Metabolic disturbance in first-episode schizophrenia

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Background Schizophrenia shortens life, e.g. through suicide and obesity-related diseases such as type 2 diabetes mellitus. It is assumed that medications play a major role, but most of the evidence for this comes from studies poorly controlled for variables such as lifestyle and medication status.

Aims To determine whether schizophrenia is associated (independently of medication) with the development of certain metabolic disturbances and whether these might be explained by stress axis dysfunction.

Method Literature review.

Results Most studies did not control for confounding factors such as previous usage of medication, lifestyle, age and ethnicity. A few conducted in drug-naïve patients with first-episode schizophrenia appear to indicate that these patients have higher than expected rates of visceral obesity and impaired fasting glucose concentrations, which may be related to a subtle disturbance of the hypothalamic–pituitary–adrenal axis.

Conclusions Schizophrenia is independently associated with physical illnesses that have a metabolic signature. Therefore, patients need to have a thorough physical assessment at diagnosis and at regular intervals thereafter. Metabolic disturbances have been found in drug-naïve patients with first-episode illness and may be an inherent part of the illness.

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Schizophrenia is a life-shortening disease (Brown, 1997). Premature death is common, with life expectancy reduced by over 20%. Although suicide remains the single largest cause of death at 28%, the lifetime risk of suicide has been adjusted from 10% to 4% because most of the deaths occur within the first year following diagnosis (Inskip *et al*, 1998). Over 60% of the deaths in schizophrenia are accounted for by natural causes such as cardiovascular illness; the standardised mortality ratios for cardiovascular illness in schizophrenia are twice as high as those for the general population (Brown *et al*, 2000). Predisposing factors for cardiovascular illness include non-modifiable factors such as age, gender and family history, and modifiable risk factors such as lifestyle and various biochemical parameters, of which obesity is one (Goldbourt & Neufeld, 1988; Wood *et al*, 1998).

METHOD

The topics of obesity, type 2 diabetes mellitus and hypothalamic–pituitary–adrenal (HPA) axis, and schizophrenia, were reviewed using an electronic database (Medline) and a manual search of papers published before 1966. In addition, studies conducted by J.H.T. pertaining to these issues are described.

RESULTS

Obesity and schizophrenia: location, location, location?

Obesity is a worldwide epidemic and it is estimated that 300 million people are obese, defined as having a body mass index (BMI) in excess of 30 kg/m^2 (for review, see Hill *et al*, 2003). A meta-analysis (Allison *et al*, 1999*b*) and review (Taylor & McAskill, 2000) have suggested that antipsychotic drugs – in particular, certain atypical antipsychotic agents – are associated with this weight gain, and schizophrenia has been associated with obesity (Brugha *et al*, 1989; Kendrick, 1996; Allison *et al*, 1999*a*). Certain illnesses such as type 2 diabetes mellitus, insulin resistance, dyslipidaemias and cardiovascular disorders, together with obesity, have been termed the metabolic syndrome (Reaven, 1988) and appear to occur more frequently in people with schizophrenia, as has been shown by a recent study conducted in Finland (Heiskanen *et al*, 2003). It is believed that obesity-related illnesses may be associated particularly with an increase in visceral fat, the most metabolically active constituent of abdominal obesity (Ryan & Thakore, 2002).

In order to control for the confounding effects of medication, we measured visceral fat distribution using computed tomography in 15 patients with schizophrenia and matched them with healthy controls in terms of age, exercise, diet, smoking habits and alcohol intake (Thakore *et al*, 2002). Seven patients were drug-naïve and the rest had not taken any oral neuroleptic preparation for at least 6 weeks and had had no intramuscular preparation for 6 months; none of the patients had been taking any form of atypical neuroleptic agent prior to entering the study. Patients with schizophrenia had a higher mean BMI than the control group: 26.7 (s.d.=1.1) kg/m^2 *v.* 22.8 (s.d.=0.5) kg/m^2. Patients and controls had similar amounts of total body fat and subcutaneous fat, but the patients had over 3.4 times more intra-abdominal fat than the normal controls: 13 232.0 (s.d.=2666.5) mm^2 *v.* 3879.9 (s.d.=571.9) mm^2 However, there was no difference in intra-abdominal fat distribution between patients who were drug-naïve and those who were drug-free: 12 442.4 (s.d.=9762.6) mm^2 *v.* 14 133.9 (s.d.=11 656.8) mm^2.

An increase in visceral fat is not merely a 'mass effect' of a raised BMI; Enzi *et al* (1986) found that healthy volunteers with BMI values $\geqslant$26 had less intra-abdominal fat (4650 mm^2) than the patients in our study (13 232 mm^2). Chronically elevated levels of cortisol, also seen in our study, may provide an explanation for the increase in intra-abdominal fat, as the density of glucocorticoid receptors (cytosolic signal transducers for steroids such as cortisol) and the concentrations of the lipogenic enzyme lipoprotein lipase (a key enzyme in fat deposition) are higher in visceral fat than in subcutaneous fat (Ottoson *et al*, 1994; Pedersen *et al*, 1994).

