Elevated C reactive protein in adults predicts the later development of late-onset or very-late-onset schizophrenia

Faith Dickerson

Correspondence to Sheppard Pratt Health System, 6501 North Charles St, Baltimore, MD 21204, USA; fdickerson@sheppardpratt.org

ABSTRACT FROM: Wium-Andersen MK, Ørsted DD, Nordestgaard BG. Elevated C-reactive protein associated with late- and very-late-onset schizophrenia in the general population: a prospective study. *Schizophr Bull* 2014;40:1117–27.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Some cross-sectional studies have shown that individuals with schizophrenia have higher levels of some markers of inflammation, including pro-inflammatory cytokines and C reactive protein (CRP), than controls.[1 2] CRP is one of the most commonly used markers of inflammation. During acute inflammation (eg, bacterial infection), levels of CRP may increase up to 300-fold.[3] In apparently healthy individuals, plasma levels of CRP are usually below 3 mg/L but can be up to 10 mg/L;[4] however, slightly elevated CRP levels below 10 mg/L in normal subjects may indicate a state of low-grade inflammation[3] which has been associated with increased risk of several diseases, including major depression and bipolar disorder.[5] It has also been shown that a history of autoimmune disease or severe infection increases the risk of schizophrenia.[6] A better understanding of the role of these risk factors would help identify the pathophysiology of schizophrenia.

METHODS OF THE STUDY

CRP levels were measured in 78 810 white Danish adults from the general population; individuals were divided into groups based on CRP quartiles within the study population. Most people were assessed when they were aged 45–70 (range 20–100). Individuals who had a current or past diagnosis of schizophrenia were excluded. Individuals in the cohort were then followed prospectively for up to 20 years and those who were later hospitalised for schizophrenia were identified from two large Danish population studies, the Copenhagen General Population Study and the Copenhagen Heart Study; individuals in the studies could be linked to Danish national case registers, which have complete population-wide information about hospital discharge diagnoses and on causes of death. Cox proportional hazards regression models and Kaplan-Meier survival curves were used to examine the association of elevated CRP with late-onset schizophrenia (onset after age 40) or very-late-onset schizophrenia-like psychosis (onset after age 60), adjusting for numerous covariates and potentially confounding factors including age, gender, education, smoking status, body mass index, levels of blood lipids and chronic disease.

WHAT DOES THIS PAPER ADD

- The study is the first to look prospectively at the level of CRP as a predictor of schizophrenia in the general population.
- The size of the sample is also unprecedented in examining the association between CRP and schizophrenia. A total of 168 out of 78 810 individuals developed late-onset or very-late-onset schizophrenia.
- The study showed that people with CRP in the highest quartile of the group at baseline had a sixfold increased risk of developing late-onset or very-late-onset schizophrenia compared to those in the lowest quartile. Individuals who subsequently developed schizophrenia had CRP levels that were 63% higher than those who did not develop schizophrenia.
- The age-adjusted and gender-adjusted HRs for individuals with late-onset or very-late-onset schizophrenia versus those in the first quartile of CRP were 0.6 (95% CI 0.3 to 1.5) for the second quartile; 1.1 (95% CI 0.5 to 2.3) for the third quartile and 2.2 (95% CI 1.2 to 4.2) for the fourth quartile.
- The cumulative incidence of late-onset or very-late-onset schizophrenia in individuals with the CRP level in the fourth quartile compared with individuals with the CRP level in the first to the third quartiles was log-rank, $p=1\times10^{-3}$.

LIMITATIONS

- The findings are limited to the development of late-onset or very-late-onset schizophrenia, which is a very rare condition and whose pathophysiology may differ from early-onset schizophrenia.
- Cases were identified from diagnoses in national case registers, not from direct clinical assessment which is a limitation because the diagnoses were not confirmed by the investigators.
- CRP levels were measured on average 7–8 years before hospitalisation with schizophrenia or schizophrenia-like psychosis so it is not clear if CRP levels would be associated with psychiatric illness if assessed at an earlier time point.

WHAT NEXT IN RESEARCH

Large prospective studies should be performed in healthy individuals during adolescence or early adulthood to determine if CRP and other inflammatory markers such as Pentraxin 3, antibodies to gliadin, and retroviral antibodies may be predictors of early-onset schizophrenia. It would be of interest to determine the role that these factors have, independently or in combination with CRP, in predicting schizophrenia risk.

DO THESE RESULTS CHANGE YOUR PRACTICES AND WHY?

These results do not change clinical practice. While the association between elevated CRP and the subsequent development of late-onset or very-late-onset schizophrenia was statistically significant in this large population-based study, these results do not translate into clinical practice. It is not possible to say whether the relationship between elevated CRP and the subsequent development of schizophrenia or schizophrenia-like psychosis is causal or specific. Levels of CRP cannot be used to make reliable predictions of schizophrenia risk for individual patients.

Competing interests None. doi:10.1136/eb-2014-101996

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REFERENCES

1. **Miller BJ**, Buckley P, Seabolt W, *et al*. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry* 2011;**70**:663–71.
2. **Dickerson F**, Stallings C, Origoni A, *et al*. C-reactive protein is elevated in schizophrenia. *Schizophr Res* 2013;**143**:198–202.
3. **Gabay C**, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999;**340**:448–54.
4. **Pepys MB**, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest* 2003;**111**:1805–12.
5. **Wium-Andersen MK**, Ørsted DD, Nielsen SF, *et al*. Elevated C-reactive protein levels, psychological distress, and depression in 73, 131 individuals. *JAMA Psychiatry* 2013;**70**:176–84.
6. **Benros ME**, Mortensen PB, Eaton WW. Autoimmune diseases and infections as risk factors for schizophrenia. *Ann N Y Acad Sci* 2012;**1262**:56–66.