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Does soy-based infant formula cause ADHD?

'Lonnerdal and associates have convincingly demonstrated that infants fed soy formula will absorb considerably higher amounts of Mn in brain than breastfed infants. Thus, ingestion of soy-based formula in infancy could impair brain development.'

Expert Rev. Neurotherapeutics 3(2), 145-xxx (2003)

Attention deficit–hyperactivity disorder (ADHD) is the most prevalent of all childhood neuropsychiatric conditions [1]. Convergent evidence from cognitive, neuroanatomical, electrophysiological, pharmacological and genetic studies now indicates that the core defect in ADHD is an atypical functioning in the brain's dopamine (DA) systems [2].

Over the years, there have been isolated reports of high levels of manganese (Mn) in the head hair of children with ADHD [3–8]. The main source of Mn, a mineral that is essential for mammalian life, is through the diet and excess amounts are excreted via the bile. However, neonatal Mn absorption is greater than in adults [9,10]. Neonatal animals exposed to Mn in high concentrations show decreased brain DA as well as behavior deficits similar to those of ADHD children [11,12].

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Soy-based infant formulae have high concentrations of Mn, up to 80 times the levels found in human breast milk [13]. Since there is an absence of Mn homeostasis in the first few months of life, human neonates fed soy-based formula tend to absorb considerably more Mn than breastfed infants [9]. Some investigators feel that the relatively high Mn levels found in head hair in soy formula-fed neonates is an indication that neurotoxic exposure has occurred. Given the evidence that Mn toxicity affects DA systems, investigators hypothesize a causal relationship between neonatal exposure to soy-based infant formula and ADHD [8].

The Mn–ADHD hypothesis

In 1983, Collip and associates reported that a group of infants exposed to soy-based formula had significantly higher Mn levels in head hair than breastfed infants [8]. In this same paper, they also reported that a group of older ADHD children had head hair Mn levels almost twice those of a matched non-ADHD control group. They speculated that neonatal exposure through soy-based infant formula could be a determinant of later ADHD. Unfortunately, this was not a prospective study in that the ADHD cohort were not followed from infancy, nor were detailed nutritional histories taken to determine if head hair Mn values were related to earlier soy-based formula exposure. Similarly, other studies showing higher Mn levels in the hair of children with ADHD have not been prospective in nature. It remains to be seen how Mn values in head hair, growing at a rate of one inch per month, could link the behavior of a school-aged child to infant Mn exposure. What is known to date is summarized below.

Mn toxicity

A plethora of studies have shown that toxic exposure to Mn will result in compromised

 ISSN 1473-7175

DA metabolism [14–20]. Mn, is a powerful oxidant of DA, explaining its ability to induce toxic lesions in dopaminergic regions [21–26]. Over-absorption of Mn results in DA receptor destruction or inactivation through membrane damage mediated by free radicals or cytotoxic quinones arising from the effect of Mn in catalyzing DA auto-oxidation [27]. Furthermore, Mn has a unique disposition for neuromelanin, as contained in the pigmented dopaminergic neurons of the substantia nigra. With overabsorption of the metal, excess free radicals potentiate lipid peroxidation and result in tissue destruction in DA systems [28]. Mn is also a powerful scavenger of the superoxide radical, $O_2^{\cdot}$, required for initiation of lipid hydroperoxide activity and it is feasible that lipohydroperoxides may influence receptor binding of DA by altering membrane processes (e.g., Na-K-ATP[adenosine 5´-triphosphatase]), via Mn-influenced neuronal oxygen reduction homeostasis [29].

Neonatal absorption of Mn

The clinical risk of Mn to the neonate has been the topic of numerous investigations [10,13,19,29–32]. Mn stores do not accrue prenatally, thus the infant may be particularly susceptible to Mn deficiency [10]. For example, premature and low birthweight infants have a high risk of developing Mn deficiency, with serious survival consequences [9]. Thus, it is imperative for the neonate to absorb adequate amounts of Mn and in fact, Mn absorption is much higher in neonates than adults. Three mechanisms may account for higher Mn absorption in the neonate: a general 'leakiness' of the gut, relatively low bile flow during early life and tissue sites with high affinity for Mn that eventually become saturated. This would allow young animals to accrue Mn from sources otherwise low in Mn, such as breast milk [9]. Animal models demonstrate intestinal neonatal absorption of Mn on the order of 70–80% as compared to the 1–2% in adulthood [33]. In the rat, for example, a nodal point in the achievement of Mn homeostasis occurs 14–15 days after birth [9,10]. In human infants, Mn absorption gradually decreases to adult levels by 4 months [34].