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Hyperglycaemia, insulin resistance and schizophrenia: an illness effect?

Even though the higher rates of type 2 diabetes mellitus observed in people with schizophrenia have been attributed to the use of antipsychotic medications – in particular, atypical agents – this is by no means a universally accepted finding. For instance, Mukherjee *et al* (1996) studied a cohort of patients with schizophrenia (n=95), and observed that the prevalence of diabetes was age-dependent and greater in those taking conventional neuroleptic medications. Subramaniam *et al* (2003) reported a rate of undiagnosed diabetes mellitus of 16% and a rate of impaired glucose tolerance of just over 30% in a cohort of residential patients with schizophrenia, none of whom had ever received an atypical neuroleptic drug; yet the rate of type 2 diabetes mellitus in the general population of a similar age was over 22%, indicating that patients with schizophrenia are less likely to have their diabetes diagnosed than their counterparts without mental illness.

The introduction of atypical neuroleptics has added to this debate, although most of the evidence implicating these compounds is based on case reports and various cross-sectional epidemiological studies (Liebzeit *et al*, 2001; Sernyak *et al*, 2002). In contrast to these findings, Lieberman *et al* (2003) conducted a prospective study in a Chinese population, comparing chlorpromazine with clozapine in drug-naïve patients with first-episode schizophrenia over a 52-week period, and showed that despite significant increases in weight (which were equal between the two compounds in question), there was no significant increase in fasting plasma glucose levels at the end of the study period. However, the study did not have a normal control group as a reference population. This is important, because the rates of obesity and type 2 diabetes mellitus in this population are lower than those found in North America, or indeed in Europe. Furthermore, lifestyle issues such as diet and exercise were not discussed either before or during the treatment period.

Is it possible that a mechanism other than medication might be responsible for such findings? A number of papers from the era before the use of antipsychotic drugs add credence to this hypothesis, although problems with diagnosis, small size of study group and other methodological issues make it difficult to interpret the significance of these valuable earlier studies (Lorenz, 1922; Braceland *et al*, 1945; Freeman, 1946; Langfeldt, 1952). It is notable that a family study found that up to 19% of first-degree relatives of patients with schizophrenia had type 2 diabetes mellitus, which indicates that this endocrine condition and schizophrenia might have a genetic association (Mukherjee *et al*, 1989).

In an attempt to determine whether schizophrenia is associated with abnormal glucose metabolism, we compared fasting levels of plasma glucose, insulin, lipids and cortisol measures in a group of hospitalised, drug-naïve patients with first-episode schizophrenia (n=26) with those of a healthy volunteer group matched in terms of age, ethnicity, exercise, diet, smoking habits and alcohol intake (Ryan *et al*, 2003). Anthropometric and lifestyle data indicated that the only significant difference between the two groups was that patients had a higher saturated fat intake than did controls. Over 15% of patients with schizophrenia had impaired fasting glucose levels – compared with none in the control group – as defined by the American Diabetes Association (1997) criteria. Patients with schizophrenia, compared with the control group, had significantly higher plasma levels of fasting glucose (5.3 (s.d.=0.9) mmol/l *v.* 4.8 (s.d.=0.3) mmo/l), insulin (68.2 (s.d.= 64.6) pmol/l *v.* 55.2 (s.d.=26.5) pmol/l) and cortisol (499.4 (s.d.=161.4) nmol/l *v.* 303.2 (s.d.=10.5) nmol/l), and were more insulin-resistant: 2.3 (s.d.=1.0) *v.* 1.7 (s.d.=0.7). Both the control and the patient groups had similar levels of lipids. Finally, there was no significant association between severity of symptoms and plasma levels of glucose, indicating that the 'stress of hospitalisation' was an unlikely cause of the hyperglycaemia.

The rate of impaired fasting glucose concentration observed in our group of patients (>15%) is greater than that found in a recent European study (8.5%, Gourdy *et al*, 2001). Type 2 diabetes mellitus and vascular complications occur in a third of those with impaired fasting glucose levels (Alberti, 1996). Medication, age, ethnicity, physical inactivity and smoking are unlikely to explain our findings (King & WHO Ad Hoc Reporting Group, 1993; Shaten *et al*, 1993). Although our patients consumed more saturated fat, studies do not indicate a positive association between a high intake of saturated fat and hyperglycaemia (Colditz *et al*, 1992; Salmeron *et al*, 1997, 2001), however, patients with schizophrenia did have higher levels of cortisol than did normal controls.

Are patients with schizophrenia biologically stressed?

