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The Impact of Hypocalcemia on Full Scale IQ in Patients with 22q11.2 Deletion Syndrome

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Abstract

Hypocalcemia has been reported in ~50% of patients 22q11.2DS and calcium regulation is known to play a role in neuronal development and synaptic plasticity. Because calcium ions play a role in neuronal function and development, we hypothesized that hypocalcemia would be associated with adverse effects on full scale IQ index (FSIQ) in patients with 22q11.2DS. A retrospective chart review cataloguing the presence or absence of hypocalcemia in 1073 subjects with a laboratory confirmed chromosome 22q11.2 deletion evaluated at the Children's Hospital of Philadelphia was conducted. 852/1073 patients had an endocrinology evaluation with laboratory confirmed calcium levels. 466/852 (54.7%) had a diagnosis of hypocalcemia. 265/1073 subjects ranging from 0-51 years of age had both calcium levels measured and a neuropsychological evaluation yielding a FSIQ. The mean FSIQ for 146/265 patients with hypocalcemia was 77.09 (SD=13.56) and the mean FSIQ for 119/265 patients with normocalcemia was 77.27 (SD=14.25). The distribution of patients with intellectual disability (ID) (FSIQ<69), borderline IQ (FSIQ 70-79), and average IQ (FSIQ>80) between the hypocalcemic and normocalcemic groups was not statistically significant ($\chi^2=0.2676$, $p=0.8748$). Neonatal hypocalcemic seizures were not found to be associated with ID. We found no difference in FSIQ between the hypocalcemic and non-hypocalcemic patients with 22q11.2DS. As our findings differ from a previous report in adult subjects, we speculate that this may reflect a potential benefit from early treatment of hypocalcemia and may support early

22q11.2 deletion detection in order to offer prompt diagnosis and subsequent treatment of hypocalcemia.

Keywords

22q11.2 deletion syndrome; hypocalcemia; intellectual disability; cognitive; endocrine; DiGeorge syndrome

INTRODUCTION

Chromosome 22q11.2 deletion syndrome (22q11.2DS) is the most frequent cause of DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome, and is the most common microdeletion syndrome known in humans. This copy number variant (CNV) usually occurs as a de novo event, most likely related to Low Copy Repeats (LCRs) that predispose the region to non-allelic meiotic recombination. However, approximately 10% of patients have inherited this mutation from an affected parent [McDonald-McGinn et al., 2001; McDonald-McGinn et al., 2015; Scambler, 2000]. The prevalence of 22q11.2DS has been reported to be between 1/3000 - 1/6000 live births, but more recently was found in ~1/1000 unselected fetuses, specifically, those without congenital heart disease (CHD) or palatal anomalies seen on ultrasound, rendering it one of the most common chromosomal conditions in humans [Grati et al., 2014; McDonald-McGinn et al., 2015]. The clinical presentation of 22q11.2DS is highly variable including multiple organ system involvement with manifestations that vary in presence and severity. Most frequent physical and cognitive characteristics include CHD, immunodeficiency, hypocalcemia, palatal differences, gastrointestinal problems, renal anomalies, skeletal abnormalities, cognitive deficits, and behavioral differences including high rates of psychiatric illness [McDonald-McGinn et al., 2001; McDonald-McGinn et al., 2015].

Similarly to the overall clinical presentation of patients with 22q11.2DS, endocrine manifestations are highly variable, the most common being hypocalcemia, which is generally attributed to hypoparathyroidism. The prevalence of hypocalcemia has been reported to range from 17-60% [Kapadia et al., 2008; Bassett et al., 2011; McDonald-McGinn et al., 2015]. Symptoms of hypocalcemia can include seizures, feeding difficulties, tetany, stridor and fatigue. In 22q11.2DS, hypocalcemia is often transient in the neonatal period, however, it can recur during times of stress, including perioperatively or during illness [Bassett et al., 2011; Cheung et al., 2014; Cheung et al., 2014; De Smedt et al., 2009; McDonald-McGinn et al., 2001; McDonald-McGinn et al., 2015].

