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Vitamin D status and age of onset of demyelinating disease

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Abstract
Objective: To evaluate the prevalence of and associated factors impacting vitamin D insufficiency and deficiency in childhood versus adult-onset demyelinating disease.
Methods: We conducted a retrospective, cross-sectional, chart-review, cohort study on geographically-similar pediatric, young adult, and adult patients with a diagnosis of demyelinating disease identified at the University of Virginia from 2008 to 2013. Group prevalence of vitamin D insufficiency and deficiency as well as relevant factors associated with vitamin D status was analyzed and compared.
Results: We identified 24 childhood-onset (CO), 33 young adult-onset (Y-AO), and 59 adult-onset (AO) cases. There was no difference in the prevalence of vitamin D insufficiency or deficiency between the cohorts. Non-Caucasian race and elevated body mass index were significantly associated with low vitamin D levels, regardless of age of onset. In regression models, race and obesity were independent predictors of vitamin D status. The prevalence of obesity was significantly higher in the childhood-onset cohort (CO=58.5%; Y-AO=31%; AO=34%; $p=0.02$).
Conclusions: Our findings demonstrate no difference in the prevalence of vitamin D insufficiency/deficiency between childhood and adult-onset demyelinating disease, suggesting age at disease onset is irrelevant to vitamin D status in demyelinating disease. Both race and obesity are independent factors associated with vitamin D insufficiency/deficiency, regardless of age of disease onset. Obesity, independent of gender, is significantly higher in children compared to adult patients diagnosed with multiple sclerosis and may have a role in the development of childhood-onset demyelinating disease.

1. Introduction

Several modifiable risk factors for the development of multiple sclerosis have been identified; however, the work

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is ongoing. In some cases, risk factor exposure in childhood and potentially even in utero appears to be important (Mirzaei et al., 2011; Salzer et al., 2012). In the adult-onset MS (AOMS) population, several studies have reported a high prevalence of vitamin D deficiency (Munger et al., 2006; Nieves et al., 1994). Evidence also suggests that vitamin D levels impact, not only the risk of developing MS (Munger et al., 2006), but also the risk of relapse after diagnosis (Auer et al., 2000; Embry, 2000). In a single, retrospective study looking at childhood-onset MS (COMS), lower serum 25-hydroxyvitamin D levels were associated with higher rates of relapse (Mowry et al., 2010). Recently, obesity in childhood has been postulated to play a role in developing demyelinating disease in childhood, particularly in females (Langer-Gould et al., 2013). Interestingly, obesity is associated with lower serum vitamin D levels (Wortsman et al., 2000).

To our knowledge, there has not yet been a study that has directly compared serum 25-hydroxyvitamin D levels in geographically-similar adults and children with demyelinating disease; nor has there been a direct comparison of demographic factors that may impact vitamin D status in these two distinct populations. In healthy cohorts of children and adults, studies have demonstrated a higher prevalence of vitamin D insufficiency in the adult population (Looker et al., 2002). In other studies of healthy cohorts, several risk factors for low vitamin D status (reduced sun exposure and obesity) have been identified, and are more often seen in the adult population (Hedley et al., 2004). Similar to these studies on healthy cohorts, we hypothesized that in demyelinating disease, childhood-onset and adult-onset groups would demonstrate differences in vitamin D status. Understanding the similarities and differences between COMS and AOMS is important in the tailored and optimal management of each.

2. Materials and methods

This retrospective, cross-sectional, chart review, cohort study was approved by the University of Virginia's Institutional Review Board. Childhood-onset patients were identified via a search of the administrative database using ICD-9 codes representing the diagnoses of: transverse myelitis (341), optic neuritis (377), and clinically-isolated syndrome/multiple sclerosis (340; including its many subtypes). The adult cohort, including both young adult (Y-AO) and adult-onset (AO) patients, was identified using a clinical care database. The search included patients seen and/or diagnosed from 2008 to 2013 at the University of Virginia. Inclusion criteria consisted of: neurologist-confirmed diagnosis of a clinically-isolated syndrome or multiple sclerosis based on the 2010 McDonald criteria (Pohlman et al., 2011). Demyelinating disease clinical categories included: clinically isolated syndrome, relapsing-remitting multiple sclerosis, primary relapsing multiple sclerosis, primary progressive multiple sclerosis, and secondary progressive multiple sclerosis.

Childhood-onset (CO) cases were defined as patients aged less than 18 years at the time of the initial demyelinating event. The young adult-onset (Y-AO) cases were defined as those aged 18–21 years, and the adult-onset (AO) cohort was defined as those aged older than 21 at the time of their initial demyelinating event. Data collected for all eligible case included: diagnosis, age at onset, current age, race, gender, 25-hydroxyvitamin D level, season of vitamin D draw, body mass index, and smoking history (including a history of passive smoking for children). All patients had a 25-hydroxyvitamin D level checked within 12 months before or after the established diagnosis was made. Only patients with 25-hydroxyvitamin D levels drawn prior to any chart-documented vitamin D supplementation (including multivitamins) were included. All body mass indices for patients were obtained within a 3 month period of the vitamin D level draw.

2.1. Statistical analysis

Statistical analysis was completed using SAS 9.2 software. For analysis, vitamin D levels were stratified as "deficient"=levels <20 ng/ml, "insufficient"=levels <30 ng/ml, and "normal"=levels ≥ 30 ng/ml. Race was divided into three categories: white, African American, or "other". Body mass index for each patient older than 20 was classified based off of CDC and WHO definitions (Organization WH, 2000) and was labeled as "normal"=BMI 25 or less, "overweight"=BMI of >25–30, and "obese"=BMI of >30. As recommended by the Centers for Disease Control (CDC), body mass index for subjects younger than 20 was defined using gender-specific CDC growth charts (Center for Disease Control, 2013): "normal"=5th–85th percentile, "overweight"=85th–95th percentile, and "obese"=$>$95th percentile. Patients were classified as "smokers" if there was a history of smoking or current smoking, including a history of exposure via passive smoking for our childhood-onset cohort (Mikaeloff et al., 2007). Demographic traits were compared using *T*-test and chi-squared as appropriate for continuous and ordinal variables. Mean vitamin D levels were calculated for all cohorts within demographic subsets and were compared using ANOVA.

Multiple regression models were used to identify significant variables associated with vitamin D status. We analyzed the impact of smoking status, body mass index, gender, race, age of disease onset, and season checked on vitamin D status as well as both vitamin D insufficiency and deficiency dichotomized groups. Based on significant factors in regression analysis, we performed additional group factor analysis using ANOVA.

3. Results

An administrative database search identified 37 cases of childhood-onset demyelinating disease and 174 cases of young adult and adult-onset demyelinating disease. We excluded 12 cases of childhood-onset demyelinating disease due to the absence of a vitamin D level. There was a single case excluded from our study due to pre-lab vitamin D supplementation. We excluded 51 cases of young adult/adult demyelinating disease as there was no vitamin D level checked. Thirty-one young adult/adult-onset cases were excluded secondary to vitamin D supplementation prior to lab assessment. The resultant population available for analysis included 24 childhood-onset and 92 adult-onset