THE ROLE OF FKBP5POLYMORPHISMS IN RESISTANCE TO DEVELOPMENTAL CHANGE OF EXECUTIVE FUNCTIONS IN CHILDREN WITH PERSISTENT ASTHMA

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Introduction: Asthma is a lifelong condition that places children at increased risk for developing neurocognitive difficulties especially with respect to executive functions (EF) which are fundamental in daily life and support the child in adapting to the demands of the surrounding environment. Neurocognition is furthermore influenced by disease related symptoms, corticosteroid treatment and the environment that all require the correct functioning of the hypothalamic pituitary adrenal (HPA) axis and the glucocorticoids receptor (GR). HPA axis sensitization and alterations in GR regulation are thought to play an important role in the reactivity to stress, and impairments in this system have been widely implicated in psychiatric disorders, such as anxiety but also in the development of cognitive problems. Moreover, the correct functioning of the HPA-axis, which confers resilience or vulnerability to children with asthma with respect to the development of disease or treatment related neurocognitive problems, is related to various genetic, as well as, molecular pathways that regulate the sensitivity to context of the child. The purpose of our study was to test the hypothesis that FKBP5single nucleotide polymorphisms (rs3800373and rs1360780), which affect the correct function of the GR and HPA axis, constitute an additional risk for compromised executive function in children with asthma.

Material and methods: Sixty-three children with asthma aged 6-12years and their parents were enrolled in this longitudinal prospective study at two time points (T0 and T1). Parents reported on daily executive functions on the Behavior Rating Inventory of Executive Function (BRIEF), while DNA was collected from the children by buccal swab.

Results: From data-driven subgrouping we detected two distinct clusters. Cluster 1represent one third of the sample and was composed of patients who displayed significant EF difficulties. Overall, patients at T1displayed improved EF scores related which relates to brain maturation and development but children who were carriers of FKBP5polymorphisms worsened over time or at best displayed no improvement, especially if they already had EF difficulties at T0.

Discussion: FKBP5SNPs, by altering HPA axis efficacy and GR functioning, represent a risk for the development of deficits in daily executive function, independently from the type of asthma, severity, gender and age of the patient. Carriers of the rs1360780 and rs3800373mutations exhibit increased FKBP5activity leading to a change in GR sensitivity, which results in impaired normalization of cortisol levels that remain elevated. Indeed, we found that not only does the presence of the mutation constitute an enhanced vulnerability in children who have more difficulties in EF, but in addition, the mutation makes these children more resistant to change.

Conclusions: This study confirms that children with asthma are at higher risk for difficulties in executive functions related to daily life and that HPA axis functionality is fundamental for executive function and its development. In the presence of enhanced vulnerability, the polymorphism of FKBP5confers additional resistance to development over time. More studies are needed to confirm the role of FKBP5's polymorphisms on EF in children with asthma but we cannot ignore the risk posed by resistance to change especially when it comes to the developmental where change is at the base of the correct growth of the child as an individual. Moreover, we consider it important to include FKBP5allelic testing in the comprehensive risk assessment of children with asthma, often treated with corticosteroids, as proxy of HPA-axis and GR integrity because this may help the development of individualized programs, aimed at reducing the negative consequences of therapy.