The pharyngeal pouches give rise to the superior and inferior parathyroid glands. The pharyngeal pouch expands during the sixth week of development and begins to differentiate into an inferior parathyroid gland. T-box protein 1 (*TBX1*) is required for the development of the pharyngeal pouches, is located within the LCR22A-LCR22B region of chromosome 22q11.2, and is missing in the presence of a standard LCR22A-LCR22D or proximally nested 22q11.2 LCR22A-LCR22B deletion. Studies have suggested that genes located in the typically deleted region, such as *TBX1*, influence the development of the parathyroid glands

[Lindsay et al., 2001; McDonald-McGinn et al., 2015; Merscher et al., 2001; Taddei et al., 2001; Scambler, 2000; Yagi et al., 2003].

As variable expressivity has been reported with 22q11.2DS, it is important to study phenotype-phenotype correlations, specifically here, the effect of hypocalcemia on cognitive deficits. As with nearly all other clinical manifestations in patients with 22q11.2DS, cognitive manifestations are quite variable. Approximately two-thirds of patients with 22q11.2DS have an FSIQ in the range of 55-85 with a mean FSIQ of ~70, compared with the reference range of 85-115 in the general population with a mean FSIQ of 100 [De Smedt et al., 2009; McDonald-McGinn et al., 2015; Wang et al., 2000] Although some patients have more severe intellectual disability, it is rare and present in less than 10% of patients [Biswas and Furniss, 2016; Evers et al., 2014; McDonald-McGinn et al., 2015].

Despite numerous reports on associated findings in 22q11.2DS, specific examination of endocrine manifestations is limited, including the relationship between hypocalcemia and Full Scale IQ (FSIQ) levels. In 2014, Muldoon, et al., reported hypocalcemia in association with social and communication skill deficits in young children with 22q11 DS [Muldoon et al., 2014]. This study was limited by a small sample size ($n=20$) and scores based on parental questionnaires assessing children's social and communication skills. Likewise in 2014, Cheung, et al., examined an adult cohort with 22q11.2DS ($n=149$) and a history of neonatal seizures, likely caused by hypocalcemia which resulted in an increased risk for intellectual deficits. The authors pointed out the importance of recognizing and treating hypocalcemia in neonates with 22q11.2DS to avoid such long-term sequelae [Cheung et al., 2014].

The present study aims to examine the relationship between hypocalcemia and FSIQ levels in a large cohort of primarily pediatric patients with 22q11.2DS who were identified in childhood.

MATERIALS AND METHODS

Subjects

We retrospectively reviewed the patient records of 1073 patients with 22q11.2DS (ages 0-51years) followed in the 22q and You Center at The Children's Hospital of Philadelphia, a multidisciplinary clinic for children and adults with 22q11.2DS. Written informed consent was obtained and this study was performed with approval from The Children Hospital of Philadelphia and Arcadia University's Institutional Review Board as part of a genetic counseling thesis project. The chromosome 22q11.2 deletion was confirmed in all patients by standard fluorescence *in situ* hybridization (FISH), array comparative genomic hybridization (CGH), multiplex ligation probe-dependent amplification (MLPA), and/or genome wide microarray. Demographic information of the subjects is presented in Table 1.

Methods

Medical records were reviewed for demographics and lifetime laboratory measurements including ionized calcium and serum calcium, age, and treatment, where available. As the guidelines for managing patients with 22q11.2DS were published in 2011, not all patients

underwent routine screening for hypocalcemia. Subjects were considered to have hypocalcemia if laboratory evidence was available in the medical record and/or the laboratory values were below the reference range for the individual laboratory performing the respective test.

The IQ outcome measure consisted of standardized psychometric testing resulting in FSIQ scores using the Wechsler Intelligence Scale for Children (WISC) and Wechsler Preschool and Primary Scale of Intelligence (WPPSI). In the event that a patient had more than one FSIQ performed, we used an established strategy of using the mean of the FSIQ values. These tests were done between the ages of 2 and 7 (WPPSI) and 6 and 17 (WISC).

Statistical Analyses

Pearson's chi-squared test was used to statistically analyze the data.

RESULTS

Calcium Values

Of the 1073 patients in the study, 852 had an endocrinology evaluation with laboratory confirmed calcium levels; 466 (54.7%) had a diagnosis of hypocalcemia, 241 (51.7%) were male and 225 (48.3%) female. 386 (45.3%) patients had laboratory confirmed normal calcium levels, of which, 196 (50.8%) were male and 190 (49.2%) were female. Of the patients with normocalcemia, 167 were considered normocalcemic based on one laboratory measurement.

