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The effect of hypocalcemia in early childhood on autism-related social and communication skills in patients with 22q11 deletion syndrome

Meghan Muldoon, MPH^a, Opal Y. Ousley, PhD^{b,c}, Lisa J. Kobrynski, MD, MPH^e, Sheena Patel, MPH^a, Matthew E. Oster, MD, MPH^{a,e}, Samuel Fernandez-Carriba, PhD^c, Joseph F. Cubells, MD, PhD^{b,c,d}, Karlene Coleman, RN, MN, CGC^{e,f}, and Bradley D. Pearce, PhD^{a,b}

^aEmory University Rollins School of Public Health Dept. of Epidemiology. 1518 Clifton Rd., Atlanta, GA 30322

^bCenter for Translational Social Neuroscience, 101 Woodruff Circle Atlanta, GA 30322

^cEmory University School of Medicine, Emory Autism Center, Department of Psychiatry, 101 Woodruff Circle Atlanta, GA 30322

^dDept of Human Genetics, 101 Woodruff Circle Atlanta, GA 30322

^eChildren's Healthcare of Atlanta; Emory University School of Medicine, Department of Pediatrics, 1405 Clifton Road, Atlanta, GA 30329

^fNell Hodgson Woodruff School of Nursing, Emory University, 101 Woodruff Circle Atlanta, GA 30322

Abstract

22q11 deletion syndrome (22qDS), also known as DiGeorge Syndrome, is a copy number variant disorder that has a diverse clinical presentation including hypocalcaemia, learning disabilities, and psychiatric disorders. Many patients with 22q11DS present with signs that overlap with autism spectrum disorder (ASD) yet the possible physiological mechanisms that link 22q11DS with ASD are unknown. We hypothesized that early childhood hypocalcemia influences the neurobehavioral phenotype of 22q11DS. Drawing on a longitudinal cohort of 22q11DS patients, we abstracted albumin-adjusted serum calcium levels from 151 participants ranging in age from newborn to 19.5 years (mean 2.5 years). We then examined a subset of 20 infants and toddlers from this group for the association between the lowest calcium level on record and scores on the Communication and Symbolic Behavior Scales-Developmental Profile Infant-Toddler Checklist (CSBS-DP ITC). The mean (SD) age at calcium testing was 6.2 (8.5) months whereas the mean (SD) age at the CSBS-

Corresponding Author: Brad D. Pearce, Ph.D., Department of Epidemiology (RSPH), Emory University, Office: 1518 Clifton Rd. CNR 4049 (1518-002-AA), Atlanta, GA 30322, Administrative: Rachael Miller, rmiller6@emory.edu (011 404-727-3497), Fax: 011 404-727-8737, Office Phone 011 404-727-4914, bpearce@emory.edu.

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This human study has been approved by the appropriate ethics committee (Emory IRB) and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

DP ITC assessment was 14.7 (3.8) months. Lower calcium was associated with significantly greater impairment in the CSBS-DP ITC Social ($p<0.05$), Speech ($p<0.01$), and Symbolic domains ($p<0.05$), in regression models adjusted for sex, age at blood draw, and age at the psychological assessment. Nevertheless, these findings are limited by the small sample size of children with combined data on calcium and CSBS-DP ITC, and hence will require replication in a larger cohort with longitudinal assessments. Considering the role of calcium regulation in neurodevelopment and neuroplasticity, low calcium during early brain development could be a risk factor for adverse neurobehavioral outcomes.

Keywords

Calcium; DiGeorge syndrome; autism; neurodevelopment; parathyroid

Introduction

The 22q11-deletion syndrome (22q11DS) is a copy number variant disorder entailing a hemizygous microdeletion in chromosome 22q11.2, and is associated with elevated risk for congenital heart defects [1], immunodeficiency [2], hypocalcemia [3–7], learning disabilities [8], and neuro-psychiatric disorders [9–11]. The relationship between 22q11DS and idiopathic ASD has not been established and remains controversial. While there is general agreement that the behavioral profile in 22q11DS is qualitatively different than idiopathic ASD, and that these disorders should not be conflated, there is controversy as to the portion of individuals with 22q11DS who meet diagnostic criteria for ASD as part of the complex neuropsychological manifestations of 22q11DS. Some studies have reported that 14 to 50% of individuals with 22q11DS meet criteria for ASD [12–14], while one study reported that none of the 29 participants assessed met strict criteria for ASD [15]. In our center, we found that 16% of 22q11DS participants met the stringent Collaborative Program for Excellence in Autism (ASD-CPEA) criteria for an ASD diagnosis [10]. In any case, the physiological mechanisms that link 22q11DS with social and communication endophenotypes are important to ascertain.

