The metabolic syndrome, omega-3 fatty acids and inflammatory processes in relation to schizophrenia

Malcolm Peet

Doncaster and South Humber Healthcare NHS Trust, Rotherham Services, Early Intervention Service, Aughton Road, Swallownest, Sheffield, S26 4TH, UK

Abstract

Although schizophrenia is normally regarded as a brain disease, there is clear evidence that schizophrenia is strongly associated with a variety of physical conditions. These include an increased rate of the metabolic syndrome and its physical complications including diabetes and coronary heart disease, and a reduced rate of rheumatoid arthritis. It is argued that these associations may point to a commonality of some aetiological factors. Evidence implicating omega-3 fatty acids in all of these disorders is presented. The associations may derive either from genetic or from environmental factors, including nutrition. Further investigation of these associations may give important clues regarding the aetiology of schizophrenia.

1. Introduction

Schizophrenia is conventionally regarded as a brain disorder, and biological treatment is focused on agents which alter brain function, particularly through effects on neurotransmitters. There is a growing literature to suggest that schizophrenia is not just a brain disease, but is associated with abnormalities in many body systems, including those related to the metabolic syndrome, fatty acid metabolism, and inflammatory and immune processes. This review aims to synthesise these apparently disparate findings. It is suggested that these bodily abnormalities are not simply secondary features, but may be intrinsic to the schizophrenic illness itself.

2. The metabolic syndrome and schizophrenia

It is now well established that the metabolic syndrome and the physical illnesses associated with it, occur with increased frequency in patients who suffer from schizophrenia.

Impaired glucose tolerance in schizophrenic patients was demonstrated long ago, before modern antipsychotic drugs became available [1]. With the advent of antipsychotic drugs, this relationship became confounded by the fact that many of these drugs, and particularly some of the newer so-called “atypical” antipsychotics, can themselves promote weight gain and insulin resistance [2]. However, the inherent relationship between the metabolic syndrome and schizophrenia was confirmed in a recent study of unmedicated first episode schizophrenic patients who showed impaired glucose tolerance and increased visceral adiposity relative to control subjects [3].

As a result of this association of the metabolic syndrome with schizophrenia, the morbidity and mortality from diseases of the metabolic syndrome is much increased in schizophrenic patients. Thus, diabetes is two to four times more prevalent amongst schizophrenic patients than the general population [4,5]. Likewise, the mortality from coronary artery disease in schizophrenic patients is two to three times greater than in the general population [5–7].

It is well recognised that diseases of the metabolic syndrome are promoted by dietary factors [8]. People from the indigenous population of Australia, when
living their traditional hunter/gatherer lifestyle, rarely develop the metabolic syndrome and its associated physical illnesses. When they move into a modern “western” environment and change their diet accordingly, they develop levels of obesity, diabetes and heart disease greater than those of the general population [9]. The specific dietary constituents which are recognised to promote metabolic syndrome and its consequences include high saturated fat and trans-fatty acids, low omega-3 fatty acids, foods with high glycaemic load, and low levels of fresh fruit and vegetables [8,10]. The normal western diet contains many of these elements, and it has been shown repeatedly that the diet of schizophrenic patients is even worse than that of the general population, with high levels of saturated fat and sugar and low levels of fresh fruit and vegetables, fibre and antioxidants [11,12]. The consequent physical health problems in schizophrenic patients are further compounded by a sedentary lifestyle [13,14] and high levels of cigarette smoking [15].

The development of the metabolic syndrome is commonly seen as secondary to the lifestyle of schizophrenic patients, but there is evidence of a more fundamental relationship between the two conditions. One line of evidence comes from ecological studies. It is well recognised that the long-term outcome of schizophrenia is better in developing countries such as India and Nigeria, than in so called developed countries such as UK and USA [16]. It is striking that this epidemiological finding mirrors similar studies of diseases of the metabolic syndrome which are less prevalent in developing countries than in the western world [17]. It is widely accepted that this is due to differences in nutrition. In a recent study, the long-term outcome of schizophrenia was correlated with national diet, and an association was found between diets high in sugar and saturated fat, and a poor outcome of schizophrenia [18]. The association between poor outcome and diets with a high ratio of saturated to polyunsaturated fats, has been reported previously [19]. At present these findings remain at the level of association rather than proven causation, but the parallel with the metabolic syndrome is striking. In addition to the environmental effect of a poor diet contributing to both the metabolic syndrome and the maintenance of schizophrenic symptoms, a possible genetic association between diabetes and schizophrenia has been proposed [20]. It has been shown previously that type 2 diabetes occurs at an increased rate in the first degree relatives of schizophrenic patients [21].

