Letter to the Editor

**Omega-3 fatty acid deficiency: A preventable risk factor for schizophrenia?**

Dear Editors,

Epidemiological and monozygotic twin studies indicate that the risk for developing schizophrenia is conferred equally by genetic and environmental factors. While the search for genes that increase susceptibility for schizophrenia has been a focus of recent research efforts, similar efforts need to be made to identify environmental risk factors, particularly those that are amenable to modification. A body of evidence has emerged over the past 50 years that implicates a dysregulation in polyunsaturated fatty acid (PUFA) homeostasis in the pathophysiology and treatment of schizophrenia (McNamara, 2008). PUFAs are lipid family comprised of both omega-3 and omega-6 fatty acids, and PUFA status is governed by both genetic (fatty acid desaturase and elongase genes) and environmental (dietary intake) factors. Long-chain PUFAs, including docosahexaenoic acid (22:6n−3) and arachidonic acid (20:4n−6), are both essential for normal brain development (McNamara and Carlson, 2006), and long-chain PUFA deficiencies are frequently observed in schizophrenic patients.

While these and other data suggest that ‘PUFA deficiency’ is a risk marker for schizophrenia, its status as a risk factor has remained uncertain. A risk factor, unlike a risk marker, implies a causal link with the disease/disorder, correction of which reduces the risk of developing the disease/disorder. Multiple criteria, including prediction, consistency, response to treatment, dose–response, specificity, and biological plausibility, have been established to evaluate the validity of a risk factor (Hill, 1965). The recent findings of Amminger et al. (2010) provide three critical, previously missing, pieces of evidence that are directly relevant to the evaluation of omega-3 fatty acid deficiency as a ‘risk factor’ for schizophrenia.

First, this study demonstrates that adolescents at ultra-high risk for developing psychosis (i.e., subsyndromal symptoms and having a biological parent with schizophrenia) exhibit low erythrocyte levels of two principal long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA, 20:5n−3) and DHA (22:6n−3), prior to psychosis onset. Specifically, mean erythrocyte EPA+DHA composition (termed the ‘omega-3 index’) was 31.1%, a value that is approximately 40% lower than that observed in healthy adolescents (Jakobik et al., 2009). These findings support the ‘prediction’ criterion.

Second, lower blood EPA + DHA levels are consistent with several prior case-control studies finding significantly lower erythrocyte omega-3 fatty acid levels in medication-naïve first-episode or early-episode psychotic patients (Evans et al., 2003; Reddy et al., 2004). These findings support the ‘consistency’ criterion. Third, and most importantly, this study demonstrated that increasing long-chain omega-3 fatty acids status through dietary EPA + DHA supplementation is more effective than placebo for preventing or delaying the onset of psychosis in ultra-high risk subjects. This finding supports the ‘response to treatment’ criterion. It is also relevant that atypical antipsychotic medications, including risperidone, olanzapine, and clozapine, increase omega-3 fatty acid status (Evans et al., 2003; Horrobin, 2003; McNamara et al., 2009) and risperidone was also found to prevent or delay the onset of psychosis in ultra-high risk subjects (McGorry et al., 2002).

Although not directly evaluated in the Amminger et al. (2010) study, the ‘dose–response’ criterion, which would require that subjects with the lowest erythrocyte EPA + DHA levels at baseline would be at higher risk for transitioning to psychosis, does receive indirect support by their finding that supplementation with EPA + DHA, but not placebo, increased erythrocyte EPA+DHA composition and reduced psychosis transition rates. The ‘specificity’ criterion (i.e., specific to schizophrenia), however, cannot be met because omega-3 fatty acid deficiency has been implicated in the pathophysiology of other psychiatric disorders, and may be associated with overlapping clinical, neurochemical, and histopathological features. Indeed, evidence now supports the existence of an ‘omega-3 fatty acid deficiency syndrome’ comprised of a constellation of psychiatric, cognitive, and metabolic features (McNamara, 2008). Finally, the ‘biological plausibility’ criterion is satisfied by multiple findings linking omega-3 fatty acid deficiency during perinatal development with several putative pathophysiological features associated with schizophrenia, including delays in neuronal migration and cortical expansion as well as a long-standing dysregulation in central dopamine neurotransmission (McNamara and Carlson, 2006). Moreover, omega-3 fatty acid deficiency has been found to alter serotonin 5-HT2 receptor binding in rat brain (Delion et al., 1996), and EPA treatment augments blunted platelet 5-HT2 receptor responsiveness in schizophrenic patients (Yao et al., 2004).

Taken collectively, this body of evidence provides empirical support for omega-3 fatty acid deficiency as a ‘risk factor’ for schizophrenia. As in other areas of medicine, identification of a preventable risk factor holds tremendous promise for...
mitigating disease risk and ultimately prevalence rates. Fortunately, omega-3 fatty acid deficiency is a diagnosable (i.e., erythrocyte EPA + DHA composition) and preventable/reversible condition (i.e., increasing dietary EPA + DHA intake). Furthermore, because increasing dietary EPA + DHA intake has been found to be safe and well tolerated following long-term supplementation, it is ideally suited for early (prodromal) intervention, particularly in view of uncertainties regarding when and whether a subject will develop the disorder. Clearly, additional research is required to replicate and extend the findings of Amminger et al. prior to implementing omega-3 fatty acid supplementation in high risk individuals. Nevertheless, this line of research may bring our field closer to achieving the ‘holy grail’ of prevention, and the prospect of improving the lives of millions currently projected to develop this chronic and debilitating disorder.

References


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