Approximately 80% of 22q11DS patients carry a well-delimited 3 megabase (Mb) deletion. Although the genes in the 3 Mb deletion region have been identified and studied, their functions within cellular and molecular networks, and their roles in risk for social and communication deficits have yet to be elucidated [16]. In 22q11DS a diminished parathyroid hormone reserve leads to a predisposition to hypocalcemia, especially under conditions of high stress or illness [3–7]. Hypocalcemia is common in neonates with 22q11DS and is present in approximately 50% of 22q11 patients at the time of diagnosis [17]. Moreover, hypoparathyroidism and hypocalcemia in 22q11DS can manifest latently and be first diagnosed in early childhood, adolescence or in adulthood [7,17,5]. The majority of patients with 22q11DS will experience hypocalcemia, and the severity will fluctuate as a function of stress, illness, and treatment [18]. Although many of the details have not been studied, problems with calcium regulation in 22q11DS occur in the neonatal period and can be especially problematic during surgery [18].

Calcium regulation plays a major role in neurodevelopment and synaptic plasticity [19–21]. For example, the parathyroid gland senses levels of calcium through the extracellular calcium-sensing receptor (CASR), and this receptor, which is responsive to prevailing levels of extracellular calcium, is also present on developing neurons and helps control neurite outgrowth in the developing postnatal brain [22,23]. Thus, chronic or intermittent hypocalcemia in some 22q11DS patients may have a deleterious effect on neurite outgrowth and synaptogenesis, which may predispose these patients to neurodevelopmental alterations that ultimately manifest as neuropsychiatric sequelae. The mechanistic overlap between 22q11DS and ASD is unknown but there is accumulating evidence for a causal role of calcium dysregulation in ASD [24–26]. Indeed, calcium dysregulation recently emerged as the most prominent biological factor in ASD risk when both genetic and environmental factors are taken into account [25], and calcium homeostasis has also been implicated in the etiopathogenesis of schizophrenia [27,28]. Remarkably, 22q11DS is a confirmed genetic risk factor for schizophrenia [29], and a recent multi-site study determined that 41% of adults with 22q11DS have a psychotic disorder [30].

Impairment in communication and language are core features of ASD [31], and are also of considerable interest in 22q11DS. To test the hypothesis that impaired calcium homeostasis early in life contributes to communication and language deficits in children with 22q11DS, we examined the relationship between serum calcium levels and social-communication skills in young children with molecularly-confirmed 22q11DS.

Materials and Methods

To determine the association between serum calcium level and social-communication skills in 22q11DS patients, we collected medical record data from patients attending the Emory-CHOA 22q11DS Multidisciplinary Clinic. This study was performed with approval from the Emory University IRB (IRB00045086) in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Study data were collected and managed using REDCap electronic data capture tools hosted at Emory University. We obtained data from 151 patients with confirmed 22q11DS diagnosis and laboratory values for serum calcium level and a corresponding albumin level. All calcium levels were corrected for albumin as described (corrected Ca = $[0.8 \times (\text{normal albumin} - \text{patient's albumin})] + \text{serum Ca level}$ [32]). Both the earliest calcium on record and the lowest calcium were recorded. The lowest on record was used as the exposure variable. The behavioral outcome measure consisted of scores on the Communication and Symbolic Behavior Scales-Developmental Profile Infant-Toddler Checklist (CSBS-DP ITC). The CSBS-DP ITC is a parent questionnaire that assesses gestural, vocal, and verbal communication, social-affective signaling, and symbolic understanding and yields three composite scores: social, speech, and symbolic [33]. This questionnaire has been validated as a broadband screener to assess for communication delays, including ASD-related delays [34]. Higher scores represent better developmental attainment. There were 20 children who had CSBS-DP-ITC scores, and also had complete calcium level data. Thus our final dataset for regression analysis was 20 participants.

