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Autism and Neuroinflammatory Biomarkers

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Mini Review

In the past many decades, there has been tremendous struggle to find sensitive and specific markers for ASD that could indicate an immune or inflammatory reaction in the CNS. The goal of finding some markers will be useful in predicting risks, course of the disease and the response of the treatment. A number of recent reviews in literature that include multiple markers in the serum or CSF that have been studied. Some postulated biomarkers include increased levels of plasma serotonin, decreased levels of oxytocin, decreased levels of melatonin, increased head circumference and increased levels of inflammatory cytokines Cohen et al. [1].

Oxytocin levels have been altered in autism; however the studies were not consistent parker et al. [2]. Due to immune related problems in mothers of ASD children this brought the concept of ASD as an immue-related condition and neuroinflammatory state to be investigated Anderson. Multiple findings that lead to the immune hypothesis of ASD and that include present of antibodies, altered T cell function and decreased complement level, alterations in cytokines level Zimmerman et al. [3] Altered levels of cytokines including interleukin and interferon families have been reported Onore et al. [4]. Cytokines are small proteins used by the immune system to communicate between cells and to guide immune responses. Cytokines also play a role in the development of brain (Bauer et al 2007).

They are also classified either as pro-inflammatory such as IL-1β, IL-6, IL-4, IL-5, IL-12, IL-13 TNF-α and IFN-γ or anti-inflammatory such as IL10 of TGF based on their purpose Dinarello CA et al. [5]. Recent papers also found an increase in T helper cell 1 cytokines while no change in T Helper cell 2 cytokines which means neuroinflammatory response in autism could be due to TH 1 pathway. This was observed along with a normal IL10 levels which again indicates inability of the brain to mount a response to the offending agent Li et al. [6]. Placental function has also been looked at in ASD and other neurodevelopmental disroders, and serotonins in placental cells Walker et al. [7], the serotonin theory goes back to first publication in 1961 elevated levels of platelet serotonin in autism Schain and Freedman [8]. The finding seems specific for ASD as it has been compared to other conditions of intellectual disability and other neuropsychiatric disorders. Mc Bride et al. [9]; Mulder et al. melatonin has also been looked at in ASD, studies have shown lower levels in plasma and also lower levels of melatonin sulphate which is a principle metabolite Tordjam et al. [10].

Oxidative stress is increased in ASD; many studies have shown less of reduced glutathione and higher oxidized glutathione levels in ASD Anderson. Recent study that have looked at quinolinic acid and few other markers. Quinolinic acid which is a sensitive marker of acute activation of a microglia, also neopterin production occurs in monocyte-macrophage lineage cells after activation of the enzyme guanosine triphosphate cyclohydrolase I by interferon gamma, endotoxin, or tumor necrosis factor-alpha Heyes MP et al. [11]. Quinolinic acid slightly increased in some subjects while the biopterin was reduced this shows that the process of inflammation is not a clear activation and elevation of most known inflammatory markers in CSF but it does show that there is definitely some dysregulation in the immune system in the central nervous system in autism Zimmerman et al. [3].

This could also indicate the inability of an autistic brain to raise a reaction to the offending agent that's ''causing'' autism. Another possibility that these markers are indeed elevated but remain localized in the brain and will not be in CSF Vargas et al. [12]. Chemokines have also been looked at in ASD patient, they are chemo-attractive cytokines they are involved in lymphoid trafficking, lymphoid organ development, wound healing, TH 1 and TH 2 development, angiogenesis and angiostasis, metastasis, cell recruitment and inflammation, MCP-1, MIP 1α, MIP 1β, RANTES Bauman ML et al. [13]. Other studies have looked at cytokines profile in mid gestational period in mothers who delivered ASD children,, IL-4, IL5 and IFN- γ to be elevated in the serum Goines et al. [14]. A study that was performed in Denmark looked at cytokines levels in amniotic fluid and found

significantly higher amniotic fluid levels of IL-4, IL-10, TNF-[alpha] and TNF-[beta] Abdallah et al. [15]. Studies have also shown that severity of behavior problem correlate with TGF β, MCP-1, MIP 1α, MIP 1β and ADOS scores as well Grigorenko et al. [16].

Conclusion

In conclusion evidence of inflammation in ASD patients have been found, many markers have been studied and many show a great potential for being a sensitive marker that could be used clinically such as cytokines, however the different results of replicated studies on specific cytokines make us thing that there is other factors such as epigenetics and environment [17].

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