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Immunoglobulin Levels in Schizophrenia and OCD during Rituximab Treatment:

Associations with Clinical Response, CSF Cytokines and onset age

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Background:

Immunological/inflammatory mechanisms may be involved in the pathophysiology, in **schizophrenia** (SCZ) as well as in **obsessive-compulsive disorder** (OCD), at least in sub-groups of patients. However, despite major research efforts within the relatively new field of immunopsychiatry, we still lack a coherent view of the detailed immune mechanisms and possible pathogens that may be involved. Hitherto, the immunoglobulins have been insufficiently investigated.

Aim:

To scrutinise the **clinical effects** in SCZ and OCD *(Bejerot et al. 2022)* of a potent immuno-modulatory treatment, **rituximab** (a B-cell depleter, targeting CD20), that is proven useful in clearly auto-immune disorders (such as rheumatoid arthritis or multiple sclerosis) and relate these to **immuno-chemical findings**, here focussing on immunoglobulins.

Patients:

Severely ill, treatment-resistant patients:
Mean age: 27 years (19 – 39)
Mean age at onset: 14 years (6 – 27)
Sex: 12 females, 7 males
9 with SCZ (mean PANSS-total = 99)
10 with OCD (mean Y-BOCS = 28)

Intervention:

One single infusion of **1000 mg Rituximab** (Mabthera®) at baseline. Maintenance drug treatment was unchanged one month before, and 5 months after the rituximab treatment. All with SCZ were on stable treatment with antipsychotic agents.

Measurements:

Clinical improvement was rated with PANSS, Y-BOCS and CGI-I and global psychosocial functioning with the Personal and Social Performance scale (PSP). Before the treatment and 5 months post-treatment, serum levels of the immunoglobulin classes IgA, IgG and IgM were measured. In 11/19 patients, cerebro-spinal fluid (CSF) was acquired through lumbar puncture and cytokines were analyzed with electrochemi-luminescence immunoassay. Immunochemical measures were then related to therapeutic outcomes and other clinical variables.

Results:

A significant symptomatic and functional improvement was seen in 7/9 patients with SCZ and in 2/10 patients with OCD.

Before treatment, IgA-values were bimodally distributed (.63 – 2.0 and 2.6 – 3.7 g/L, respectively, population reference .88 – 4.5, **Fig 1**). Two non-responder patients (one SCZ, one OCD) were IgA-deficient. The SCZ patients in the higher mode responded significantly better than those in the lower ($\chi2$ = 5.1, df 1, p =.023, **Fig 2**). All five individuals with comorbid autism belonged to the low mode ($\chi2$ = 6.1, df 1, p =.013).

Baseline IgG ranged between 7.5 and 16.5 (reference 6.7 – 14.5 g/L) and IgM between .35 and 2.9 (.27 – 2.1 g/L). Two OCD patients had supranormal levels of IgM, one of them (a rituximab responder) also of IgG.

In SCZ, increased IgA levels after 5 months were associated with clinical improvement **(rho = .84; p = .009, Fig 3)**. Similarly, only in SCZ, IgA levels were associated with CSF cytokines (**Fig 4).**

References:

Bejerot S et al. **2023**: Rituximab as an adjunctive treatment for schizophrenia spectrum disorder or obsessive-compulsive disorder. *J Psychiatr Res.* 158: 319–329.

Griffiths K et al. **2024**: Changes in immunoglobulin levels during clozapine treatment in schizophrenia. *Brain Behav Immun.* 115: 223-228.

Maes M et al. **2019**: In schizophrenia, increased plasma IgM/IgA responses to gut commensal bacteria are associated with negative symptoms, neurocognitive impairments, and the deficit phenotype. *Neurotox Res.* 35: 684-698.

