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Use of anti-histamines and osthole in autistic children

To the Editor

The recent paper by Kordulewska et al., reported that osthole, i.e. 7-methoxy-8-(3-methyl-2-butenyl)-2H-1-benzopyran-2-one), found in plants from the genus *Cnidium,* may synergize with the anti-histamine drug fexofenadine (FXF) in reducing hypersensitivity response via an inhibition of cyclooxygenase-2 (COX2) in autistic subjects [1,2]. Allergy in autism spectrum disorder (ASD) seems to be a consequence of the influence exerted by mast cells and immunity on the cognitive and behavioural features associated with ASD [1,3]. Although this was simply a suggestive hypothesis, yet it is well recognized that immunity affects neurobehavioural functions [4,5] An intricate cross-talk held by many inflammatory pathways between allergy and ASD seems to characterize this paper, with some confusing trait, somehow. Anyway, the paper by Kordulewska et al., actually deserves some further comment, whereas in order to elucidate their evidence and expand the debate about, some interesting aspect has yet emerged. Comments arose therefore while reading the paper.

First, while sample distribution regarding ASD assessment and allergy appears quite homogeneously settled, the authors did not address one of the main confounder in their study, i.e. patients' age. Children with diagnosed ASD without asthma might have within, due to the very young mean age, subjects quite close to the neonatal life (1.06 ± 2.05 SD) and probably still breastfed respect to the cohort of patients recruited in the different groups of investigation. If breastfeeding in those children was kept throughout the first year of life, as it could be expected, then allergic asthma was probably prevented from the relative mothers, a condition that may introduce a confounding factor not included in the evaluation of the other groups [1,6]. In this case, Kordulewska et al.'s study should limit to the investigation of ASD manifestation in asthmatic allergy children. The question we can put is, therefore, how ASD affects the efficacy of osthole associated with FXF in asthmatic children? Due to the age confounder, we cannot account on the investigation about osthole and FXF on the solely ASD manifestation. This consideration is not so trivial. Some anti-histamines, as 5-hydroxytriptamine (5-HT) antagonists, such as cyproheptadine, ameliorate both the ABC-C and the Childhood Autism Rating Scale (CARS) scores in autistic children without allergy diagnosis [7]. This aspect was important, as well.

Second, the authors addressed the role of FXF and osthole on the COX2 expression. In the paper by Kordulewska et al., the expression of cyclooxigenase 2 (COX2) mRNAs appears as being related to the simple ASD, besides asthma [1]. At least in animal models, abnormalities in the genetic expression of the COX-PGE_2 signaling pathway were recently associated with autism [8]. The role of COX2, which rules the major enzymatic pathways leading to prostanoids synthesis such as prostaglandins PGD_2, $PGF_{2\alpha}$, PGE_2, prostacyclin PGI_2 and tromboxane TXA_2, plays a fundamental meaning in neuronal inflammation via the PGE_2 receptor, contributing as a possible causative mechanism in ASD pathogenesis, a role in neurology reported also by the authors in their Discussion [1,9]. Therefore, besides to focus onto COX2 and allergy, the authors should encompass in their discussion the relationship between COX2 and autism. Kordulewska et al., showed that FXF increased COX2 mRNA levels in children with asthma and without ASD. It would be very interesting to investigate if this was caused by a dose effect of FXF, as reported elsewhere for COX2, where increasing doses of FXF reduced, instead of increasing, the inhibitory effect on COX2, suggesting a possible hormetic effect of this drug [10]. However, authors' concluding evidence was that the basal expression in COX2 mRNA increased with allergy and ASD comorbidity [1]. Kordulewska et al., showed that 300 ng/ml osthole, inhibited COX2 activity in PBMCs, in an extent quite perfectly comparable to 300 ng/ml FXF and this activity was slightly higher in controls and ASD group without allergy, probably because in non-allergic subjects basal COX2 was lower [11]. Furthermore, the coexistence of ASD and allergy decreased the inibition exerted on COX2 activity by either FXF or osthole to the levels of 150 ng/ml histamine in controls [1]. This evidence suggests that the co-activity of FXF and osthole on COX2 function might be simply additive in a *milieu* where allergy is a comorbidity of ASD. This mechanism should be further investigated, anyway, at least on the light of a further insightful comprehension of how to use anti-histamines in autistic children with allergic manifestations.

Whatever mechanism actually accurred, an interesting discrepancy between COX2 mRNA increase in ASD with allergy comorbidity and the reduced effect of FXF and osthole, strongly suggests that in ASD children with chronic allergy dosage and treatment protocols of anti-histamines should be thoroughly reappraised.

Declaration of Competing Interest

The Authors state they have no conflict of interest.

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