Statistics

To determine if calcium levels predicted CSBS-DP ITC assessment scores, separate hierarchical multiple regression models were used with the lowest calcium level on record as the exposure variable and scores on each of the three CSBS-DP ITC composites as the outcomes. To control for possible confounding factors, models were run with age at calcium blood draw, age at CSBS-DP ITC assessment, and gender forced into the first step of the regression models as covariates. Statistical tests were implemented in SAS Version 9.3 software (SAS Institute Inc., Cary, NC), and SPSS (IBM, Armonk, New York).

Results

Calcium levels

After excluding samples lacking concurrent albumin levels, 151 individuals (71 females and 80 males) with confirmed 22q11DS had calcium values for this analysis. These were divided into the earliest on record, and the lowest on record (Figure 1). In 61/151 the same value/blood draw represented both the earliest and lowest, and hence the lowest was used for subsequent regression analysis. We examined the portion of these calcium levels that were low relative to age specific reference values, using a cutoff of < 8 mg/dL for age < 12 months, < 8.7 mg/dL, for 12–24 months, and < 8.9 mg/dL for over 24 months. The number of patients whose lowest Ca++ level on record was below the age-specific cut off was 42/102 (age < 12 months), 5/9 (age 12–24 months), and 27/40 (age > 24 months); and corresponding number below the cutoff for the earliest Ca++ on record was 21/112, 0/6, 15/33, in the respectively by age groups.

Association of Ca++ Levels with Behavioral Test Scores

Figure 2 shows CSBS-DP ITC raw scores of infants assessed. Table 1 shows the results of hierarchical multiple regression analyses with lowest serum calcium as the predictor (exposure) variable and CSBS-DP ITC scores as the outcome for 20 participants with both calcium data and CSBS scores. The blood draw preceded the CSBS-DP ITC assessment by 4.0 to 17.3 months in 18/20 cases. However, in two cases the CSBS-DP ITC assessment preceded the blood draw of the lowest calcium on record. In one of these the CSBS-DP ITC was performed at 12.7 months, and the calcium level drawn at 15.2 months, and in the other the CSBS-DP ITC was administered at 23.0 months and the calcium was tested at 35.8 months. The mean (SD) age at the blood draw and at the CSBS-DP ITC assessment were 6.2 (8.5) months, and 14.7 (3.8) months, respectively. Calcium levels were below the age specific cut-off in 7/20 of these children. Hierarchical multiple regression analyses were completed to examine the impact of the lowest calcium on the CSBS-DP ITC social, speech, and symbolic composite scores, while controlling for age at CSBS-DP ITC assessment, age at lowest calcium blood draw, and gender. Thus, Step 1 included the covariates, whereas Step 2 included the lowest calcium values. As shown in Table 1, the addition of the lowest calcium value (i.e., Step 2) resulted in a statistically significant change in R^2 for each of the models. Table 1 also lists the parameter estimates, standard errors, and t-ratios. Calcium level was a statistically-significant predictor of social, speech, and symbolic CSBS-DP ITC scores (Table 1).

Discussion

This study explores the association between serum calcium levels and severity of developmental problems in communication and symbolic behavior in young children with 22q11DS. We found that the lowest corrected calcium value on medical record was a robust predictor of CSBS-DP ITC assessment scores in models adjusted for sex, age at blood draw, and age at the psychological assessment. Lower calcium values were associated with lower CSBS-DP ITC scores, suggesting that hypocalcemia may be a modifiable risk factor for problems in social-communication development in children with 22q11DS. Our study suggests peripheral risk factors such as hypocalcemia may impact neurodevelopmental outcomes in 22q11DS patients. Moreover, the complex phenotype of 22q11DS includes an elevated rate of Attention Deficit Hyperactivity Disorder (ADHD) and schizophrenia, and each of these disorders has a putative connection with calcium dysregulation [35,28,27].

A limitation of this study is the small sample size ($n=20$) that had data for both Ca^{++} and CSBS. Additionally there was a variable gap between the age of lowest Ca^{++} levels and CSBS-DP ITC testing. However, since 18 out of 20 participants had their lowest Ca^{++} level on record taken prior to the CSBS-DP ITC, this suggests that Ca^{++} is a predictor of CSBS-DP ITC scores, and raises the possibility that improvement of Ca^{++} homeostasis may be an early modifiable factor that could abrogate social and communication impairments in 22q11DS patients.

