Elevated Proinflammatory Markers in 22q11.2 Deletion Syndrome Are Associated With Psychosis and Cognitive Deficits

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ABSTRACT

Objective: 22q11.2 deletion syndrome (22q11.2DS) is a neurogenetic disorder whose phenotype includes high rates of a schizophrenia-like psychotic disorder and immune system abnormalities. Thus, 22q11.2DS is an ideal model for studying the relationship between psychosis and inflammation. The aim of the present study was to identify inflammatory markers that may play a role in the pathophysiologic pathways associated with psychosis and cognitive deficits in 22q11.2DS.

Methods: Forty-nine individuals with 22q11.2DS (13 with psychotic disorders according to *DSM-IV* criteria and 36 without psychotic disorders) and 30 age- and sex-matched healthy controls underwent psychiatric and cognitive assessments at an outpatient clinic. Blood samples from all participants were analyzed for C-reactive protein (CRP), interleukin (IL)-6, IL-10, tumor necrosis factor alpha (TNFα), and IL-1 receptor antagonist levels. The study was conducted between August 2014 and September 2015.

Results: The 22q11.2DS participants had elevated levels of CRP ($P = .004$), IL-6 ($P = .001$), TNFα ($P < .001$), and IL-10 ($P = .028$) compared with controls. Furthermore, the psychotic 22q11.2DS participants had higher levels of IL-6 ($P < .001$) and IL-6/IL-10 ratio (used as an indicator for proinflammatory activation, $P < .001$) compared with the nonpsychotic 22q11.2DS individuals and controls. IL-6 levels and the IL-6/IL-10 ratio correlated with the severity of the cognitive deficits in the 22q11.2DS participants.

Conclusions: Our preliminary findings indicate an involvement of inflammatory processes in the pathophysiology of psychosis and cognitive deficits in 22q11.2DS and are in line with the accumulating evidence for the role of neuroinflammation in nonsyndromic schizophrenia.

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The complexity of identifying a definitive pathophysiologic mechanism(s) for schizophrenia stems from its etiologic heterogeneity. One way to try to delineate mechanisms leading to schizophrenia is by studying individuals with clinical syndromes that have clear genetic etiologies and a highly increased risk for schizophrenia. One such genetic syndrome is 22q11.2 deletion syndrome (22q11.2DS), also known as velocardiofacial syndrome and DiGeorge syndrome. 22q11.2DS syndrome is a common neurogenetic disorder with an estimated prevalence of 1:3,000–1:6,000 live births.[1] It is caused by a microdeletion in the long arm of chromosome 22 and has a characteristic phenotype, including typical facial features, cleft palate, and congenital cardiovascular anomalies, as well as hypocalcemia and immunologic abnormalities. In addition, all individuals with 22q11.2DS cope with cognitive deficits within the borderline range (an average IQ of 75), and 70% of them have psychiatric comorbidities.[1,2] Most strikingly, about one-third of individuals with 22q11.2DS develop schizophrenia-like psychotic disorders,[3] making it the most common genetic syndrome currently associated with schizophrenia.[3]

Several lines of evidence suggest that neuroinflammatory factors are involved in the pathophysiologic mechanisms leading to schizophrenia in the general population. Epidemiologic studies have demonstrated that children of mothers who were exposed to viral, bacterial, or parasitic infections during pregnancy have an increased risk of developing schizophrenia.[4] An increased prevalence of autoimmune conditions (eg, autoimmune thyroiditis, celiac disease, or systemic lupus erythematosus) has been reported in patients with schizophrenia.[5] Additionally, aberrant circulatory levels of several markers of inflammation have been found in patients with schizophrenia, including high levels of C-reactive protein (CRP) and high levels of proinflammatory and anti-inflammatory cytokine levels.[6–9] Several studies investigated the association between serum levels of cytokines and schizophrenia. The most replicated associated findings were with interleukin 6 (IL-6) followed by tumor necrosis factor alpha (TNFα), interleukin 10 (IL-10), and interleukin 1 receptor antagonist (IL-1ra).[6–10] These 4 cytokines have been suggested as trait or state markers for the psychosis as well as for the cognitive deficits associated with schizophrenia.[6,9]

Immunologic abnormalities are part of the 22q11.2DS phenotype. Such abnormalities range from immunologic deficits (eg, thymic hypoplasia and T lymphocytopenia) to an increased risk of autoimmune diseases (eg, hypothyroidism, idiopathic thrombocytopenia, celiac disease, and juvenile rheumatoid arthritis).[11,12]

Because salient features of the 22q11.2DS phenotype include cognitive deficits and an increased risk of schizophrenia and immunologic abnormalities, it is a potentially good model for

