Comment on: “Association between Atopic Dermatitis and Autism Spectrum Disorders: A Systematic Review”

Keith Fluegge¹

Published online: 29 February 2016
© Springer International Publishing Switzerland 2016

Billeci et al. [1] published a meta-analysis in the *American Journal of Clinical Dermatology*, wherein an association between autism spectrum disorders (ASDs) and atopic dermatitis was found. The authors' synthesis of the research literature suggests a positive association exists, however there seems to be some heterogeneity in the association, leading the authors to call for investigations to clarify this association and the underlying pathophysiological mechanisms.

The author of this correspondence has previously been the first to suggest that chronic exposure to increasing levels of nitrous oxide (N₂O), an environmental air pollutant and greenhouse gas, may be the principal factor in the etiology of autism and related neurodevelopmental disorders [2]. Interestingly, McAuliffe et al. [3] have previously hypothesized that aerosolized intravenous anesthetics may sensitize medical personnel to opioid addiction, suggesting that very-low-level environmental exposures to opioid-targeting compounds may augur human health consequences. The precise environmental burden of N₂O is not known, although recent research suggests that current emission factors are underestimating the pollutant burden [4]. This hypothesis takes on more significance given the evidence supporting an increased risk of ASD from maternal air pollution exposures [5].

The author posited previously that gestational exposure to N₂O may contribute to a vitamin D deficiency in ASD populations through autonomic dysregulation and irregular

induction of opioidergic activity [2]. Here, that hypothesis is extended in two ways to explain the findings of Billeci et al. [1]. First, exposure to N₂O targets the developing opioidergic system, specifically the dynorphin/kappa-opioid receptor system, and kappa receptor agonists have been found to exert antipruritic properties [6]. Second, gestational exposure to N₂O may confer parasympathetic dominance and thus a vitamin D-deficient state in the ASD child, and vitamin D deficiency has been implicated in the severity of atopic dermatitis [7].

First, Gmerek et al. [8] reported that excessive scratching, improved social interaction, grooming of other monkeys, and yawning were side effects in monkeys chronically treated with a selective kappa-opioid receptor agonist and withdrawn from the drug. The improved social interactions may explain the withdrawal symptoms of increased grooming of other monkeys and yawning. Interestingly, autistic children displayed decreased contagious yawning compared with typically developing children, which may be a function of compromised social abilities [9]. That withdrawal from a kappa-opioid receptor agonist induces social connectedness, scratching, grooming of other monkeys, and yawning in monkeys suggests that a heightened activity of the dynorphin/kappa-opioid receptor system (via gestational N₂O exposure) may play a role in the development of autistic symptoms. However, the medical use of opioid antagonists, including naltrexone, among ASD populations may modulate opioidergic activity [10], potentially inflating the associations between autism and atopic dermatitis, and hence contributing to the heterogeneous reporting found by Billeci et al. [1] in their meta-analysis. It may also be true that reduced baseline vitamin D status may contribute to skin conditions in ASDs.

✉ Keith Fluegge
keithfluegge@iher.org

¹ Institute of Health and Environmental Research,
P.O. Box 18442, Cleveland, OH 44118, USA

Second, gestational N₂O exposure may lead to autonomic dysregulation, conferring a parasympathetic dominance and subsequent vitamin deficiencies in ASD subjects [2]. A recent clinical study by Camargo et al. [11] demonstrated the amelioration of winter-related atopic dermatitis symptoms in Mongolian children supplemented with vitamin D, while Wang et al. [12] demonstrated an association between vitamin D deficiency and atopic dermatitis and total immunoglobulin (Ig) E in Hong Kong Chinese children. El Taieb et al. [13] showed an association between vitamin D deficiency and increasing severity of atopic dermatitis using the AD Scoring System Index. These studies point to an association between vitamin D status and presence of atopic dermatitis. The vitamin D deficiency noted in ASDs may contribute to an increase in atopic dermatitis seen in some studies included in the meta-analyses performed by Billeci et al. [1], although more research is needed to elucidate a causal connection, if one exists.

