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Letter to the Editors

Patients with schizophrenia show raised serum levels of the pro-inflammatory chemokine CCL2: Association with the metabolic syndrome in patients?

Dear Editors,

Serum levels of the pro-inflammatory cytokines IL-1β, IL-6 and TNF-α are raised in schizophrenia (Schuld et al., 2004). However, apart from these pro-inflammatory cytokines, chemokines play an important role in modulating brain function (Adler and Rogers, 2005). The system of chemokines and their receptors has been described as a major regulating system of the brain and the receptor for CCL2, CCR2, is expressed in the brain by astrocytes, microglia and neurons (Bajetto et al., 2002). CCL2 (Chemokine (C–C motif) ligand 2) is an important pro-inflammatory chemokine, playing a key role in the recruitment of monocytes to inflammatory foci (Kamei et al., 2006; Simeoni et al., 2004). Interestingly, a genotypic association was found between the A-2518G polymorphism of the CCL2 gene and resistance to anti-psychotic medication (Mundo et al., 2005) and a predominance of negative symptoms over positive symptoms (Pae et al., 2004). The A-2518G polymorphism affects the production of CCL2 (Mundo et al., 2005). However, it is unclear if CCL2 serum levels are changed in patients with schizophrenia. One study reported a normal level of CCL2 in the serum of a small group of institutionalized male patients (Teixeira et al., 2007), while another study reported an elevation of CCL2 in the cerebrospinal fluid of a small group of patients with psychosis serving as controls for a study on neuro-psychiatric lupus (Iikuni et al., 2006).

Here we present a study on the CCL2 levels in the serum of 145 patients with chronic schizophrenia. Patients participated in a study on the prevalence of abnormalities in glucose metabolism in patients with schizophrenia or schizo-affective disorder treated with anti-psychotics; the demographic data, study design, hyperglycemia measurements, diabetes and metabolic syndrome definition and outcomes have been reported in detail before (Cohen et al.,

Fig. 1. a: CCL2 levels are significantly ($p<0.026$) higher in patients with schizophrenia with the metabolic syndrome (diamond: $n=52$, median 221.91 pg/ml, range up to 955.60 pg/ml) compared to patients without the metabolic syndrome (circle: $n=93$, median 179.08 pg/ml, range up to 781.80 pg/ml), while the CCL2 levels of the latter group are significantly higher ($p<0.001$) compared to the levels of healthy controls (quadrangle: $n=105$, median 141.41 pg/ml, range up to 310.35 pg/ml). CCL2 levels are also significantly ($p<0.02$) higher in the nested age and gender-matched patients with schizophrenia with the metabolic syndrome (closed diamond: $n=23$, median 261.61 pg/ml, range up to 711.82 pg/ml) compared to patients without the metabolic syndrome (closed circle: $n=42$, median 156.63 pg/ml, range up to 504.21 pg/ml), while the CCL2 levels of the latter group are significantly higher ($p<0.04$) compared to the levels of healthy controls (closed quadrangle: $n=65$, median 151.12 pg/ml, range up to 310.35 pg/ml). b: TNF-α levels are significantly ($p<0.001$) higher in patients with schizophrenia (open circle: $n=145$, median 22.15 pg/ml, range up to 271.06 pg/ml) compared to healthy controls (open quadrangle: $n=105$, median 0 pg/ml, range up to 98.68 pg/ml). Note that 49 healthy controls have non-detectable TNF-α levels compared to 38 patients with schizophrenia (indicated by 49=□ and 38=O). TNF-α levels are also significantly ($p<0.035$) higher in the nested age and gender-matched patients with schizophrenia (closed circle: $n=53$, median 20.02 pg/ml, range up to 146.69 pg/ml) compared to healthy controls (closed quadrangle: $n=58$, median 13.93 pg/ml, range up to 72.35 pg/ml) Note that 25 healthy controls have non-detectable TNF-α levels compared to 16 patients with schizophrenia (indicated by 25=■ and 16=●). IL-1β levels are significantly ($p<0.001$) higher in patients with schizophrenia (open circle: $n=145$, median 9.09 pg/ml, range up to 43.34 pg/ml) compared to healthy controls (open quadrangle: $n=105$, median 1.37 pg/ml, range up to 25.80 pg/ml). Note that 51 healthy controls have non-detectable IL-1β levels compared to 29 patients with schizophrenia (indicated by 51=□ and 29=O). IL-1β levels are also significantly ($p<0.007$) higher in the nested age and gender-matched patients with schizophrenia (closed circle: $n=57$, median 10.61 pg/ml, range up to 43.34 pg/ml) compared to healthy controls (closed quadrangle: $n=62$, median 6.89 pg/ml, range up to 20.28 pg/ml). Note that 26 healthy controls have non-detectable IL-1β levels compared to 11 patients with schizophrenia (indicated by 26=■ and 11=●). IL-6 levels are significantly ($p<0.001$) higher in patients with schizophrenia (open circle: $n=145$, median 31.95 pg/ml, range up to 617.10 pg/ml) compared to healthy controls (open quadrangle: $n=105$, median 0 pg/ml, range up to 182.46 pg/ml). Note that 50 healthy controls have non-detectable IL-6 levels compared to 43 patients with schizophrenia (indicated by 50=□ and 43=O). IL-6 levels are also significantly ($p<0.032$) higher in the nested age and gender-matched patients with schizophrenia (closed circle: $n=52$, median 36.49 pg/ml, range up to 208.47 pg/ml) compared to healthy controls (closed quadrangle: $n=57$, median 26.20 pg/ml, range up to 72.35 pg/ml). Note that 28 healthy controls have non-detectable IL-6 levels compared to 18 patients with schizophrenia (indicated by 28=■ and 18=●).