Fig 4

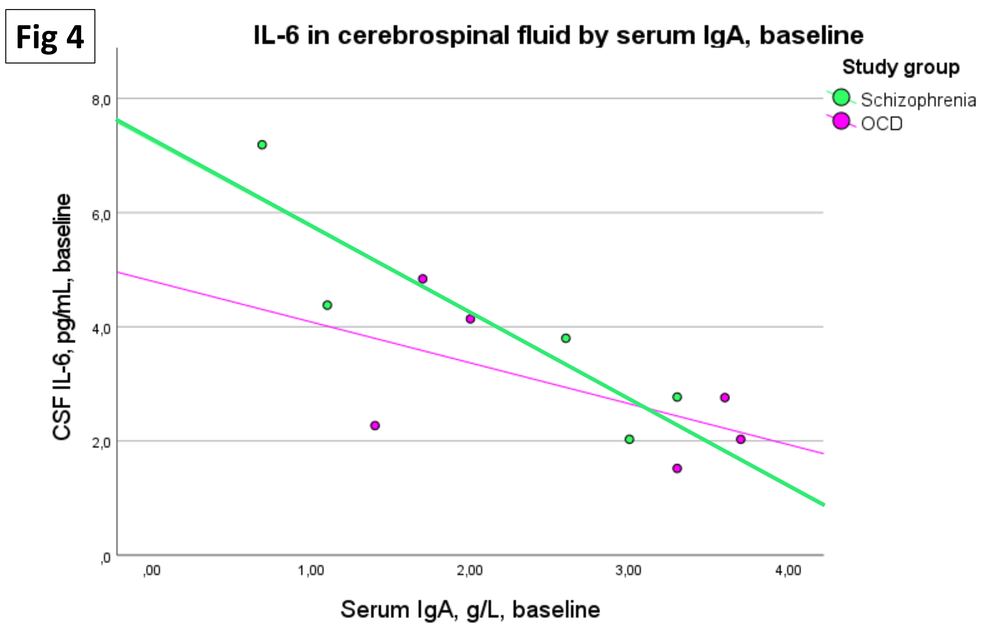

Fig 1

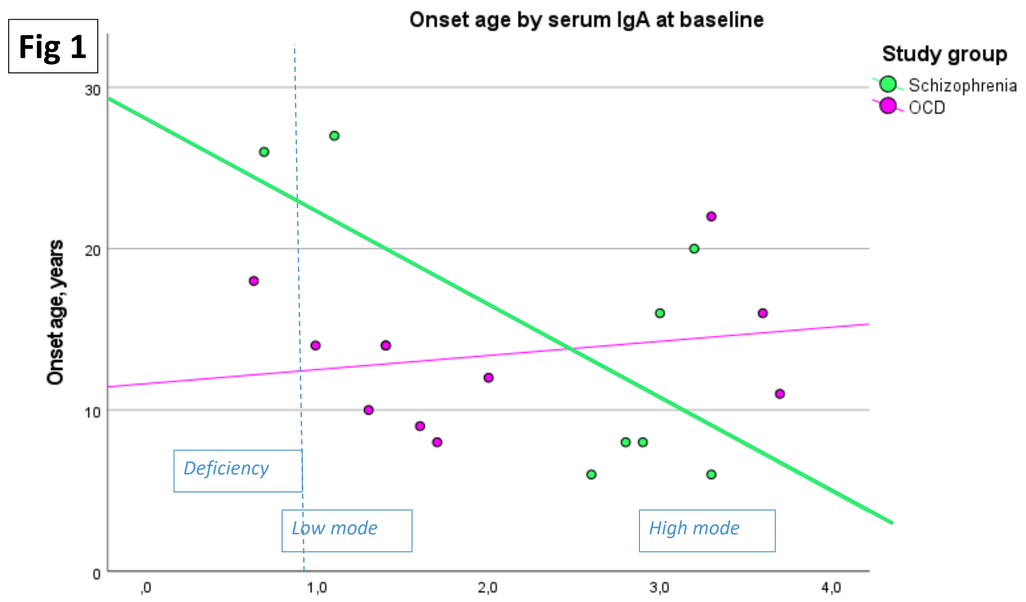

Fig 2

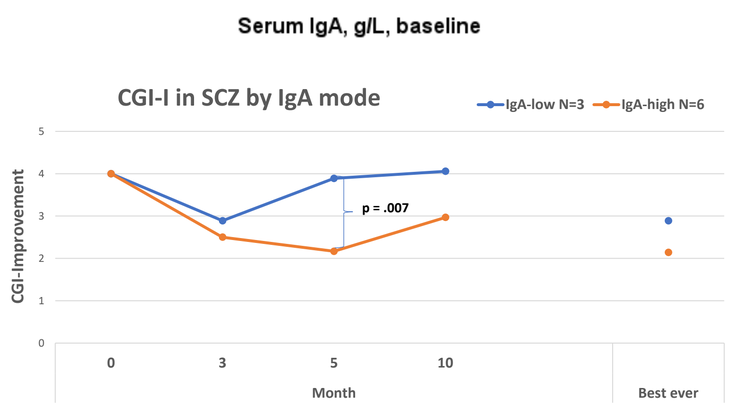

Fig 3

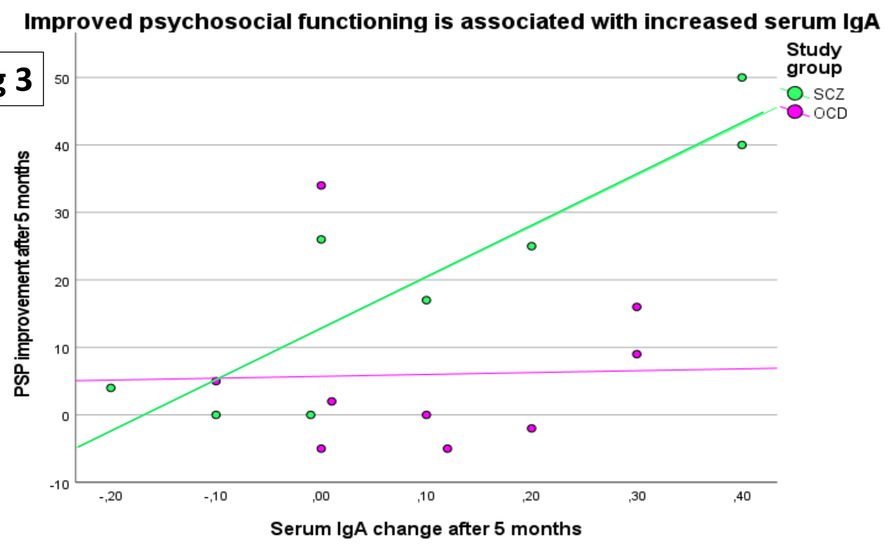

Fig 4: ***Associations with cytokines in the cerebrospinal fluid (CSF):***

In SCZ (n = 5), baseline **serum IgA** correlated *negatively* with **CSF IL-6 (rho = -.90; p = .037)**, showed a *positive* trend with **CSF IL-18 (rho = .78; p = .12)** and a *negative* trend with **CSF TGF-β1 (rho = -.70; p = .19)**.
In SCZ, serum IgG and IgM were not associated with any CSF cytokine measured.

In OCD (n = 6), baseline **serum IgG** was *negatively* correlated with **CSF TNF-α (rho = -.89; p = .019)**.
In OCD, serum IgA and IgM were not associated with any CSF cytokine measured.

Fig 1: ***Bimodal distribution and association with onset age:***

In SCZ (n = 9), the baseline IgA levels were significantly correlated with age at onset **(r = .68; p = .040).**
IgG and IgM were not associated with onset age.

In OCD (n = 10), no correlations between onset age and any immunoglobulin were seen.

For onset age, any reliable psychiatric disorder was considered, not necessarily the adult primary diagnosis.

Discussion:

Here we show an association between **symptomatic improvement** and serum IgA levels in SCZ, but not in OCD. Higher IgA at baseline was related to better clinical response in SCZ but not in OCD. In SCZ, response was also associated with increased levels of IgA and IgG, 5 months after rituximab treatment.

We also found associations between serum IgA and **CSF cytokines** in SCZ, indicating possible links between the peripheral immune system and neuro-inflammatory processes.

Finally, those with SCZ and a higher serum IgA had their **onset of psychiatric disorders** at an earlier age.

Since most serum IgA has its origin in the gut-associated lymphoid tissues (GALT), our findings suggest that interactions between the GALT and the enteric microbiome may be involved in the **developmental immunopathogenesis** of SCZ. Related mechanisms involving IgA have been implicated in deficit SCZ (Maes et al. 2019). Interestingly, in **clozapine** treatment of SCZ, reductions in IgA and IgG were associated with greater reductions in symptom severity, IgA having the strongest association (Griffiths et al. 2024).

Limitations: The study was explorative and due to the small sample size (especially for CSF measures), all results should be viewed with utmost caution. Another limitation is that no subclasses or isotypes of the immunoglobulins were determined..