Methylene Tetrahydrofolate Reductase Deficiency:

Practical Impact on Pediatric Medical and Dental Practice

Prepared by

Darleen Claire Wodzenski, MS ESE, MA CMHC, PhD Psychology Candidate

Orchard Human Services, Inc.

October 23, 2018

Abstract

Methylenetetrahydrofolate reductase is an enzyme that facilitates the biochemical pathway that converts homocysteine to methionine. Research over the past twenty years implicates polymorphisms of the gene that is responsible for producing Methylenetatrahydrofolate reductase in folate deficiency and other critical biochemical pathways and disease processes. Research implicates the MTHFR mutation in folate-involved conditions such as neural tube defects; in cardiac conditions that are linked to elevated homocysteine levels; and a spectrum of fertility and pregnancy related conditions. A survey of the literature points to a significant portion of research hailing from nations with a substantial vegetarian population. Research from countries with significant vegetarian populations may point to vegetarian diets as an aggravating factor for individuals with the MTHFR mutation. One study identified a non-vegetarian diet as a protective factor for some of the conditions associated with MTHFR mutations. One group who is potentially at risk for the negative effects of mutation of the MTHFR gene are infants and young children with the MTHFR mutation, who are documented to experience significantly higher risks of serious or fatal complications from anesthesia, demanding a careful response by medical and dental pediatric practitioners who treat this affected population. Preliminary findings that connect MTHFR mutations with gastric reflux, which in turn promotes dental erosion, present further complications for dental pediatric practice and patient wellbeing in populations affected by MTHFR mutation and MTHFR deficiency.

Methylene Tetrahydrofolate Reductase Deficiency:
Practical Impact on Pediatric Medical and Dental Practice

The enzyme methylenetetrahydrofolate reductase facilitates the methylation of homocysteine (NIH, 2018). The gene that produces this enzyme is commonly referred to as the MTHFR gene (NIH, 2018). The literature cites polymorphisms of the MTHFR gene as a possible link to a spectrum of negative health outcomes (NIH, 2018). In increase in plasma homocysteine levels associated with some MTHFR polymorphisms may account for an increased incidence of heart disease, preeclampsia, glaucoma, stroke, hypertension, and vascular disease (NIH, 2018). MTHFR polymorphisms have also been linked to an increased incidence of certain cancers (NIH, 2018).

Exposure to nitrous oxide can lead to dangerous neurologic deterioration of infants with B^{12} deficiency (Felmet, Robins, Tilford, & Hayflick, 2000). The literature cites one cause of cobalamin deficiency as potential deactivation of the nutrient by chemical reaction with nitrous oxide anesthesia administered by inhalation (Singer, Lazaridis, Nations, Wolfe, 2007). Nitrous oxide interferes with vitamin B^{12} levels by irreversible oxidization of the cobalt atom; the duration of this inhibition can be several days (Nagele at al., 2008). Active B^{12} is a required cofactor for methionine synthase, which is implicated in the folate cycle and remethylation of homocysteine (Nagele at al., 2008).

Implications for pediatric medical and dental practice demand a careful choice of anesthesia for affected populations (Orhon et al., 2017). Recent investigation of sevoflurane and propofol administration in pediatric patients with MTHFR deficiency revealed no harmful impact on homocysteine levels (Orhon et al., 2017). Orhon et al. (2017) cited the prevalence of

MTHFR polymorphism in Japanese, Middle Eastern, and European populations as 30% to 40% for heterozygous and 10% to 15% for homozygous mutations. Orhon et al. (2017) report that nitrous oxide is strictly contraindicated for individuals with methylenetetrahydrofolate reductase deficiency; and further suggest contraindication of nitrous oxide administration for patients with clinical presentation consistent with MTHFR deficiency. The incidence of MTHFR polymorphisms in normal populations in combination of the potential deleterious effects of nitrous oxide administration cause for a review of the common usage of nitrous oxide (Orhon et al., 2017).

MTHFR polymorphism can trigger elevation in concentrations of plasma homocysteine following administration of nitrous oxide anesthesia (Nagele et al., 2008). Nagele et al. identified homozygous mutations of MTHFR as implicated in clinically significant elevations of plasma homocysteine following nitrous oxide administration; some cases resulted in patient fatality.

