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Genetic–environmental interaction in a unique case of Muenke syndrome with intracranial hypertension

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Introduction

Craniosynostosis, the premature fusion of one or more of the cranial sutures, is relatively common, with an incidence of approximately 1 in 3,000 live births [3]. Although craniosynostosis typically occurs in an isolated manner, without accompanying anomalies, it is also a feature of more than 150 genetic syndromes, the most common of which is Muenke syndrome [4, 15, 19]. Of all patients with craniosynostosis, 8% are estimated to have Muenke syndrome; 24% of patients with craniosynostosis and a known genetic cause have Muenke syndrome [15, 19, 29]. Muenke syndrome is an autosomal dominant

cranosynostosis syndrome due to the defining point mutation, c.749C>G, in the *FGFR3* gene, resulting in p.Pro250Arg [1, 16]. The condition is characterized by coronal cranosynostosis (bilateral more often than unilateral), carpal and/or tarsal bone fusion, hearing loss, and developmental delay. Following surgical treatment of the cranosynostosis, individuals with Muenke syndrome are five times more likely than individuals with non-syndromic cranosynostosis to need transcranial reoperation for raised intracranial pressure [28].

Vitamin A, which is necessary for the synthesis of visual pigments and is an important component of membrane stability, is obtained from two sources: preformed vitamin A (derived from animal sources) and provitamin A (from carotenoids, fruits, and vegetables) [11, 12]. Preformed vitamin A is efficiently absorbed and used by humans at absorption rates of 70–90%. Provitamin A, derived from carotenoids and plant foods, is absorbed much less efficiently, at rates of 20–30% [12]. Vitamin A toxicity has traditionally been thought of as being unlikely to result from provitamin A due to its relatively poor absorption efficiency and the fact that the conversion of carotenoids to vitamin A is highly regulated. For this reason, carotenemia, a term used to describe excess levels of carotene (a source of provitamin A) in the blood, has been described as being benign aside from the yellow pigmentation of skin. There have been several reports of benign carotenemia secondary to carrot ingestion, the most common cause of carotenemia, as well as dietary dried seaweed, green beans, and nutrient supplementation [14, 17, 26, 27].

The association of vitamin A with intracranial hypertension is well established. In one study of idiopathic intracranial hypertension, affected patients had significant elevation of serum retinal (a derivative of vitamin A) compared to controls [13]. Vitamin A is also one of the known contributors to the pathophysiology of idiopathic intracranial hypertension, although its exact role has yet to be elucidated [8]. Hypervitaminosis A has also been associated with hydrocephalus, a known structural cause of increased intracranial pressure [22].

Case report

This patient participated in the IRB-approved National Human Genome Research Institute protocol on Muenke syndrome, with informed consent obtained.

The patient was a 3.5-year-old Caucasian male with bicoronal cranosynostosis secondary to Muenke syndrome (formally diagnosed with Muenke syndrome following genetic testing at the age of 20 months) who underwent bilateral fronto-orbital advancement and reconstruction at 9 months. Genetic testing revealed that his mutation was a de-novo mutation (not inherited from either of his parents). He had the following additional findings on further investigation, all consistent with the diagnosis of Muenke syndrome: bilateral sensorineural hearing loss, digital anomalies (broad toes and thumbs, brachydactyly), and mild developmental delay. At the age of 3.5 years, he presented with moderate papilledema and yellow skin discoloration. This yellow discoloration had been present for the prior 8 months but had increased over the past month. There was no yellow discoloration of his sclera (this finding is used to clinically distinguish hypercarotenemia from jaundice), nor did he have vomiting, abdominal pain, dark urine, or acholic stools. Dilated funduscopy showed

moderately swollen optic discs bilaterally. Neurological exam revealed no focal neurological deficits. He had no symptoms of increased intracranial pressure (ICP), with no headache, nausea, vomiting, irritability, change in appetite, or change in behavior. Head CT showed asymmetric lateral ventricles, with the left more effaced than the right, lack of well defined sulci, and cranial crowding (Figs. 1, 2 and 3). ICP monitoring showed an elevated ICP at 20–26 mmHg (normal 1–15 mmHg). Dietary history revealed high carotene intake from vegetables high in carotene (carrots and zucchini) and from intake of a commercial “fruit and veggie” juice, which has high carotene content. Serum carotene was elevated at 9.9 $\mu\text{mol/L}$ (normal 1–4 $\mu\text{mol/L}$); serum vitamin A levels were not obtained. Due to the known association of vitamin A (of which carotene is a source) with increased ICP, it was advised that “fruit and veggie” juice intake be discontinued and that the amount of carotene-containing vegetables and fruits in his diet be reduced. Two months after the juice was discontinued, ophthalmology exam revealed normal vision and resolving papilledema. At this time, plans for reoperation were canceled, and he was determined to have no major need for surgery. However, approximately 2 months later, he presented with worsening papilledema, this time with bilateral sixth nerve palsies. He remained clinically asymptomatic, and his physical and neurological exam was otherwise stable and non-focal. He underwent re-operation at the age of 4 years. He is without a recurrence of the intracranial hypertension at 1.5-year follow-up.