Of the 466 patients with a history of hypocalcemia, 444 had a confirmed age of onset, including; 282 (63.5%) diagnosed in infancy (0-1 year), 130 (29.3%) diagnosed in childhood (1-18 years), and 32 (7.2%) diagnosed in adulthood (>18 years).

Table 2 compares age at 22q11.2DS diagnosis to diagnosis of hypocalcemia.

Calcium Levels and Deletion Size

The presence of hypocalcemia was compared with deletion size (Table 3). Of the 798 patients with a standard chromosome 22q11.2 deletion (LCR22A-LCR22D deletion), 442 (55.4%) had a diagnosis of hypocalcemia and 356 (44.6%) had normal calcium levels. Of the 54 patients with an atypical nested deletion (LCR22A-LCR22B; LCR22A-LCR22C; LCR22B-LCR22D; LCR22C-LCR22D; LCR22C-LCR22E; or LCR22D-LCR22E deletions), 24 (44.4%) had a diagnosis of hypocalcemia and 30 (55.6%) had normal calcium levels. Fisher's exact test for A-D, A-B, A-C vs. B-D, C-D: $p = .0175$. Fisher's exact test for A-D vs. A-B, A-C, B-D, C-D: $p = .1993$. Fisher's exact test found no association between hypocalcemia and a standard typical 22q11.2 deletion versus a nested atypical 22q11.2 deletion: $p = 0.1226$. However, it did show an enriched hypocalcemia population in deletions that included *TBX1*.

Of the 54 patients with atypical nested deletions, 27 were LCR22A-LCR22B (50%), 6 were LCR22A-LCR22C (11.1%), 13 were LCR22B-LCR22D (24.1%), 6 were LCR22C-LCR22D (11.1%), one was LCR22C-LCR22E (1.9%), and one was LCR22D-E (1.9%)

(Table 3). 14/27 (51.9%) patients with LCR22A-B had a diagnosis of hypocalcemia and 13/27 (48.1%) had normal calcium levels. 5/6 (83.3%) patients with LCR22A- LCR22C had a diagnosis of hypocalcemia and 1/6 (16.7%) had normal calcium levels. 2/13 (15.4%) patients with LCR22B- LCR22D had a diagnosis of hypocalcemia and 11/13 (84.6%) had normal calcium levels. 3/6 (50%) patients with LCR22C- LCR22D had a diagnosis of hypocalcemia and 3/6 (50%) had normal calcium levels.

Calcium Levels and FSIQ Scores

Of the 852 patients with an endocrinology evaluation with laboratory confirmed calcium levels, 265 also had a neuropsychology evaluation yielding a full scale IQ index (FSIQ); 146 (55.1%) with a diagnosis of hypocalcemia and 119 (44.9%) with normal calcium levels. Of the 146 with hypocalcemia, 74 (50.7%) were male and 72 (49.3%) were female.

In assessing cognitive outcomes, patients with multiple IQ assessments were assigned a singular mean score yielding a FSIQ. Calcium levels and FSIQ scores were assessed in relation to deletion size (Table 4). For subjects with a LCR22A-LCR22D and hypocalcemia (n=138), the mean FSIQ was 77.09 (SD=13.56). For subjects with a LCR22A-LCR22D and normal calcium levels (n=112), the FSIQ was 77.27 (SD=14.36). For subjects with a LCR22A-LCR22B and hypocalcemia (n=14), the mean FSIQ was 88.50 (SD=9.29). For subjects with a LCR22A-LCR22B and normal calcium levels (n=13), the mean FSIQ was 83.75 (SD=9.88).

Of the 146 subjects with hypocalcemia, 38 (26%) had intellectual disability (ID) (FSIQ 69), 42 (28.8%) had a borderline IQ (FSIQ 70-79), and 66 (45.2%) had an average IQ (FSIQ 80). Of the 119 with normal calcium levels, 28 (23.5%) had ID, 34 (28.6%) had a borderline FSIQ, and 57 (47.9%) had an average FSIQ. Pearson's chi-squared test showed that these results were not statistically significant ($\chi^2 = 0.2676$, $p=0.8748$) (Table 5).