While extensive investigation of nutritional strategies to reduce risks associated with MTHFR mutation are sparse, Chan, Ortiz, Rogers, and Shea (2011) reported that food supplementation may attenuate the negative effects of folate deficiency in mice that tested positive for the MTHFR mutation. Administration of preoperative B-vitamins failed to protect affected individuals from nitrous oxide-related elevation of plasma homocysteine (Rao, Francis, Wilcox, Miller, & Nagele, 2010).

The implications of genetic anomalies in pediatric dentistry are complex and significant (Kuchler et al., 2013). Some cases of high caries have been linked to genetic phenomena (Kuchler et al., 2013). Preliminary research links MTHFR polymorphisms with gastrointestinal disorder including reflux (Kumar, Mungara, Venumbaka, Vijayakumar, Karunakaran, 2018). Investigation of the connection between reflux disease and dental caries reveals significant

correlation (Kumar et al., 2018). While no direct connection between MTHFR polymorphism and gastric reflux has been identified, evidence suggests a strong positive correlation between elevated homocysteine levels and reflux (Vasavi et al., 2006). The existing evidence connecting MTHFR mutation with homocysteine level points to the need for careful investigation of this connection, and thorough consideration of the potential impact of MTHFR mutation on the health of the individual, especially with respect to homocysteine elevation and related health conditions including GERD and dental caries.

The contraindications for use of nitrous oxide as a dental anesthetic present a confounding situation for children with MTHFR polymorphism as this mutation is also associated with such conditions as reflux esophagitis (Ekiz et al., 2012). Reflux is cited as a source of intrinsic acids that can cause dental erosion, which involves an irreversible and progressive destruction of dental tissue (Scardina & Messina, 2012). Further investigation of genetic and epigenetic phenomena is required to increase the dependable information available about how best to care for individuals with epigenetic polymorphisms, especially MTHFR polymorphism. Pediatric medical and dental practitioners must evaluate the MTHFR, B^{12}, folate, and homocysteine status of patients prior to dental or other procedures involving anesthesia. Patients with a clinical presentation consistent with MTHFR polymorphism require careful handling with respect to dental caries, dental procedures, and any condition requiring use of anesthesia.

References

Chan, A., Ortiz, D., Rogers, E., Shea, T.B. (2011). Supplementation with apple juice can compensate for folate deficiency in a mouse model deficient in methylene tetra hydrofolate reductase activity. *Journal of Nutrition, 155*(3), 211-225.

Felmet, K., Robins, B., Tilford, D., & Hayflick, S.J. (2000). Acute neurological decompensation in an infant with cobalamin deficiency exposed to nitrous oxide. *Journal of Pediatrics, 137*(3), 427-428.

Kuchler, E.C., et al. (2013). Genetic mapping of high caries experience on human chromosome 13. *BMC Medical Genetics, 14*, 116-116. doi:10.1186/1471-2350-14-116

Kumar, K.S.S., Mungara, J., Venumbaka, N.R., Vijayakumar, P., & Karunakaran, D. (2018). Oral manifestations of gastroesophageal reflux disease in children: A preliminary observational study. *Journal of Indian Society of Pedodontics and Preventitive Dentistry, 36*, 125-129.

Nagele, P., Zeugswetter, B., Wiener, C., Burger, H., Hüpfl, M., Mittlböck, M., & Födinger, M. (2008). Influence of methylenetetrahydrofolate reductase gene polymorphisms on homocysteine concentrations after nitrous oxide anesthesia. *Anesthesiology, 109*(1), n.p. doi:10.1097/ALN.0b013e318178820b

NIH. (2018). *MTHFR gene: Methylenetetrahydrofolate reductase.* U.S. National Library of Medicine. Retrieved from https://ghr.nlm.nih.gov/gene/MTHFR#conditions

Rao, L. K., Francis, A. M., Wilcox, U., Miller, J. P., & Nagele, P. (2010). Pre-operative vitamin B infusion and prevention of nitrous oxide-induced homocysteine increase. Anaesthesia, 65(7), 710-5.

Scardina, G.A., & Messina, P. (2012). Good oral health and diet. *Journal of Biomedicine and Biotechnology, 12,* 1-8. doi:10.1155/2012/720692

Singer, M.A., Lazaridis, C., Nations, S.P., Wolfe, G.I. (2007). Reversible nitrous oxide-induced myeloneuropathy with permicious anemia: Case report and literature review. *Muscle Nerve, 37,* 125-129.

Vasavi, et al. (2006). DNA methylation in esophageal diseases including cancer: special reference to hMLH1 gene promoter status. *Europe PMC.* (PMID:16724696)