Discussion

Although there is strong evidence for the association of hypervitaminosis A and increased ICP, the precise mechanism is not well understood. It is often speculated that vitamin A affects the absorption of the cerebrospinal fluid via the arachnoid villus [8].

Likewise, the mechanism of increased ICP in patients with Muenke syndrome and other forms of syndromic craniosynostosis has yet to be elucidated. It is known, however, that *FGFR3*, the gene whose mutation causes Muenke syndrome—in addition to being expressed in the cartilage of developing bone, cranial sutures, and inner ear—is also diffusely expressed in the central nervous system [18]. It is likely that the increased intracranial pressure observed in patients with Muenke syndrome is due to a combination of differences in signaling, formation, and morphology of the skull, brain, dura, and cranial sutures.

Interestingly, most of the association between vitamin A and intracranial hypertension has been associated with preformed vitamin A, and not with the ingestion of carotene, which is thought to be benign even in excessive amounts. This case, along with a prior reported case of intracranial hypertension associated with carotene intake, challenges this assumption [9].

Donahue [9] reported a patient with idiopathic intracranial hypertension, which resolved after weight loss but recurred in association with a large, sustained dietary intake of fresh carrots. After cessation of carrot intake for 7 weeks, papilledema markedly decreased along with blood retinol levels. The author concluded from this study that carrot intake is a mechanism for idiopathic intracranial hypertension associated with hypervitaminosis A. Vitamin A levels were not obtained in our patient; however, he did have elevated carotene levels. The rapid increase in the yellow discoloration of his palms and soles at the same time

period of his increased ICP suggests that not only did his dietary intake of carotene play a role in his increased ICP, but also that he likely had hypervitaminosis A, as it is from the conversion to vitamin A that excess carotene intake leads to intracranial hypertension.

While this report involves a hypothetical complex interplay between both genetic and environmental causes of intracranial hypertension, it is admittedly difficult to delineate the precise role each played in this case. Both vitamin A and Fibroblast Growth Factor Receptors (*FGFRs*) play roles in development, differentiation, bone formation, and inner ear development [7, 10, 24]. Regulation of local retinoid (a derivative of vitamin A) concentrations is essential to appropriate patterning and development of the inner ear [10]. In fact, retinoids, its nuclear receptors, and the enzymes required for retinoid synthesis are endogenous to the developing ear [2, 20, 21]. *Fgfr3* has been shown in multiple animal models to be essential for normal inner ear development [5]. Further, Fibroblast Growth Factor (FGF) signaling is required for the normal induction, patterning, and morphogenesis of the inner ear epithelium [23, 25, 30]. Additionally, animal studies have shown that retinoid signaling is important for development of the brain, an organ where *Fgfr3* is diffusely expressed during development [18, 31]. Vitamin A and FGFR3 are effectors of similar pathways and processes that likely intersect and interact at certain points along the different pathways.

Given this, the most plausible explanation is that there is synergism between these two entities. Corroborating evidence includes the fact that immediately after cessation of carotene intake, his papilledema and intracranial hypertension significantly improved to the point where plans for re-operation were canceled, and then later worsened. It is possible that this patient may have had a mild, sub-clinical increase in ICP that was un-masked by the excess carotene intake. This possibility is further supported by the fact that postoperative intracranial hypertension, while more common in Muenke syndrome than non-syndromic or non-genetic causes of craniosynostosis, is relatively rare compared to the other more severe craniosynostosis syndromes, such as Apert, Crouzon, and Pfeiffer syndromes [6].

These cases demonstrate the importance of placing a clinical picture in context; possibly, excess carotene intake is benign in individuals without pre-existing risks for intracranial hypertension, whereas in those individuals with pre-existing risk factors, excess carotene intake is more dangerous. This case suggests excess carotene intake as an environmental susceptibility factor for intracranial hypertension, particularly in at risk individuals.

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Fig. 1. Computed tomography (CT scans) of the brain showing asymmetry of the lateral ventricles, with more effacement of the left ventricle (*white arrow*) compared to the right. Note the lack of well-defined sulci secondary to the effect of cranial crowding

Fig. 2.
Cranial crowding on head CT, with cerebellar tonsils (*black arrows*) approaching the foramen magnum

Fig. 3.
Head CT. Note the lack of well-defined sulci, due to the effect of cranial crowding and increased intracranial pressure