Of the 146 patients with hypocalcemia, 63 (43.2%) had onset in infancy and had a mean FSIQ score of 75.37. Of these 63 patients, 22 (34.9%) had ID, 14 (22.2%) had a borderline FSIQ, and 27 (42.9%) had an average FSIQ. 57 (39.0%) patients had onset in the juvenile period (1-18 years) and had a mean FSIQ score of 79.50. Of these 57 patients, 9 (15.8%) had ID, 19 (33.3%) had a borderline FSIQ, and 29 (50.9%) had an average FSIQ. 16 (11.0%) patients had onset in adulthood (>18 years) and had a mean FSIQ score of 76.38. Of these 16 patients, 5 (31.3%) had ID, 4 (25%) had a borderline FSIQ, and 7 (43.7%) had an average FSIQ. Ten patients did not have a verified date for age of onset of hypocalcemia. These results were not statistically significant using Pearson's chi-squared test ($\chi^2 = 6.126$, $p=0.1899$) (Table 6).

FSIQ Scores and Neonatal Hypocalcemic Seizure

Of the 146 patients with hypocalcemia and FSIQ data, 15 (10.3%) had at least one neonatal hypocalcemic seizure. The mean FSIQ for these patients was 77.60 (SD=15.8) and specifically 4 (26.7%) had ID, 4 (26.7%) had borderline intelligence, and 7 (46.6%) had an average FSIQ.

DISCUSSION

Hypocalcemia has been reported in ~50% of patients with 22q11.2DS. Consistent with the literature, we found hypocalcemia to be present in 54.7% of patients with 22q11.2DS in our larger cohort. From a neurocognitive perspective, mild to moderate ID has been observed in ~1/3 of patients with 22q11.2DS, whereas, severe ID is quite rare [Evers et al., 2014; Swillen and McDonald-McGinn, 2015]. We identified ID in 24.9% of the subset of our cohort where calcium levels and FSIQ measures were available. This frequency of ID is less than what would have been expected from the literature, which it is unclear why this is.

In a retrospective study, Cheung, et al., previously reported neonatal seizures, likely due to hypocalcemia, positively associated with intellectual disability in adults with 22q11.2DS [Cheung et al., 2014]. In contrast, our study found no association between hypocalcemic seizures and FSIQ scores. Moreover, we found no statistically significant difference in FSIQ between our large primarily pediatric cohort of patients with 22q11.2DS with or without hypocalcemia. Thus, we wonder if early identification of hypocalcemia may, with appropriate therapeutic intervention, provide a potential long term cognitive benefit.

Calcium ions are secondary messengers that transfer signals carried by extracellular molecules to a wide range of intracellular target molecules in all cells, including neurons in the brain. In neurons, calcium ions play an important role in controlling neuronal excitability and regulating activity-dependent signaling [Gleichmann and Mattson, 2011]. It has been proposed that because calcium has been shown to influence neurodevelopment, there is a possibility that dysregulation of calcium could play a role in lower IQ levels. [Cheung et al., 2014; Cheung et al., 2014; Muldoon et al., 2014]. Interestingly, calcium signaling pathways have been shown to regulate neuronal functions that have been implicated in other neurodevelopmental disorders, such as bipolar disorder, schizophrenia, and autism spectrum disorder, further suggesting that calcium levels could have an influence on the neurodevelopmental phenotype in 22q11.2DS [Berridge, 2014; Schmunk and Gargus, 2013].

Limitations of our study include lack of calcium and FSIQ data for our entire cohort. The international 22q11.2 healthcare community created guidelines for patients with 22q11.2DS, which were published in 2011 [Bassett et al., 2011]. These guidelines recommended calcium levels be assessed at the time of diagnosis, in infancy every 3 to 6 months, then every 5 years through childhood, and every 1 to 2 years thereafter adding assessments at time of stress, such as perioperatively and at times of illness. There are no set guidelines for when or how to administer standardized psychometric testing in these guidelines [Bassett et al., 2011]. Because these guidelines were not published until 2011, not all of the patients in our study had records of endocrinology evaluations or calcium levels. Along the same lines, we do not have all of the records for parathyroid function measurements. Another limitation is that if the patients were not followed at The Children's Hospital of Philadelphia, it is likely that they did not receive standardized psychometric testing or it was not available for our review. This is because current guidelines recommend assessing development and school performance, however, there is not a specific test recommended. Unfortunately, we also did not have treatment records for all of the patients who were found to have hypocalcemia, but we assume that if an individual was found to have hypocalcemia, then they were treated.

Similarly, we do not have records for all treatment, severity, and duration of neonatal seizures.