3. Omega-3 polyunsaturated fatty acids

Abnormalities of lipid metabolism including dyslipidaemias are a core feature of the metabolic syndrome. There is also evidence that adiposity and insulin resistance are related to skeletal muscle membrane lipid composition. In Pima Indians, who are particularly prone to the metabolic syndrome, Pan et al. [22] found that delta-5 desaturase activity was independently associated with both insulin resistance and adiposity, as measured by BMI, percentage fat or waist/thigh ratio. Of the individual levels of fatty acids, docosahexaenoic acid (DHA) correlated with adiposity and arachidonic acid (AA) correlated with both insulin resistance and adiposity [23]. The fatty acid composition of skeletal muscle effects dietary fat composition in humans. Thus, it appears that low levels of AA and DHA, possibly due to low dietary intake or reduced delta-5 desaturase activity, are associated with the metabolic syndrome. Low levels of AA and DHA have also been found in red blood cell membranes of patients suffering from diseases of the metabolic syndrome. Min et al. [24] found a significant reduction of AA and a marked reduction of DHA in patients with gestational diabetes. In coronary artery disease, Paganelli et al. [25] found no change in AA but a significant reduction in DHA. This finding mirrors studies in patients suffering from schizophrenia [26]. Of 11 published studies of red blood cell membrane levels of fatty acids in schizophrenia, seven showed significant reductions of AA with the remainder showing no difference from controls. For DHA, again seven studies showed a reduction in RBC membrane DHA levels, two showed no change, and two reported significant increases.

In addition to findings of reduced cell membrane PUFA levels in the metabolic syndrome and schizophrenia, there is also evidence that PUFA treatment, particularly with omega-3 fatty acids, can be beneficial in both conditions. Thus, there is evidence that low dietary intake of omega-3 fatty acids predicts the future development of coronary heart disease [27,28] and possibly diabetes [29]. In schizophrenia, there have been six double blind placebo controlled trials of omega-3 fatty acids used as an adjunct to antipsychotic drugs in the treatment of schizophrenia. Although a meta-analysis of the main effects in these studies was not statistically significant, four of the studies gave positive findings in either the primary or secondary analysis, one study was positive in a sub group analysis, and only one study was entirely negative in outcome [30].

The factors affecting cell membrane of omega-3 levels are complex and are shown diagrammatically in Fig. 1. It is well-established that dietary intake of omega-3 fatty acids affects cell membrane omega-3 levels [23,31]. The synthesis of AA and DHA as well as their incorporation into cell membranes is under genetic control [32,33]. There is also good evidence that omega-3 fatty acids can modulate gene expression, including those genes which are involved in brain function [34]. Smoking and excessive alcohol use have been shown to reduce tissue
omega-3 levels [35,36]. As we have seen there is an association between insulin resistance and cell membrane levels of AA and DHA [22].

4. The strange case of rheumatoid arthritis

Rheumatoid arthritis shares a number of common epidemiological features with schizophrenia [37]. There was an increased prevalence of both rheumatoid arthritis and schizophrenia during the industrial revolution in western countries. It is said that rheumatoid arthritis was virtually unknown prior to the industrial revolution, except amongst the indigenous population of North America. For schizophrenia, there has been debate about whether the increased prevalence during the industrial revolution was due to increased incidence or a worse outcome, but the fact that prevalence did increase is supported by convincing evidence [38]. Both rheumatoid arthritis and schizophrenia are associated with increased levels of some inflammatory markers, so much so that it has been hypothesised that schizophrenia is fundamentally an inflammatory disorder [39]. The metabolic syndrome is also associated with immune activation. Finally, anti-inflammatory treatments which are effective in rheumatoid arthritis, are also beneficial as adjunctive treatments in schizophrenia. These include omega-3 fatty acids [30] and the COX-2-inhibitor celecoxib [40].

Despite all these similarities, it is a well-established observation that rheumatoid arthritis is rare in patients who suffer from schizophrenia [41]. This implies that a number of aetiological factors, including an inflammatory response, are common to both conditions but that the expression of rheumatoid arthritis is blocked in schizophrenia. Kronig et al. [42] recently demonstrated that schizophrenic patients have low levels of soluble inter cellular adhesion molecule -1 (ICAM-1), and that the expression of this molecule in relation to different alleles of the ICAM-1 gene was abnormal in schizophrenic patients relative to healthy control subjects. ICAM-1 is normally elevated in patients with rheumatoid arthritis, [43] and this finding may reflect a disease-related mechanism leading to reduced levels of ICAM-1 in schizophrenia. However, there are many other possible reasons for the low rate of rheumatoid arthritis in schizophrenia.

5. Synthesis

Evidence has been presented to show that schizophrenia carries many of the core features of the metabolic syndrome, including visceral adiposity, insulin resistance and an increased risk of diabetes and coronary heart disease. Schizophrenia and the metabolic syndrome share some other associated features including low cell membrane levels of DHA and increased expression of inflammatory markers. There is emerging evidence that the nutritional associations with schizophrenia (poor outcome with high sugar, high fat diet; improvement with omega-3 fatty acids) mirror those of the metabolic syndrome. It can therefore, be hypothesised that the metabolic syndrome is not simply secondary to schizophrenia, but that the two conditions share some common aetiologies and pathologies. The aetiological factors could be either genetic or environmental or a combination of the two.

The fact that schizophrenia occurs at the same baseline frequency throughout all contemporary human populations has been taken to imply that a genetic basis for schizophrenia was present at a very early stage in human evolution, before the separation of the races [44]. Indeed, it has been suggested that a proneness to schizophrenia is an intrinsic part of being human and possibly related to such fundamental human attributes as language [45]. Therefore, when searching for the genetic basis of schizophrenia, it is appropriate to examine genetic differences between Homo sapiens and their nearest primate ancestors. In fact, very few such differences have been identified. The most prominent identified genetic difference which has functional consequences, is a mutation inactivating the gene encoding the enzyme CMAH which leads to a deficiency
References