Clinical Points

- 22q11.2DS is associated with immunologic abnormalities especially in individuals with schizophrenia-like psychotic disorder, and therefore this syndrome is an excellent model to study the potential role of neuroinflammatory processes leading to schizophrenia.
- Psychotic 22q11.2DS participants had higher levels of proinflammatory markers (ie, IL-6 and IL-6/IL-10 ratio) compared with nonpsychotic 22q11.2DS individuals and controls.
- In the 22q11.2DS group, IL-6 levels correlated with poorer cognitive performance.

studying a possible role of the immune system in the risk for psychosis and cognitive deficits in 22q11.2DS. We hypothesized that immune activation, as reflected by higher levels of CRP and proinflammatory cytokines (ie, IL-6 and TNFα) will be more pronounced in individuals with 22q11.2DS compared with typically developing healthy controls as well as in psychotic 22q11.2DS compared with nonpsychotic 22q11.2DS individuals. We also hypothesized that there will be an association between the severity of the neurocognitive deficits and the immune markers among the 22q11.2DS individuals.

METHODS

Participants

Forty-nine individuals with 22q11.2DS (13 with psychotic disorders and 36 without psychotic disorders) were recruited from the Behavioral Neurogenetics Center at the Sheba Medical Center, Tel Hashomer, Israel. The Behavioral Neurogenetics Center is a large tertiary referral center that coordinates treatment and research on individuals with 22q11.2DS identified by genetic departments and through parents' associations nationwide. The diagnosis of 22q11.2DS had been confirmed in all participants by fluorescent in situ hybridization and by multiplex ligation probe amplification.[13] Thirty typically developing healthy controls were recruited through advertisements within the local community, and they completed the SCL-90-R questionnaire[14] to rule out any major psychopathology. All participants were age- and sex-matched (Table 1), and they were recruited and assessed between August 2014 and September 2015. All participants were screened to verify that they had no inflammatory or infectious conditions prior to inclusion in the study. Weight, height, and cigarette smoking were recorded, according to participant reports.

The study protocol was approved by the Institutional Review Board of the Sheba Medical Center, and informed consent was obtained from all participants or their parents or guardians.

Measures

Neuropsychiatric assessment. All 22q11.2DS participants and their parents were interviewed using the Hebrew version of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime (K-SADS-PL)[15] or the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID).[16]

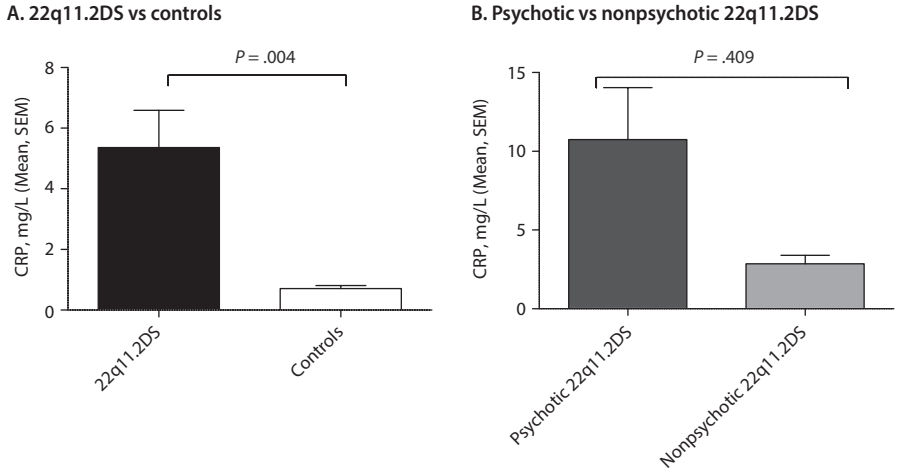
Neurocognitive assessment. Neurocognition was assessed by the Penn Computerized Neurocognitive Battery (CNB). The CNB is a 1-hour long computerized battery consisting of 14 tests assessing 5 neurocognitive domains: executive function, episodic memory, complex cognition, social cognition, and sensorimotor speed. With the exception of 2 tests that are purely speed tests, each test provides measures of both accuracy (number of correct responses) and speed (median time for correct responses), and an efficiency score is calculated by averaging the accuracy and speed scores of each test. Then, the score for each CNB test was *z*-transformed using the mean and standard deviation of a demographically matched typically developing sample, as previously described.[17] An additional domain is the general neurocognitive profile (GNP) that is calculated as the mean of the 5 other domains. The CNB was developed for large-scale genomic studies[17] and applied in developmental samples,[18] schizophrenia consortia,[19] as well as studies of 22q11DS,[20,21] and it is highly correlated with IQ.[22] The CNB was translated into Hebrew and its use in Israeli 22q11.2DS individuals has been recently validated.[23]