These data suggest that the relationship between autism and atopic dermatitis may be a complex interaction of enhanced opioidergic activity and a reduced baseline vitamin D status, both developed from gestational exposure to the air pollutant, N₂O. The heterogeneity of the association may reflect these innate conflicting physiological dynamics as well as underlying genetic vulnerabilities, all of which could be further confounded by environmental exposures to N₂O, or lack thereof, and/or the use of opioid antagonists or other medications to treat autistic symptoms.

Compliance with Ethical Standards

Funding No sources of funding were used to assist in the preparation of this letter.

Conflict of interest Keith Fluegge has no competing interests to declare.

References

1. Billeci L, Tonacci A, Tartarisco G, Ruta L, Pioggia G, Gangemi S. Association between atopic dermatitis and autism spectrum disorders: a systematic review. *Am J Clin Dermatol*. 2015;16:371–88.
2. Fluegge K. A reply to Wang T, Shan L, Du L, Feng J, Xu Z, Staal WG, et al. Serum concentration of 25-hydroxyvitamin D in autism spectrum disorder: a systematic review and meta-analysis. *Eur Child Adolesc Psychiatry*. 2015; doi: [10.1007/s00787-015-0786-1](https://doi.org/10.1007/s00787-015-0786-1). *Eur Child Adolesc Psychiatry*. 2015. doi: [10.1007/s00787-015-0803-4](https://doi.org/10.1007/s00787-015-0803-4).
3. McAuliffe PF, Gold MS, Baipai L, Merves ML, Frost-Pineda K, Pomm RM, et al. Second-hand exposure to aerosolized intravenous anesthetics propofol and fentanyl may cause sensitization and subsequent opiate addiction among anesthesiologists and surgeons. *Med Hypotheses*. 2006;66:874–82.
4. Turner PA, Griffis TJ, Lee X, Baker JM, Venterea RT, Wood JD. Indirect nitrous oxide emissions from streams within the US Corn Belt scale with stream order. *Proc Natl Acad Sci*. 2015;112(32):9839–43.
5. Ornoy A, Weinstein-Fudim L, Ergaz Z. Prenatal factors associated with autism spectrum disorder (ASD). *Reprod Toxicol*. 2015;56:155–69.
6. Umeuchi H, Kawashima Y, Aoki CA, Kurokawa T, Nakao K, Itoh M, et al. Spontaneous scratching behavior in MRL/lpr mice, a possible model for pruritus in autoimmune diseases, and antipruritic activity of a novel kappa-opioid receptor agonist nalfurafine hydrochloride. *Eur J Pharmacol*. 2005;518(2–3):133–9.
7. Baek JH, Shin YH, Chung IH, Kim HJ, Yoo EG, Yoon JW, et al. The link between serum vitamin D level, sensitization to food allergens, and the severity of atopic dermatitis in infancy. *J Pediatr*. 2014;165(849–54):e1.
8. Gmerek DE, Dykstra LA, Wood JH. Kappa opioids in rhesus monkeys. III. Dependence associated with chronic administration. *J Pharmacol Exp Ther*. 1987;242:428–36.
9. Helt MS, Eigsti IM, Snyder PJ, Fein DA. Contagious yawning in autistic and typical development. *Child Dev*. 2010;81(5):1620–31.
10. Roy A, Roy M, Deb S, Unwin G, Roy A. Are opioid antagonists effective in attenuating the core symptoms of autism spectrum conditions in children: a systematic review. *J Intellect Disabil Res*. 2015;59:293–306.
11. Camargo CA Jr, Ganmaa D, Sidbury R, Erdenedelger Kh, Radnaakhand N, Khandsuren B. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children. *J Allergy Clin Immunol*. 2014;134:831–5. doi: [10.1016/j.jaci.2014.08.002](https://doi.org/10.1016/j.jaci.2014.08.002).
12. Wang SS, Hon KL, Kong AP, Pong HN, Wong GW, Leung TF. Vitamin D deficiency is associated with diagnosis and severity of childhood atopic dermatitis. *Pediatr Allergy Immunol*. 2014;25:30–5.
13. El Taieb MA, Fayed HM, Aly SS, Ibrahim AK. Assessment of serum 25-hydroxyvitamin d levels in children with atopic dermatitis: correlation with SCORAD index. *Dermatitis*. 2013;24(6):296–301.