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Association of hypocalcemia with congenital heart disease in 22q11.2 deletion syndrome

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Abstract

Hypocalcemia is one of the cardinal features of the chromosome 22q11.2 deletion syndrome (22q11.2DS), the most common cause of DiGeorge syndrome. Hypocalcemia and other features of 22q11.2DS including congenital heart disease (CHD) are primarily ascribed to problems with morphogenesis and function of the pharyngeal arch system derivatives including the parathyroid glands, the aortic arch, and the cardiac outflow tract. In light of the aforementioned embryology, we hypothesized that hypocalcemia would be identified more frequently in those patients with 22q11.2DS and CHD. We conducted a retrospective IRB approved chart review on 1,300 subjects with 22q11.2DS evaluated at the Children's Hospital of Philadelphia. χ^2 test was used to evaluate the statistical significance of differences in hypocalcemia between the two groups. Eight hundred fifty-two patients had calcium levels available for review. Of these, 466 (54.69%) had a history of hypocalcemia and 550 (64.55%) had CHD. Of those with CHD, 343 (62.36%) had a history of hypocalcemia, and of those without CHD, only 123 (40.73%) had a history of hypocalcemia. Thus, the frequency of diagnosed hypocalcemia was greater in patients with 22q11.2DS and CHD as compared to those without CHD ($p < .001$). We also analyzed age of onset of hypocalcemia and found that 66.47% of CHD/hypocalcemia group had neonatal/infantile hypocalcemia versus 43.09% in the non-CHD/hypocalcemia group. In our large cohort of patients with 22q11.2DS, the prevalence of diagnosed hypocalcemia is elevated among patients with CHD, in whom it is more likely to be diagnosed during the neonatal/infancy period.

Keywords

congenital heart disease; hypocalcemia 22q11.2 microdeletion

1 | INTRODUCTION

Microdeletion of chromosome 22q11.2 results in maldevelopment of the third and fourth pharyngeal pouches and is the most common interstitial deletion syndrome, affecting 1/2,000–6,000 live births and 1/1,000 unselected fetuses (Botto et al., 2003; Grati, Gomes, Ferreira, & Dupont, 2015). Cardinal features of this condition include congenital heart disease (CHD), hypoparathyroidism, immunodeficiency, palatal abnormalities, gastrointestinal differences, renal anomalies, developmental differences, and psychiatric illness (McDonald-McGinn, 2015). CHD is the most common cause of mortality in this syndrome (McDonald-McGinn, 2001).

Endocrinopathies are also frequent in 22q11.2DS, with hypoparathyroidism being the most common (Choi et al., 2005). Hypocalcemia is reported in approximately 50%–69% of patients with 22q11.2DS and is caused by agenesis or hypoplasia of the parathyroid glands, which are derivatives of the third and fourth pharyngeal pouches (Weinzimer, 2001). Hypoparathyroidism in this condition generally seems to be a result of decreased PTH reserve, with a predisposition to develop hypocalcemia during periods of stress or illness (Kapadia, Kim, McDonald-McGinn, Zackai, & Levitt Katz, 2008). Other endocrine manifestations include hypothyroidism, Graves' disease, and growth hormone deficiency (Choi et al., 2005).

22q11DS is characterized by variable expressivity, and phenotypic discordance between monozygotic twins (McDonald-McGinn, 2001; Halder, Jain, Chaudhary, & Varma, 2012). In light of the variable expressivity, it is important to identify clinical correlations between cardinal features.

Hypocalcemia and congenital heart disease are two of the most common features of 22q11.2DS. CHD is reported in 60%–74% of patients, particularly conotruncal malformations (malformations of the cardiac outflow tracts), such as Tetralogy of Fallot, pulmonary atresia with ventricular septal defect, truncus arteriosus, interrupted aortic arch, and conoventricular septal defects (Scambler, 2000; McDonald-McGinn, 2015). Given the aforementioned common embryology of the cardiac outflow tracts and the parathyroid gland, we hypothesized that a history of hypocalcemia would be identified more frequently in those patients with 22q11.2 DS and CHD than patients with 22q11.2DS and no CHD. Additionally, the stress involved with having CHD and its management may make it more likely to identify hypocalcemia in patients with 22q11.2 DS and CHD.

2 | MATERIALS AND METHODS

This study was a quantitative retrospective IRB approved medical chart review of 1,300 patients with 22q11.2DS, followed in the “22q and You” Center at The Children’s Hospital of Philadelphia, a multidisciplinary clinic for children and adults with 22q11.2DS. Since the “22q and You” Center is a large multidisciplinary clinic for children and adults, we have a combination of patients who are followed at CHOP primarily and who come to CHOP for first time consultations while being primarily followed elsewhere. In order to ensure patient confidentiality, the patients were de-identified.

CHOP medical records and any available outside hospital medical records of patients seen between 1995 and 2015 at “22q and You” center were reviewed. Data collection involved collecting all lifetime laboratory measurements of Ca, age at which time Ca levels were obtained, and CHD status for each patient. 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.