Table 1. Demographic and Clinical Variables of the Study Subgroups

Variable	22q11.2DS With Psychosis (n = 13)	22q11.2DS Without Psychosis (n = 36)	Controls (n = 30)	*P* Value (ANOVA, χ^2, or Kruskal-Wallis)
Age, mean (SD), y	28.27 (9.84)	22.9 (8.18)	25.39 (7.35)	.114
Age range, y	14.75–44.33	12.08–44.67	12.50–40.75	
Sex, n (%) female	6 (46.2)	15 (41.7)	12 (40.0)	.932
BMI, kg/m^2, mean (SD)	28.31 (3.69)	23.62 (5.15)	22.46 (2.15)	<.001
Cigarettes smoked per day, mean (SD)	1.82 (6.03)	1.42 (4.54)	0.90 (2.27)	.480
Medications				
Antipsychotics, n (%)	11 (84.6)	3 (8.3)	0 (0.0)	<.001[a]
Mood stabilizers, n (%)	4 (30.8)	1 (2.8)	0 (0.0)	.014[a]
Antidepressants, n (%)	2 (15.4)	8 (22.2)	0 (0.0)	.467[a]
Stimulants, n (%)	1 (7.7)	6 (16.7)	0 (0.0)	.392[a]
Benzodiazepines, n (%)	2 (15.4)	1 (2.8)	0 (0.0)	.168[a]
Blood draw time, h (SD)	11:47 (1:09)	12:26 (0:50)	12:07 (1:24)	.200

[a]Results of χ^2 test between psychotic and nonpsychotic 22q11.2DS participants.
Abbreviations: ANOVA = analysis of variance, BMI = body mass index, SD = standard deviation.

Figure 1. Comparison of C-Reactive Protein Levels Among the Study Groups[a]



[a]Analysis of covariance with age, sex, body mass index, and cigarettes smoked per day entered as potential covariates or fixed factors.

Immunologic testing. Blood samples were collected from all participants on the same day the behavioral assessments were carried out. All samples were drawn around noon (mean time for all samples was 12:13 ± 1:09 h) and processed within an hour. Samples were analyzed for CRP levels in the automated mega-laboratory at Sheba Medical Center. In addition, sera were separated and frozen at −80°C until assayed for IL-1ra, IL-6, IL-10, and TNFα. Cytokine assessment was performed for the entire cohort at the same run using multiplex Luminex X-MAP technology (Cat # ECSTM09, R and D Systems, Minneapolis, Minnesota) according to the manufacturer's instructions. The ratio between IL-6 and IL-10 was calculated in order to assess for a possible shift of the immune system in favor of proinflammatory over anti-inflammatory activity.

Data Analyses

Statistical analyses were conducted using IBM SPSS Statistics for Windows v.20 (IBM Corp, Armonk, New York). First, the 22q11.2DS individuals and the healthy controls were compared. Then, the psychotic 22q11.2DS participants were compared with the nonpsychotic 22q11.2DS participants. Variables that did not distribute normally underwent log transformation to obtain normality (except for the cigarettes smoked per day variable). Analysis of covariance (ANCOVA) was used to compare group differences in CRP levels (first for 22q11.2DS vs healthy controls and then for the psychotic vs the nonpsychotic 22q11.2DS subgroups). Body mass index (BMI) values were calculated and entered alongside age, sex, and cigarette smoking status as potential covariates or fixed factors.

To reduce the possibility of type 1 error, we used 2 multivariate analyses of covariance (MANCOVAs) to test for overall differences in cytokine levels between groups: one was for proinflammatory cytokines (IL-6 and TNFα) and the other was for anti-inflammatory cytokines (IL-1ra and IL-10), with age, sex, BMI, and cigarette smoking status as potential covariates or fixed factors. When significant effects were observed for the MANCOVA, univariate ANCOVAs were conducted to evaluate group differences in individual cytokines. The IL-6/IL-10 ratio was compared among the 22q11.2DS psychotic subgroup, the nonpsychotic subgroup, and the controls by ANOVA with Scheffe post hoc tests. Within the 22q11.2DS group, Pearson product-moment correlations were conducted to test for correlations between the immune markers and CNB domain scores. In addition, a MANCOVA was conducted to test the potential effect of age, BMI, sex, and cigarette smoking on the association between IL-6 and neurocognitive function.