'What remains unknown is whether or not Mn absorption level will be reflected in DA and/or behavioral deficits.'

In addition to other organ sites, Mn enters the neonatal brain at a much higher rate than the adult brain. Infants are therefore at considerable risk of neurotoxicity upon exposure to excess amounts of Mn [9–12,35,36]. In fact, it has been found that immature animals are adversely affected by ingestion of seemingly small additional doses of Mn, with neurological injury from this exposure that includes abnormalities in areas, such as the frontal cortex and nigrostriatal DA system. Lonnerdal and associates have convincingly demonstrated that infants fed soy formula will absorb considerably higher amounts of Mn in the brain than breastfed infants. Thus, ingestion of soy-based formula in infancy could impair brain development [9].

Patterns of neonatal nutrition

Breastfeeding has declined significantly since the early part of this century, concomitant with the widespread availability of infant formulae. Women selecting to breastfeed declined to an all time low in the early 1970s. Even though there has been a slight resurgence, only about 50% of women in the USA initiate breastfeeding and with many fewer continuing for as long as six months [37]. The prevalence of breastfeeding varies among socioeconomic groups. For example, Caucasian, well-educated women are more likely to breastfeed than minority, poorly-educated women [37,38]. In general, low income and/or minority women have less access to prenatal education regarding the benefits of breastfeeding as well as fewer support systems to enable them to breastfeed. In addition, low-income women can receive free formula through participation in the Women, Infant and Children's (WIC) supplemental nutritional program [39–42]. A further influence on the decision to breastfeed has been accelerated re-entry of women into the workforce following childbirth. Many women who initiate breastfeeding change to supplementation with formula or discontinue breastfeeding completely upon returning to work [41,42]. The duration of breastfeeding for 6 months is approximately 18% for the roughly 50% of women who initiate breastfeeding in the USA–in other industrialized countries, such as New Zealand, 50% of women who initiate breastfeeding continue for at least six months [43].

The health benefits of breastfeeding have been widely reported and have recently been reviewed comprehensively by several authors [44]. Most investigators have focused on clinical syndromes, such as diarrhea, respiratory ailments, otitis media, diabetes mellitus and dental caries. The exceptions have been studies that show intellectual superiority of breastfed verses formula-fed children. The best known and most impressive of these was that of Lucas and associates, published in 1992. They reported an 8.3 point average IQ advantage in preterm children who consumed mother's milk in the early weeks of life as contrasted with infants who received no maternal milk [45]. The infants were tube fed, controlling for the interpersonal benefits of the nursing process and the contrasts properly adjusted for socioeconomic and educational factors. While most behaviorists assume that the cognitive benefits of breastfeeding are associated with mother–child intimacy, the Lucas study suggests that the significant effects are attributable to the nutritional advantages of breast milk. Could another advantage be that the child is also being protected against over-absorption of Mn? To date, a causal chain between formula feeding, trace mineral status and behavior deficits have not been mentioned in the breastfeeding literature [45].

Ongoing research

We have now conducted three rodent studies in which the effects of neonatal ingestion of Mn have been determined by examination of tissue absorption, striatal DA levels and neurodevelopmental/neurocognitive status [11,12,47]. These studies are the first to suggest the two known effects of dietary neonatal Mn, excessive brain absorption and striatal DA

depletion, are directly related to behavioral deficits similar to those that are found among children with ADHD, who have specifically lowered capacities for impulse control and mental set. Since rats cannot survive without maternal breast milk, these were Mn supplementation, rather than formula-feeding studies. We are now extending this paradigm to rhesus monkeys, a species that can be bottlefed from birth, contrasting the effects of soy formulae with varying levels of Mn concentration. It has already been shown in this species that neonatal exposure to soy formula will result in higher tissue Mn absorption. What remains unknown is whether or not Mn absorption level will be reflected in DA and/or behavioral deficits. We are also in the early phase of two prospective studies with human neonates whose eventual behavioral outcomes will be known in a few years.

Conclusions

While the studies to date are highly suggestive of a link between soy-based formula and ADHD, a causal chain linking Mn ingestion, Mn absorption, neurotoxic damage and behavioral deficit has not been irrefutably demonstrated. Should this hypothesized relationship receive scientific support, the public health consequences can be readily appreciated. At this time, it would seem prudent to advocate breastfeeding for at least the first six months of life, not only as a precautionary measure but also because the other health and behavioral benefits of breastfeeding have been clearly demonstrated.

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