Eight hundred fifty-two of the 1,300 patients had Ca levels drawn. In patients with multiple Ca values drawn, all values were recorded and if any were below 8.8 mg/dL, they were noted to have a history of hypocalcemia. Additionally, age of first episode or onset (neonatal period, infancy, childhood, adolescence, or later in life) of hypocalcemia was abstracted using the pediatric normal range for calcium defined as 8.8–10.1 mg/dL (the normal ranges used at The Children’s Hospital of Philadelphia). In patients with a history of multiple episodes of hypocalcemia, if the date of the first episode was unclear per outside hospital documentation, the age of onset was considered unknown.

Additionally, the presence/absence of CHD was also recorded and correlated with the presence/absence of history of hypocalcemia. χ^2 test was used to evaluate the statistical significance of differences in hypocalcemia between the two groups.

3 | RESULTS

Of the 852 patients with 22q11.2DS and Ca evaluations, there were an equal number of males and females. Patients ranged from 6 months to 59 years at time of Ca measurement (Table 1). The majority of patients ($n = 798$) had a typical LCR22A-LCR22D deletion (93.66%), whereas 54 had atypical nested deletions (6.34%) (Table 2). The overall prevalence of hypocalcemia was 54.69% ($n = 466$) while 45.31% ($n = 386$) were normocalcemic, consistent with prior literature. The overall calcium values ranged between 7.3 and 9.9 with an average Ca level of 9.0 and a standard deviation of 0.488. In patients with multiple Ca levels, the median value for each patient was used to calculate the average. Neonatal and infantile hypocalcemia (defined as occurring within the first month and between the first month and first year of life, respectively) were noted most frequently in the hypocalcemia group. However, importantly 20.82% of patients developed hypocalcemia in childhood and 13.95% during adolescence and adulthood for the first time (Table 3).

CHD was present in 550 of 852 patients (64.55%) including: Tetralogy of Fallot (25%), ventricular septal defect (21%), interrupted aortic arch (15%), other aortic arch abnormality (12%), truncus arteriosus (8%), atrial septal defect (7%), and vascular ring (4%). Forty-three of 852 patients, ages 0.5–58 years, had no CHD status recorded in the database and were included in the non-CHD group, given they had no evidence of cardiac evaluation or intervention in their charts.

In an effort to assess the relationship between comorbidities, we compared the presence of hypocalcemia in the 852 patients with the presence/absence of CHD. Three hundred forty-three of 550 (62.36%) patients with CHD had findings of hypocalcemia while 123 of 302

(40.73%) patients without known CHD had hypocalcemia. Thus, the frequency of hypocalcemia is statistically significantly higher in patients with CHD with a chi squared of 36.8 ($p < .0001$) as compared to those without a CHD. As noted in Table 4, there is a higher prevalence of hypocalcemia in severe heart disease when compared to those with mild heart disease—75.18% of patients with Tetralogy of Fallot, 77.38% of patients with interrupted of aortic arch, and 86.36% of patients with truncus arteriosus demonstrated at least one episode of hypocalcemia (Pearson's chi-squared test, $\chi^2 = 1.5$, $p < .0001$).

Additionally, among those patients with CHD and hypocalcemia, the majority had their first episode of hypocalcemia in the neonatal period and infancy, as seen in Table 5. Among patients with hypocalcemia, 66.47% of the CHD group had hypocalcemia diagnosed before 1 year of age versus 43.09% of the non-CHD group.

4 | DISCUSSION

In this large cohort of patients ($N = 852$) with 22q11.2DS, we found a history of hypocalcemia was present in 54.69% of our patients. Moreover, hypocalcemia was more often present in those patients with CHD and was more likely diagnosed in the neonatal period and infancy. This frequency is slightly higher than the previous reports from smaller populations. In fact, even within our own center, we previously reported a slightly lower prevalence of hypocalcemia (49%) in a subset of our cohort ($N = 158$ patients) (McDonald-McGinn et al., 1999). In a larger European multicenter combined cohort of 558 patients with 22q11.2 deletions (Ryan et al., 1997), 340 patients had calcium levels reported, of which 60% were found to have hypocalcemia most often in the neonatal period, although some occurred during childhood, and one patient had onset at 18 years of age.

Congenital heart disease (CHD) was present in 64.55% of our 852 patients. Previously at our center, which sees a large number of referrals for cardiac surgery, CHD was reported to be present in 74% of 250 patients (McDonald-McGinn et al., 1999); diagnoses consisted of mostly conotruncal defects with the most common including Tetralogy of Fallot, interrupted aortic arch, conoventricular ventricular septal defect, and truncus arteriosus. In the European cohort of 558 patients, CHD was noted in 75% (Ryan et al., 1997) and the spectrum of CHD included tetralogy of Fallot, VSD, interrupted aortic arch, pulmonary atresia, truncus arteriosus, pulmonary valve stenosis, ASD.