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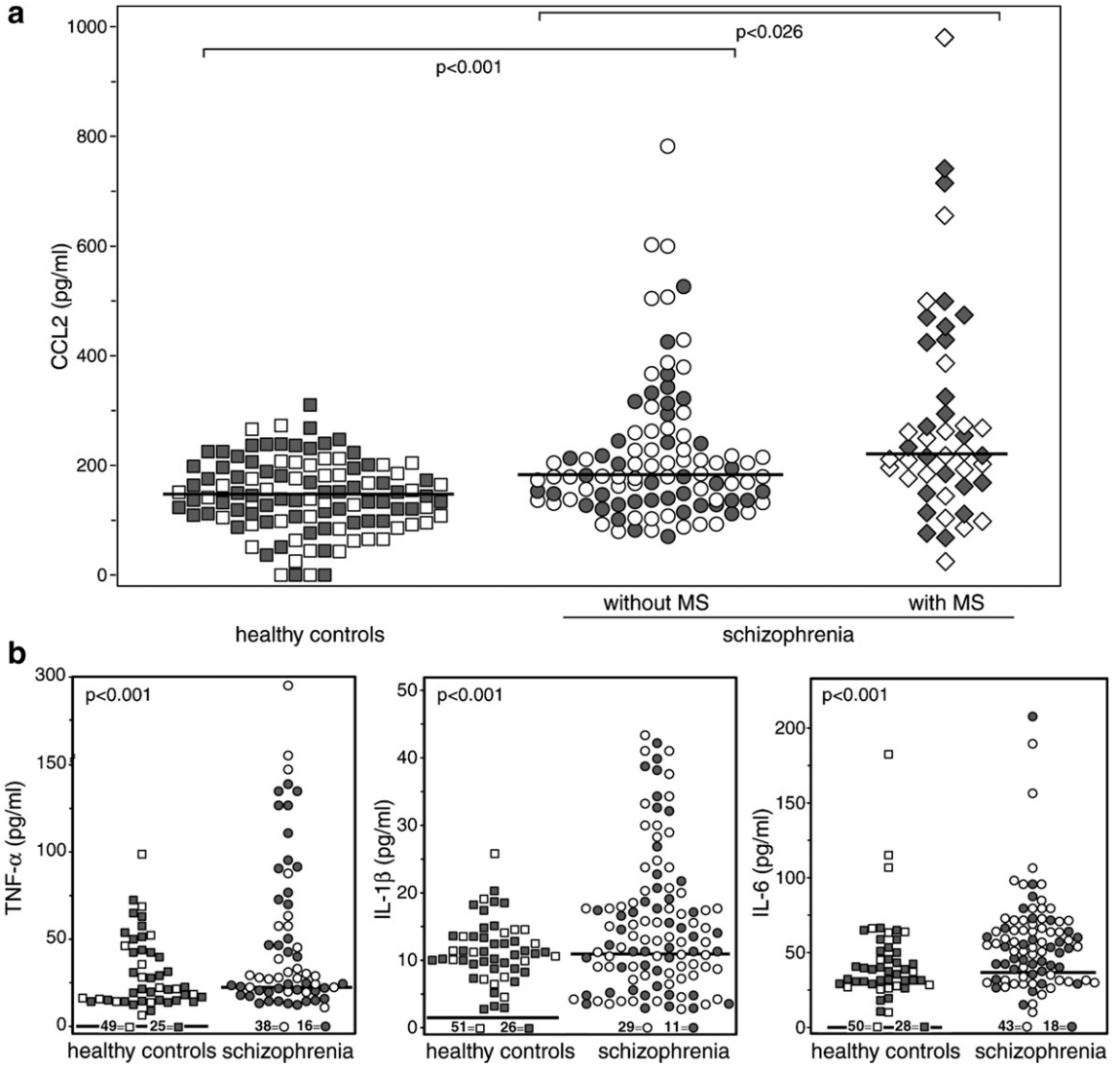
2006). Adult healthy controls (HC, $n=105$) were laboratory, medical staff and students, with blood collection at the same time as the patients. The medical ethics review board METIGG (Utrecht, The Netherlands) approved the study.