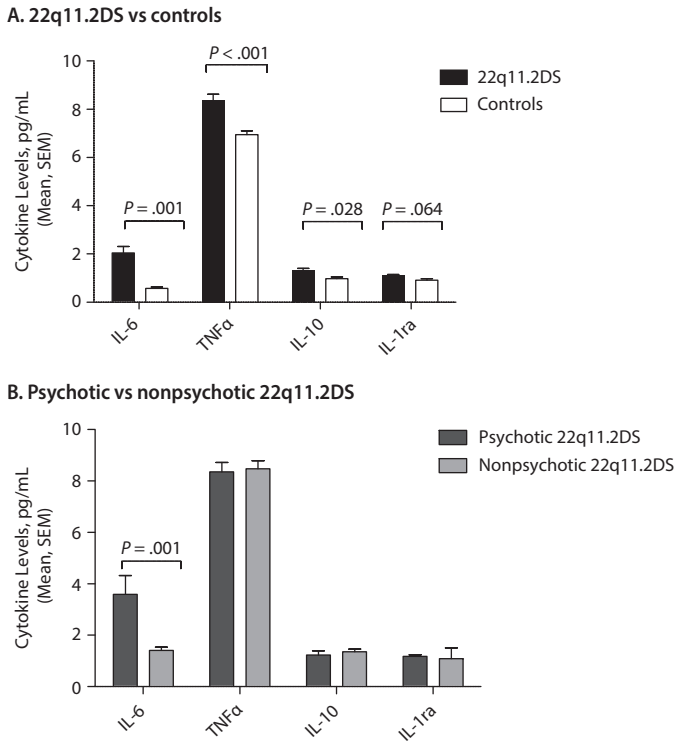
RESULTS

22q11.2DS Versus Controls

The mean ± SD CRP levels were significantly higher for the 22q11.2DS group compared with the controls (5.36 ± 7.86 vs 0.71 ± 0.52 mg/L, $F = 9.13$, $P = .004$, Figure 1A) with a significant effect of BMI ($F = 24.78$, $P < .001$). There were no significant effects of age, sex, or cigarette smoking on the CRP levels.

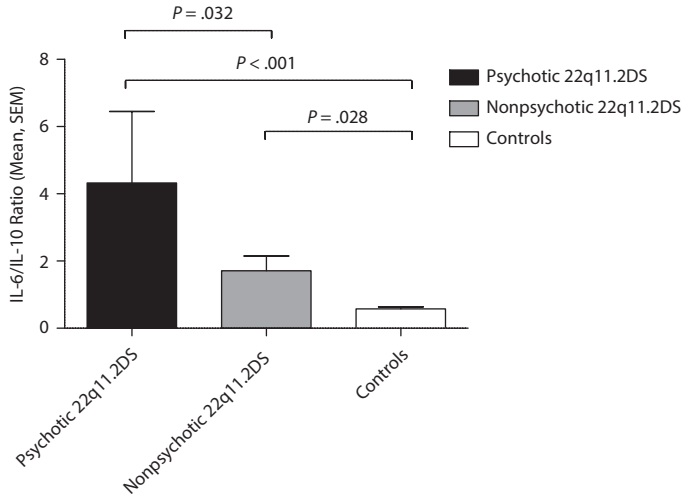
On MANCOVA, both the proinflammatory and anti-inflammatory cytokines were significantly different between the 22q11.2DS group and the control group ($F = 9.92$, $P < .001$ for the proinflammatory cytokines and $F = 3.87$, $P = .026$ for the anti-inflammatory cytokines). BMI had a significant effect on both cytokine groups ($F = 6.19$, $P = .004$ for the proinflammatory cytokines and $F = 3.83$, $P = .026$ for the anti-inflammatory cytokines). Sex, age, and cigarette smoking had no significant effect on cytokine levels. Follow-up ANCOVAs revealed that all cytokines, except IL-1ra, were significantly higher in the 22q11.2DS group compared with the healthy controls (IL-1ra was elevated in a marginally significant manner)—IL-6: 2.06 ± 1.71 vs 0.58 ± 0.13 pg/mL ($F = 12.91$, $P = .001$) with significant effects of both age

Figure 2. Comparison of Cytokine Levels Among the Study Groups[a]



[a]Multivariate analysis of covariance with age, sex, body mass index, and cigarettes smoked per day entered as potential covariates or fixed factors.
Abbreviations: IL-1ra = interleukin 1 receptor antagonist, IL-6 = interleukin 6, IL-10 = interleukin 10, TNFα = tumor necrosis factor alpha.

