Bresee et al., 2010). Similarly metabolic risk factors are usually elevated at first episode but accumulate with time (Saddichha et al., 2008). Lifestyle and cardiovascular risk factors play an important role in the physical complications but they do not appear to account for the entire variance (Connolly and Kelly, 2005). Antipsychotic drugs certainly contribute to physical co-morbidity (Oriot et al., 2008), but this effect is likely to be magnified in a vulnerable population. All metabolic risk factors are important but we should give special attention to those that are potentially reversible. Recent research has highlighted some valuable insights in the following areas.

Body weight and lipids

Body weight, and in particular abdominal obesity, is a major concern in schizophrenia and one that directly influences quality of life (Kolotkin et al., 2008). A recent meta-analysis suggested a typical weight gain of 3.8 kg in drug-naïve patients upon starting antipsychotic treatment (Tarricone et al., 2010). Approximately 50% of those with schizophrenia are overweight judging by waist circumference (De Hert et al., 2009) and this figure may be around 20% in first episode patients (De Hert et al., 2006). The cardiovascular risk attributable to obesity and elevated levels of cholesterol, triglycerides or low levels of high-density lipoproteins (HDLs) is well recognized. Saari et al. (2005) examined serum lipids in schizophrenia and related psychoses. Mean fasting total cholesterol in patients with schizophrenia was 20 mg/dl higher than in the healthy comparison group. In a controlled study of drug-naïve Chinese patients that used magnetic resonance imaging, Zhang et al. (2004) found slight elevations in fat indicators at baseline, but significantly increased subcutaneous and intra-abdominal fat, following 10-week administration of chlorpromazine and risperidone. This is important because visceral (intra-abdominal) adiposity is closely associated with hyperinsulinaemia, dyslipidaemia and impaired glucose tolerance.

Glucose and insulin resistance

The link between schizophrenia and diabetes mellitus was reported before the advent of antipsychotics (Braceland et al., 1945; Kasanin, 1926; Lorenz, 1922). In approximately half of the cases, hyperglycaemia resolves when the antipsychotic drug is withdrawn and recurs if it is reintroduced (Ananth et al., 2002). This would suggest that a large percentage of cases are drug-induced but many cases are not

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iatrogenic. Diabetes can be seen in first episode patients and impaired glucose tolerance or insulin resistance is manifest in first episode drug-naïve patients with schizophrenia (Ryan et al., 2003; Cohn et al., 2006; Spelman et al., 2007; Fernandez-Egea et al., 2009; Verma et al., 2009). However, these problems accumulate especially in those taking atypical antipsychotics (Gianfrancesco et al., 2006; Smith et al., 2008) although this effect is debated (Holt and Peveler, 2006).

Platelet activation

Walsh et al. (2002) found that drug-naïve, first-episode schizophrenic patients had altered platelet function as evidenced by a significantly increased number of integrin αIIbβIIIa receptors/platelet. Such an increase might be expected to indicate early platelet activation and to cause increased platelet aggregation, thereby potentially contributing to the observed increased risk of development of cardiovascular disease in schizophrenic patients compared with the general population.

Schizophrenia and inflammation

There is an evolving body of literature to support the view that schizophrenia is a disorder with a pro-inflammatory phenotype, not just centrally but in the periphery also. Such a view is consistent with the hypothesis that schizophrenia is a multisystem disease and may help explain the high level of physical co-morbidity. Postmortem brain studies have shown activated microglial cells in at least a subset of patients with schizophrenia (Radewiscz et al., 2000). There are also reports of an increased frequency of activated lymphocytes in the cerebrospinal fluid (CSF) of patients with acute schizophrenia (Nikkilä et al., 1999).

Cytokines are key inflammatory messengers which may be divided into a number of functional categories including T-helper type 1 (Th1) and T-helper type 2 (Th2) groups. In brief, Th1 cytokines are concerned with cell-mediated immunity and Th2 cytokines with humoral immunity. Higher white cell counts provide a crude inflammatory marker, an indirect index of cytokine activity and are associated with an increased risk for metabolic syndrome and more severe psychopathology in non-diabetic patients with schizophrenia (Fan et al., 2010). Several investigators have demonstrated elevated interleukin (IL)-6 levels, a cytokine secreted by the innate immune system and the Th2 arm of the adaptive response, in the plasma of patients with schizophrenia. Further evidence in support of Th2 arm activation derives from studies reporting increased levels of IL-10 and IL-8 in patients with schizophrenia. Overall, the data suggest a Th1/Th2 imbalance. For a review see Stober et al. (2009) and Potvin et al. (2008).

Conclusions

Schizophrenia is a disorder characterized by high rates of physical co-morbidity and very high rates of metabolic risk factors, many of which remain undiagnosed and untreated. Physical co-morbidity often impacts upon quality of life and ultimately mortality. We propose there is sufficient evidence to consider schizophrenia a multisystem disease. We suggest that reframing schizophrenia as a multisystem disease will help focus the attention of mental health specialists and non-mental health specialists on the physical needs of such patients. Further work should attempt to clarify whether the pro-inflammatory phenotype observed in schizophrenia is in essence the basis of a multisystem disorder.

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