Among the many potential mechanisms by which hypocalcemia could impact neurodevelopment, the crucial role of calcium dysregulation on neuroplasticity seems especially relevant to ASD [22,19]. Besides the moderate to severe hypocalcemia that can occur in 22q11DS, there are also subtle inter-individual differences in circulating calcium levels that are normally under genetic control. This was confirmed by a recent genome wide association analysis of several population-based cohorts that implicated the *DGKH* gene as one of the key determinates of serum calcium concentration [36]. Interestingly, schizophrenia and ADHD are associated with variants in this gene [37,38].

Although small differences in circulating calcium among the population do not likely affect neurodevelopment, significant hypocalcemia among patients with 22q11DS may cause reversible disruption of calcium-sensitive neurodevelopmental processes, and the severity and type of psychiatric manifestation that unfolds may depend on compensatory mechanisms that influence the resiliency of neural circuitry to this hypocalcemic exposure. Accordingly, common genetic polymorphisms in patients with 22q11DS may influence the neuropsychiatric sequelae of hypocalcemia. Studies are clearly needed to explore the influence of hypocalcemia, and the role of calcium management, on early and later neurodevelopmental and psychiatric outcomes in children with 22q11DS.

Administration of vitamin D is a cornerstone of treatment for hypocalcemia in 22q11DS. Several lines of evidence support the hypothesis that low levels of vitamin D during neurodevelopment are associated with risk for ASD and schizophrenia [39,40]. In addition, genotyping and biochemical studies have recently pointed to calcium regulatory pathways in the etiology of ASD and schizophrenia [28,25,24]. Thus our findings may have broader

implications for the idiopathic forms of these disorders. Looking forward, the robust pharmaceutical pipeline targeting calcium channels and calcium sensing receptors can be mined for candidates that normalize calcium signaling early in brain development, with the potential to prevent these behavioral disorders from arising.

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Fig. 1.

Circulating calcium levels on 151 people with 22q11DS, and corresponding age at blood draw. Top panel: Earliest calcium level on record, red circles denote subset with CSBS-DP ITC scores available. Bottom panel, lowest calcium level on record, inverted red triangles denote subset with CSBS-DP ITC scores available.

Fig. 2. Plot of individual CSBS-DP ITC raw social, speech and symbolic scores (square, circle, triangle,, respectively) and corresponding age at assessment of 20 participants (4 females and 16 males).

Table 1
Results of hierarchical multiple regression for the CSBS-DP ITC social, speech, and symbolic composite scores.

Model	Predictor variables	B	SE	β	t	R ²	F
1. Social	<u>Step 1</u>					.198	1.314
	Age at assessment	3.562	4.940	.214	.721		
	Age at lowest calcium	-.142	2.185	-.019	-.065		
	Gender	-4.754	2.878	-.373	-1.652		
	<u>Step 2</u>					.189	4.611*
	Age at assessment	7.817	4.883	.470	1.601		
	Age at lowest calcium	-1.174	2.031	-.159	-.578		
2. Speech							
	<u>Step 1</u>					.126	.770
	Age at assessment	3.354	2.379	.437	1.409		
	Age at lowest calcium	-1.363	1.052	-.399	-1.295		
	Gender	-.223	1.386	-.038	-.161		
	<u>Step 2</u>					.336	9.365**
	Age at assessment	5.974	2.110	.778	2.832*		
3. Symbolic							
	<u>Step 1</u>					.220	1.505
	Age at assessment	4.758	3.167	.440	1.503		
	Age at lowest calcium	.223	1.401	.046	.159		
	Gender	.709	1.845	.085	.384		
	<u>Step 2</u>					.189	4.783*
	Age at assessment	7.524	3.116	.695	2.415*		
	Age at lowest calcium	-.448	1.296	-.093	-.345		
	Gender	-1.510	1.945	-.182	-.776		

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Model	Predictor variables	B	SE	β	t	R ²	F
	Lowest calcium	1.941	.888	.557	2.187*		

Mean (SD) of scores: Social. 17.0 (5.2), Speech 6.0 (2.4), Symbolic. 7.7 (3.4).

* p < .05,

** p < .01