Figure 3. IL-6/IL-10 Ratio for Psychotic 22q11.2DS Versus Nonpsychotic 22q11.2DS and Controls



Abbreviations: IL-6 = interleukin 6, IL-10 = interleukin 10.

and BMI ($F = 4.16$, $P = .045$ and $F = 8.28$, $P = .005$, respectively); TNFα: 8.44 ± 1.65 vs 6.99 ± 0.87 pg/mL ($F = 14.15$, $P < .001$) with a significant effect of BMI ($F = 5.30$, $P = .024$); IL-10: 1.32 ± 0.63 vs 0.98 ± 0.36 pg/mL ($F = 5.05$, $P = .028$); IL-1ra: 1,114.04 ± 369.35 vs 925.05 ± 315.78 pg/mL ($F = 3.55$, $P = .064$) with a significant effect of BMI ($F = 7.68$, $P = .007$) (Figure 2A).

22q11.2DS With Psychosis Versus 22q11.2DS Without Psychosis

The 22q11.2DS psychotic subgroup (n = 13) consisted of the following diagnoses: schizophrenia (n = 10), schizoaffective disorder (n = 2), and psychotic disorder not otherwise specified (n = 1). The psychotic 22q11.2DS subgroup had higher levels of CRP compared with the nonpsychotic subgroup (10.74 ± 11.93 vs 2.86 ± 2.81 mg/L, respectively), but this difference was not statistically significant because of a confounding effect of BMI (group: $F = 0.70$, $P = .409$, BMI: $F = 11.37$, $P = .002$) (Figure 1B). Age, sex, and cigarette smoking status had no significant effects on the CRP levels. On the MANCOVAs, the psychotic 22q11.2DS subgroup had an overall significant difference in the proinflammatory cytokine levels (IL-6 and TNFα) compared with the nonpsychotic 22q11.2DS subgroup ($F = 3.80$, $P = .031$) with a marginally significant effect of BMI ($F = 3.16$, $P = .054$), but not in the anti-inflammatory cytokines (IL-1ra and IL-10). Age, sex, and cigarette smoking had no significant effects the cytokine levels. On the follow-up ANCOVAs conducted for the proinflammatory cytokines, the psychotic 22q11.2DS subgroup had significantly higher levels of IL–6 compared with the nonpsychotic subgroup (4.45 ± 2.60 vs 1.41 ± 0.67 pg/mL, $F = 18.60$, $P < .001$; Figure 2B) with a nonsignificant effect of BMI. There were no significant differences in TNFα levels between the psychotic and nonpsychotic 22q11.2DS subgroups.