Future studies prospectively screening all patients with 22q11.2DS for hypocalcemia and FSIQ are warranted to better understand the relationship between hypocalcemia/hypocalcemic seizures and long-term cognitive outcome. In the interim, based on our and other reports noting hypocalcemia in at least 50% of patients with 22q11.2DS, and as has been suggested by the international 22q11.2 healthcare community vis-à-vis their practical healthcare guidelines, testing for hypocalcemia is indicated in all patients with 22q11.2DS at diagnosis and routinely thereafter including at times of biological stress, e.g. during illness, perioperatively, during puberty, and during pregnancy [Bassett et al., 2011; McDonald-McGinn et al., 2015]. Hence, early diagnosis of 22q11.2DS, utilizing routine prenatal/neonatal screening methodologies, is paramount in supporting such identification and early treatment [Bassett et al., 2011; McDonald-McGinn et al., 2015].

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Abbreviations

22q11.2DS	22q11.2 deletion syndrome
CHD	Congenital heart disease
FSIQ	Full Scale IQ
LCR	Low copy Repeat
CNV	Copy Number Variant

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TABLE 1

Demographics of Subjects

Sex	N	%
Male	437	51
Female	415	49

Race	N	%
Caucasian	667	78
African American	79	9
Hispanic	41	5
Asian	19	2
Mixed	12	1
Other/Unknown	34	4

Age at 22q11.2 DS Diagnosis	N	%
Prenatal & Infancy	430	50
Juvenile	321	38
Adulthood	30	4
Unknown	71	8

Infancy (0-1 years of age); Juvenile (1-18 years of age); Adulthood (>18 years of age).

TABLE 2

Age at 22q11.2DS Diagnosis in Comparison to Age at Hypocalcemia Diagnosis

Age at Hypocalcemia Diagnosis	Infantile	Juvenile	Adulthood	Unknown	Normocalcemic
Age at 22q11.2DS Diagnosis					
Prenatal & Infancy	234	50	2	8	136
Juvenile	33	74	17	7	190
Adulthood	0	0	8	2	20
Unknown	15	6	5	5	40

Infancy (0-1 years of age); Juvenile (1-18 years of age); Adulthood (>18 years of age).

TABLE 3

Calcium Levels and Deletion Size

Deletion Size	Hypocalcemic		Normocalcemic	
LCR22A-LCR22D (n=798)	442	55.4%	356	44.6%
LCR22A-LCR22B (n=27)	14	51.9%	13	48.1%
LCR22A-LCR22C (n=6)	5	83.3%	1	16.7%
LCR22B-LCR22D (n=13)	2	15.4%	11	84.6%
LCR22C-LCR22D (n=6)	3	50.0%	3	50.0%

TABLE 4

Deletion size, calcium levels, and IQ levels

Deletion Size	Hypocalcemic					Normocalcemic					P-value difference in IQ
	n	%	IQ n	Mean IQ	SD	n	%	IQ n	Mean IQ	SD	
LCR22A-LCR22D (n=798)	442	55.40%	138	77.09	13.56	356	44.60%	112	77.27	14.36	0.65
LCR22A-LCR22B (n=27)	14	51.90%	6	88.50	9.29	13	48.10%	4	83.75	9.88	0.45
LCR22A-LCR22C (n=6)	5	83.30%	2	85.85	6.18	1	16.70%	-	-	-	-
LCR22B-LCR22D (n=13)	2	15.40%	-	-	-	11	84.60%	1	72.00	-	-
LCR22C-LCR22D (n=6)	3	50.00%	-	-	-	3	50.00%	1	53.00	-	-

Deletion Size and Calcium Status Effect on FSIQ

Deletion Size	Hypocalcemic	Normocalcemic
LCR22A-LCR22D	76.46	77.27
LCR22A-LCR22B	88.50	83.75
LCR22A-LCR22C	85.85	85.85
LCR22B-LCR22D	72.00	72.00
LCR22C-LCR22D	53.00	53.00

TABLE 5
Distribution of FSIQ scores

IQ, intelligence quotient; ID, intellectual disability (FSIQ < 69); Borderline (FSIQ 70-79; Average (FSIQ ≥ 80).

TABLE 6

Age of Onset of Hypocalcemia and FSIQ Distribution

Infancy (age 1-10); Juvenile (age 1-18 years of age); Adulthood (>18 years of age).