A common endocrine reaction to stress involves activation of the hypothalamic–pituitary–adrenal (HPA) axis (Axelrod & Reisine, 1984). As in Cushing's syndrome and melancholic depression (Wajchenberg *et al*, 1995; Condren & Thakore, 2001; Thakore *et al*, 2002), a dysregulated HPA axis can lead to abnormal glucose metabolism and visceral obesity (Rosmond & Bjorntorp, 2002). Schizophrenia is associated with abnormalities of this axis (Altamura *et al*, 1989; Coryell & Tsuang, 1992; Kaneko *et al*, 1992; Lammers *et al*, 1995), and we have confirmed this using a rather crude indicator of HPA axis activity in two studies (Thakore *et al*, 2002; Ryan *et al*, 2003).

To date, HPA axis disturbance has been less consistently reported in schizophrenia than in depression (Holsboer, 1998; Cotter & Pariante, 2002). With respect to schizophrenia, adrenocorticotrophic hormone (ACTH) and cortisol responses to corticotrophin-releasing hormone (CRH) are indistinguishable from controls, although pre-treatment with dexamethasone results in an exaggerated CRH-induced pituitary–adrenal response in patients (Roy *et al*, 1986; Lammers *et al*, 1995). Most (but not all) studies have shown that dexamethasone suppresses plasma levels of cortisol in patients with schizophrenia (Dewan *et al*, 1982; Tandon *et al*, 1991). Equally discordant findings have been reported in terms of basal activity of the HPA axis as measured by serum cortisol levels (Gil-Ad *et al*, 1986; Roy *et al*, 1986; Whalley *et al*, 1989; Van Cauter *et al*, 1991; Breier & Buchanan, 1992; Rao *et al*, 1995; Elman *et al*, 1998; Kaneda *et al*, 2002). Methodological problems may partly explain the differences observed between the studies quoted. For instance, the effects of medication on HPA axis activity are unclear (Hellewell, 1999), and often a single sample of cortisol has been used to determine HPA activity although it is not clear whether this accurately represents an estimate of mean 24 h activity (Muller & von Werder, 1989).

As mean or integrated measures, such as area under the curve (AUC), of plasma cortisol between 13.00 h and 16.00 h can be used to detect hypercortisolism

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(Halbreich *et al*, 1982), we decided to determine cortisol, ACTH and arginine vasopressin (AVP) levels in drug-naïve patients with first-episode schizophrenia and compare them with a group of volunteers matched for age and gender (Ryan *et al*, 2004). Baseline levels of cortisol and AVP were indistinguishable between patients and controls, although patients had higher ACTH levels. Patients with schizophrenia had a higher mean AUC of ACTH (26.3 (s.d.=6.2) nmol/l *v.* 13.9 (s.d.=3.0) nmol/l) and cortisol (279.4 (s.d.=26.0) nmol/l *v.* 213.1 (s.d.=18.4) nmol/l) but had a lower mean AUC of AVP (0.87 (s.d.=0.24) pmol/l *v.* 1.42 (s.d.=0.34) pmol/l) than controls. A positive correlation between plasma levels of AVP and cortisol, and higher levels of plasma ACTH during the test period, indicate that the pituitary–adrenal axis was more sensitive to vasopressin-mediated stimulation in our patients with schizophrenia. This may be due first to the fact that vasopressin can directly stimulate the release of cortisol from the adrenal cortex (Guillon *et al*, 1995), and second, to the fact that glucocorticoid-induced inhibition of AVP gene transcription may be overcome, thereby allowing this hypothalamic neuropeptide to stimulate the pituitary–adrenal axis (Rivier & Vale, 1983; Kovacs & Sawchenko, 1996; Aguilera & Rabadan-Diehl, 2000; Aguilera *et al*, 2000), leading to a relative hypercortisolaemia with all its consequent effects.

DISCUSSION

Conclusions are difficult to draw, either from the literature at large or even from this short paper. However, there are indications that the illness of schizophrenia is associated with not only an increase in visceral fat distribution but also impaired fasting glucose levels independently of medication, possibly due to a dysfunctional HPA axis. To clarify matters we need prospective studies examining the effects of medication on drug-naïve patients with first-episode schizophrenia. Second, all patients with schizophrenia require regular physical examinations and need to have their blood glucose and lipids measured on a regular basis by either their primary care doctor or (if necessary) their psychiatrist.

CLINICAL IMPLICATIONS

- Drug-naïve patients with first-episode schizophrenia may have important metabolic disturbances, including central obesity and impaired fasting glucose levels.
- Clinicians should be aware of the cardiovascular complications associated with such metabolic disturbances and ensure that their patients have regular contact with their general practitioner – or indeed a diabetologist.
- Appropriate clinicians should not only monitor plasma glucose levels but also check for signs of central obesity by measuring waist–hip ratios at diagnosis and also at regular intervals thereafter.

LIMITATIONS

- The definitions of diabetes and schizophrenia used by earlier researchers would not conform to the rigour of modern standards, and therefore the observations and rates quoted may not be wholly accurate.
- The numbers of patients used in the studies described were small and it may be difficult to extrapolate these findings to larger populations. Larger prospective studies need to be performed.
- A literature search over such a broad area cannot be regarded as fully comprehensive. Some papers were not translated from their original language.

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