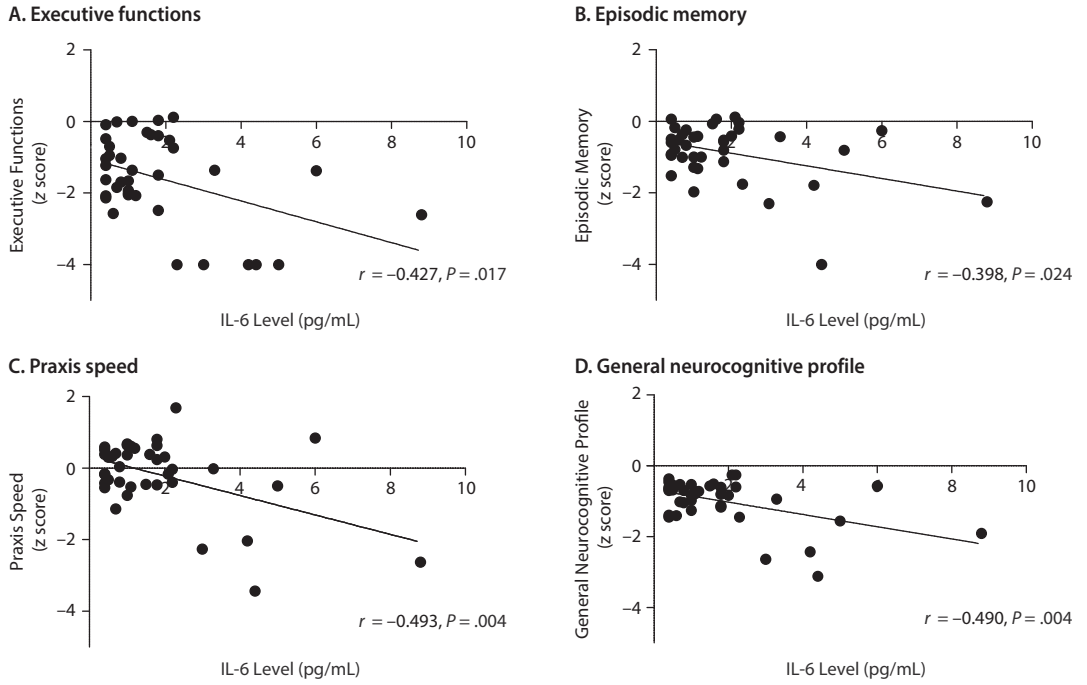
IL-6/IL-10 Ratio

There was an overall group effect on the IL-6/IL-10 ratio. Post hoc analysis revealed that the IL-6/IL-10 ratio significantly differed among all 3 groups and was significantly higher in psychotic 22q11.2DS participants compared with nonpsychotic 22q11.1DS participants that were higher than healthy controls (4.32 ± 7.69 vs 1.71 ± 2.53 vs 0.58 ± 0.31, $F = 11.44$, $P < .001$) (Figure 3).

Association Between IL-6 Levels and Neurocognitive Deficits in 22q11.2DS

The IL-6 levels in the 22q1.2DS group correlated negatively with several CNB domains: executive functions ($r = -0.427$, $P = .017$), episodic memory ($r = -0.398$, $P = .024$), praxis speed ($r = -0.493$, $P = .004$), and the GNP ($r = -0.490$, $P = .004$) (Figure 4A and 4B). To control for the potential effects of age, sex, BMI, and cigarette smoking, we repeated the association using a MANCOVA. Results showed that only IL-6 had a significant effect on the cognitive measures ($F = 3.22$, $P = .028$), and post hoc ANCOVA showed that there was significant effect of IL-6 levels on executive functions, episodic memory, praxis speed, and GNP scores.

Figure 4. Correlations Between IL-6 Levels and CNB Scores in 22q11.2DS



Abbreviations: CNB = Penn Computerized Neurocognitive Battery, IL-6 = interleukin 6.

DISCUSSION

In the present study, we sought to examine the potential contribution of immune processes to psychosis and cognitive deficits in 22q11.2DS. We first demonstrated higher levels of CRP and 3 of the 4 tested cytokines (IL-6, TNFα, and IL-10) in individuals with 22q11.2DS compared with healthy controls. We further demonstrated that psychotic 22q11.2DS individuals had higher circulatory levels of IL-6 and IL-6/IL-10 ratio compared with nonpsychotic 22q11.2DS individuals. Moreover, IL-6 level and the IL-6/IL-10 ratio were also found to be associated with several cognitive deficits in individuals with 22q11.2DS. Thus, our preliminary results support the possibility that inflammatory processes are involved not only in the somatic manifestations of 22q11.2DS (eg, high rates of infectious diseases, especially during infancy, and increased rates of autoimmunity disorders), but also in the neuropsychiatric phenotype as expressed in psychosis and cognitive deficits. We are aware of only 2 previous studies that examined cytokine levels in 22q11.2DS,[24,25] but there are no studies that examined CRP levels in this population. To the best of our knowledge, this is also the first report on the relationship among proinflammatory immune markers, psychosis, and cognitive deficits in 22q11.2DS. Our findings are in line with previous studies on nonsyndromic schizophrenia that have suggested a possible underlying low-grade inflammatory pathophysiologic mechanism for schizophrenia that differs from more overt inflammatory conditions, such as autoimmune diseases (eg, rheumatoid arthritis) or other noninfectious inflammatory conditions (eg, atherosclerosis).[26]

The finding that IL-6 levels were elevated in the psychotic compared with the nonpsychotic 22q11.2DS subjects is also consistent with findings in nonsyndromic schizophrenia that have indicated that IL-6 is the most consistently replicated inflammatory marker associated with schizophrenia.[6,27] The elevated IL-6/IL-10 ratio in the psychotic 22q11.2DS participants suggests a possible reduction in the levels of protective anti-inflammatory factors that may contribute to the development of psychosis.

As for the cognitive aspect, there are only a few studies on the relationship between inflammation and cognition deficits in schizophrenia. In line with our findings of an inverse correlation between cognitive deficits and IL-6 levels, one study on nonsyndromic schizophrenia demonstrated a correlation between IL-6 levels and poorer cognitive performance.[28]

Our study has several limitations that should be acknowledged. The sample size, especially that of the 22q11.2DS psychotic individuals, is relatively small. Therefore, our investigation needs to be replicated with a larger number of subjects to further establish our findings. In addition, we measured circulatory blood markers as indicators of brain inflammatory processes. Although commonly studied in nonsyndromic schizophrenia,[26] the relevance of an alteration of the central nervous system function by circulatory cytokines is unclear. However, it has been suggested that circulating CRP and cytokines are able to cross the blood-brain barrier, eventually leading to a neurotransmitter imbalance and cognitive deficits documented in schizophrenia,[29] thus making peripheral cytokines potentially relevant to the neuroinflammatory

mechanism. A third limitation is that some of our 22q11.2DS participants were on antipsychotics, a fact that might have influenced our results. Of note, previous studies have shown that antipsychotics (the most common type of medication taken by our 22q11.2DS participants) have an anti-inflammatory effect.[30–32] The fact that antipsychotics were taken mostly by the psychotic 22q11.2DS individuals, who still showed higher levels of IL-6 (despite the putative anti-inflammatory effect of antipsychotics), suggests that untreated psychotic 22q11.2DS participants would have shown even more prominent IL-6 levels. Still, this speculation merits further investigation.

