Cytokine Dysregulation in *MECP2*- and *CDKL5*-Rett Syndrome

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Recent studies have pointed out that MeCP2 is a key player for the healthy immune system function and MeCP2 is associated with inflammation (1,2). Mutations in the methyl-CpG binding protein 2 gene (*MeCP2*) are almost universally associated with Rett syndrome, a severe progressive neurological disorder with a cause-effect relation to oxidative stress. Mutations in cyclin-dependent kinase-like 5 (CDKL5) are also a rare cause of RTT. To date, it is unclear whether both mutations may have an impact on the circulating cytokine patterns.

In the present study, cytokines involved in the Th1-, Th2-, and T regulatory (T-reg) response, as well as chemokines, were investigated in *MeCP2*- (*MeCP2*-RTT) (n=16) and *CDKL5*-Rett syndrome (*CDKL5*-RTT) (n=8), before and after high dosage polyunsaturated fatty acids (ω-3 PUFAs) supplementation.

For the first time, a complex cytokine dysregulation is evidenced in RTT. In particular, we observed a Th2-shifted balance in *MeCP2*-RTT and a Th1-shifted balance in *CDKL5*-RTT. Chemokine levels were unchanged. In *CDKL5*-RTT, increased levels of T-reg cytokines were also present. The degree of cytokine dysregulation was found to be proportional to clinical severity, inflammatory status and redox imbalance. Omega-3 PUFAs partially rescued the cytokine dysregulation and counterbalanced the aberrant redox and inflammatory status in both RTT types. Our findings indicate that a subclinical immune dysregulation coexists in RTT, as a likely consequence of a defective inflammation regulatory signaling system: This abnormal regulation of the inflammatory response appears to be an unrecognized hallmark feature of RTT, intimately related to OS imbalance and likely contributing to disease expression.

References

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2 O'Driscoll CM, et al. J Neuroimmunol. 2015;283:23-9.

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