Serum CCL2 levels were measured using the Cytometric Bead Array kit (CBA, BD Biosciences, San Diego, USA) according to the manufacturer's protocol. Serum levels of CCL2 were significantly higher in the 145 patients (Fig. 1a, median 196.38 pg/ml, range up to 955.60 pg/ml) compared to the 105 HC (median 141.41 pg/ml, range up to 310.35 pg/ml, $p<0.001$). Because patients and HC differed in age and had different male/female ratios, data were also analyzed as randomly selected nested case–controls of 65 cases with schizophrenia and 65 age and gender-matched HC. This nested study showed that CCL2 levels were also significantly higher in patients (Fig. 1a, median 184.67 pg/ml, range up to 711.82 pg/ml) than in HC (median 151.27 pg/ml, range up to 310.35 pg/ml, $p<0.009$).

Increased CCL2 levels were independent of the use of anti-psychotic medication, both regarding the class of drug (typical versus atypical) as well as regarding the individual drug. Eleven patients did not use any anti-psychotic drug for at least three months. The CCL2 level of this "drug-free" chronic schizophrenic population was higher than that of the HC (yet numbers were too small to reach significance). To verify whether the raised CCL2 level was indeed not due to treatment we retested the 11 drug-free patients together with 13 newly collected drug-naive patients (duration of schizophrenia less than 1 year) and 36 age and gender-matched HC for their CCL2 levels in a separate assay. CCL2 levels were



statistically significantly higher than the HC (patients: median 302.20 pg/ml, range up to 595.50 pg/ml; HC: median 154.90 pg/ml, range up to 534.30 pg/ml, $p<0.001$).

Serum levels of CCL2 correlated positively ($r=0.152$, $p<0.05$) to the prevalence of the metabolic syndrome (MS, prevalence in our study population 51/145), defined according to a modified definition of the National Cholesterol Education Program's Adult Treatment panel III. And, also it correlated in particular and negatively ($r=-0.108$, $p<0.052$) to the HDL levels. As a consequence, the levels of CCL2 were significantly higher in patients with MS (Fig. 1a, median 221.91 pg/ml, range up to 955.60 pg/ml) compared to those without (median 179.08 pg/ml, range up to 781.80 pg/ml, $p<0.026$), though it must be noted that those without MS still had higher serum CCL2 levels compared to the HC population (Fig. 1a, median 141.41 pg/ml, range up to 310.35 pg/ml, $p<0.001$). It is tempting to speculate that the extra increased CCL2 levels in schizophrenia patients with the MS reflect a higher load of atherosclerotic plaques in these patients, since CCL2 plays a critical role in fatty streak development, e.g. hypercholesterolemic CCL2 deficient mice have less arterial lipid deposition (Bajetto et al., 2002).

The CBA allows the simultaneous quantification of IL-1β, TNF-α and IL-6 in the same test and we found all three cytokines elevated in the patients (Fig. 1b). These cytokines did not correlate to the MS and there was no difference between cytokine levels in patients with or without the MS. The levels of CCL2 showed a strong positive correlation to the levels of IL-6, IL-1β and TNF-α.

Limitation of our study is that outcomes are largely based on patients with chronic stable schizophrenia with the vast majority of patients on anti-psychotic medication while drug-free/naive patients have hardly been studied. Moreover we were not informed on the hyperglycemia and the MS in our HC. So, our finding that CCL2 levels are not due to medication and correlate at least in part to the presence of MS (and predominantly to a low HDL-cholesterol) should be taken cautiously and needs confirmation in a confirmative study using patients before and after treatment characterized for the MS and dito HC.

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