Our preliminary findings warrant confirmation by further research on the role of neuroinflammatory processes in the pathways leading to psychosis and cognitive deficits in 22q11.2DS. We demonstrated an association between proinflammatory immune system activation and psychotic disorders and the severity of cognitive deficits in 22q11.2DS. Our results are in line with accumulating evidence for the role of neuroinflammation in nonsyndromic schizophrenia. There are potential important clinical applications to our results. For example, if the finding of elevated IL-6 levels in 22q11.2DS-related psychosis will be replicated, an anti-IL-6 receptor agent, such as tocilizumab, could be an optional treatment in 22q11.2DS individuals with psychosis. It is noteworthy that such clinical trials with IL-6 receptor antagonists are now being conducted in nonsyndromic schizophrenia.[33] Future studies should also look at the possible association between other immune markers and mechanisms of inflammation with 22q11.2DS psychosis and cognitive deficits. Several reports considered *N*-methyl-D-aspartate receptor autoantibodies or the autoantibodies associated with systemic lupus erythematosus psychosis as being putative candidate markers.[34,35] The measurement of microglial activation by neuroimaging studies may be also relevant to 22q11.2DS psychosis. Such specific brain imaging studies have already been conducted in nonsyndromic schizophrenia and in ultra-high-risk individuals.[36]

In conclusion, our preliminary findings indicate an involvement of inflammatory processes in the pathophysiology of psychosis and cognitive deficits in 22q11.2DS and contribute to the accumulating evidence for the role of neuroinflammation in nonsyndromic schizophrenia.

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REFERENCES

1. McDonald-McGinn DM, Sullivan KE, Marino B, et al. 22q11.2 deletion syndrome. *Nat Rev Dis Primers*. 2015;1:15071.
2. Green T, Gothelf D, Glaser B, et al. Psychiatric disorders and intellectual functioning throughout development in velocardiofacial (22q11.2 deletion) syndrome. *J Am Acad Child Adolesc Psychiatry*. 2009;48(11):1060–1068.
3. Schneider M, Debbané M, Bassett AS, et al; International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry*. 2014;171(6):627–639.
4. Khandaker GM, Zimbron J, Lewis G, et al. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. *Psychol Med*. 2013;43(2):239–257.
5. Benros ME, Nielsen PR, Nordentoft M, et al. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. *Am J Psychiatry*. 2011;168(12):1303–1310.
6. Miller BJ, Buckley P, Seabolt W, et al. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry*. 2011;70(7):663–671.
7. Gao L, Li Z, Chang S, et al. Association of interleukin-10 polymorphisms with schizophrenia: a meta-analysis. *PLoS One*. 2014;9(3):e90407.
8. Hope S, Ueland T, Steen NE, et al. Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder. *Schizophr Res*. 2013;145(1–3):36–42.
9. Hope S, Hoseth E, Dieset I, et al. Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls. *Schizophr Res*. 2015;165(2–3):188–194.
10. Suvisaari J, Loo BM, Saarni SE, et al. Inflammation in psychotic disorders: a population-based study. *Psychiatry Res*. 2011;189(2):305–311.
11. Gennery AR. Immunological features of 22q11 deletion syndrome. *Curr Opin Pediatr*. 2013;25(6):730–735.
12. Lima K, Abrahamsen TG, Wolff AB, et al. Hypoparathyroidism and autoimmunity in the 22q11.2 deletion syndrome. *Eur J Endocrinol*. 2011;165(2):345–352.
13. Michaelovsky E, Frisch A, Carmel M, et al. Genotype-phenotype correlation in 22q11.2 deletion syndrome. *BMC Med Genet*. 2012;13:122.
14. Derogatis LR. *SCL-90-R: Administration, Scoring of Procedures Manual-II for the R (Revised) Version and Other Instruments of the Psychopathology Rating Scale Series*. 2nd ed. Towson, MD; Clinical Psychometric Research; 1992.
15. Kaufman J, Birmaher B, Brent D, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(7):980–988.
16. First MB, Spitzer RL, Gibbon M, et al. *User's Guide for the Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version*. Washington, DC: American Psychiatric Press; 1997.
17. Gur RC, Richard J, Calkins ME, et al. Age group and sex differences in performance on a computerized neurocognitive battery in children age 8–21. *Neuropsychology*. 2012;26(2):251–265.
18. Satterthwaite TD, Wolf DH, Roalf DR, et al. Linked sex differences in cognition and functional connectivity in youth. *Cereb Cortex*. 2015;25(9):2383–2394.
19. Calkins ME, Tepper P, Gur RC, et al. Project among African-Americans to explore risks for schizophrenia (PAARTNERS): evidence for impairment and heritability of neurocognitive functioning in families of schizophrenia patients. *Am J Psychiatry*. 2010;167(4):459–472.
20. Gur RE, Yi JJ, McDonald-McGinn DM, et al. Neurocognitive development in 22q11.2 deletion syndrome: comparison with youth having developmental delay and medical comorbidities. *Mol Psychiatry*.

2014;19(11):1205–1211.
21. Yi JJ, Calkins ME, Tang SX, et al. Impact of psychiatric comorbidity and cognitive deficit on function in 22q11.2 deletion syndrome. *J Clin Psychiatry*. 2015;76(10):e1262–e1270.
22. Swagerman SC, de Geus EJC, Kan K-J, et al. The Computerized Neurocognitive Battery: validation, aging effects, and heritability across cognitive domains. *Neuropsychology*. 2016;30(1):53–64.
23. Yi JJ, Weinberger R, Moore TM, et al. Performance on a computerized neurocognitive battery in 22q11.2 deletion syndrome: a comparison between US and Israeli cohorts. *Brain Cogn*. 2016;106:33–41.
24. Aresvik DM, Lima K, Øverland T, et al. Increased levels of interferon-inducible protein 10 (IP-10) in 22q11.2 Deletion Syndrome. *Scand J Immunol*. 2016;83(3):188–194.
25. Ross HE, Guo Y, Coleman K, et al. Association of IL-12p70 and IL-6:IL-10 ratio with autism-related behaviors in 22q11.2 deletion syndrome: a preliminary report. *Brain Behav Immun*. 2013;31:76–81.
26. Meyer U, Schwarz MJ, Müller N. Inflammatory processes in schizophrenia: a promising neuroimmunological target for the treatment of negative/cognitive symptoms and beyond. *Pharmacol Ther*. 2011;132(1):96–110.
27. Stojanovic A, Martorell L, Montalvo I, et al. Increased serum interleukin-6 levels in early stages of psychosis: associations with at-risk mental states and the severity of psychotic symptoms. *Psychoneuroendocrinology*. 2014;41:23–32.
28. Frydecka D, Misiak B, Pawlak-Adamska E, et al. Interleukin-6: the missing element of the neurocognitive deterioration in schizophrenia? the focus on genetic underpinnings, cognitive impairment and clinical manifestation. *Eur Arch Psychiatry Clin Neurosci*. 2015;265(6):449–459.
29. Na K-S, Jung H-Y, Kim Y-K. The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;48:277–286.
30. Haring L, Koido K, Vasar V, et al. Antipsychotic treatment reduces psychotic symptoms and markers of low-grade inflammation in first episode psychosis patients, but increases their body mass index. *Schizophr Res*. 2015;169(1–3):22–29.
31. Noto C, Ota VK, Gouvea ES, et al. Effects of risperidone on cytokine profile in drug-naïve first-episode psychosis. *Int J Neuropsychopharmacol*. 2014;18(4):pyu042.
32. de Witte L, Tomasik J, Schwarz E, et al. Cytokine alterations in first-episode schizophrenia patients before and after antipsychotic treatment. *Schizophr Res*. 2014;154(1–3):23–29.
33. Miller BJ, Dias JK, Lemos HP, et al. An open-label, pilot trial of adjunctive tocilizumab in schizophrenia. *J Clin Psychiatry*. 2016;77(2):275–276.
34. Strous RD, Shoenfeld Y. Schizophrenia, autoimmunity and immune system dysregulation: a comprehensive model updated and revisited. *J Autoimmun*. 2006;27(2):71–80.
35. Deakin J, Lennox BR, Zandi MS. Antibodies to the N-methyl-D-aspartate receptor and other synaptic proteins in psychosis. *Biol Psychiatry*. 2014;75(4):284–291.
36. Bloomfield PS, Selvaraj S, Veronese M, et al. Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [(11)C] PBR28 PET brain imaging study. *Am J Psychiatry*. 2016;173(1):44–52.

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