Classical hypoparathyroidism presenting with symptoms of hypocalcemia including seizures, tremors, or tetany may occur in 22q11.2DS. More commonly, however, hypoparathyroidism in 22q11.2DS manifests as transient hypocalcemia, which occurs during times of stress or illness, due to low parathyroid reserve (Kapadia, 2008). This partial hypoparathyroidism is unmasked by stressors including surgery, illness, fasting prior to surgery, or while on prolonged intravenous fluids/postoperatively. In our present study, we aimed to assess the prevalence of hypocalcemia in patients with 22q11.2DS and CHD. Given the common embryology leading to these cardinal features and the additional stress involved with the nature of CHD management, we hypothesized that a history of hypocalcemia would be identified more frequently in those patients with 22q11.2 DS and CHD. The literature regarding the associations between hypocalcemia and cardiac disease in

22q11.2DS is very limited. Previously, Fujii et al. examined a much smaller sample size of 16 patients with 22q11.2DS and CHD and found that 62.5% had a history of hypocalcemia. Our study reports a strong association of hypocalcemia and CHD in a much larger pediatric population. This important finding may reflect an embryological association or the resultant finding of associated physiologic stressors described above or a combination of these factors.

Given that hypoparathyroidism/hypocalcemia is a cardinal feature of 22q11.2DS, it can commonly be a complicating factor in CHD management and recovery from surgery. Such patients also frequently require diuretics, which can exacerbate electrolyte abnormalities. In a study of 208 patients with tetralogy of Fallot, 44 patients with 22q11.2 DS had longer cardiopulmonary bypass time (84 vs. 72 min) and duration of intensive care (6 vs. 4 days) (Mercer-Rosa, Pinto, Yang, Tanel, & Goldmuntz, 2013). The reasons for these differences are unclear, as mortality, duration of mechanical ventilation, number of extracardiac anomalies were similar in both groups. Patients with 22q11.2DS are at a higher risk for complications and hypocalcemia may be a contributor to the differences noted above. The differences may also be a result of infection as a result of immunodeficiency (Sullivan, 2004) but this was not noted in this study by Mercer-Rosa et al.

In a small study of 22 patients with 22q11.2DS/CHD and 110 patients with only CHD, postoperative hypocalcemia was observed in 86.4% of patients with 22q11.2DS compared to 47.3% of patients without a deletion—a statistically significant difference (Shen et al., 2011). In the nondeletion subjects, hypocalcemia was usually seen at cardiopulmonary bypass initiation, after which they quickly recovered, likely due to a subsequent increase in parathyroid hormone through appropriate feedback mechanisms. However, in patients with 22q11.2DS, the ability to increase production/release of PTH is limited due to parathyroid gland abnormalities, therefore likely resulting in a higher prevalence and detection rate of hypocalcemia. Given these outcomes and the results of our current analysis, it is important to screen for 22q11.2DS in infants with CHD, and also to monitor calcium in patients with 22q11.2DS undergoing surgery and postoperatively. Moreover, as hypocalcemia can complicate intraoperative management, it is also a contributor to protracted postoperative recovery.

Given that our study was a retrospective chart review of large sample size, a major limitation of our study is that we were unable to obtain specifics on recurrence/follow-up of hypocalcemia. Another limitation of our study includes lack of PTH levels obtained with hypocalcemia to confirm the presence of hypoparathyroidism. It is possible that some of the hypocalcemia may be related in part to surgery/postoperative factors in the intensive care setting that are unrelated to embryologic parathyroid gland abnormalities. Additionally, the hypocalcemia may be misleading in the setting of hypoalbuminemia that may occur in the postop setting, in the first few days of life in which there is a physiological nadir of serum calcium, which can be exaggerated leading to frank transient hypocalcemia in premature infants and infants of diabetic mothers.

While we did find that the more severe congenital heart disease (Tetralogy of Fallot, interrupted aortic arch, truncus arteriosus) was associated with higher frequency of patients

having a history of hypocalcemia, we are unable to tell if this is a result of stress of surgery in the neonatal period or even a selection bias of those that were headed to the OR and had labs ordered. In the study by Shen et al. cited above, nondeletion patients undergoing cardiac surgery were also found to have hypocalcemia. A control population of patients with CHD would be helpful in delineating the frequency of hypocalcemia in patients with isolated CHD without 22q11.2DS compared to those with 22q11.2DS.

In conclusion, in a large cohort of patients with 22q11.2DS, we found a significant association of a history of hypocalcemia with CHD, more often diagnosed in the neonatal period and infancy. Because of the high volume of cardiac surgery performed at our institution, our findings may relate to early identification of younger patients with hypocalcemia in association with CHD during neonatal hospitalization. This speaks to the importance of early diagnosis of 22q11.2DS, in particular as a cause of CHD. Therefore, identification of CHD and hypocalcemia, should prompt us to think about and to test for 22q11.2 DS.

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TABLE 1**Demographics**

Total patients	852
Sex	
Female	415 (48.70%)
Age at time of Ca draw	
<1 year	2 (0.23%)
1–12 year	278 (32.63%)
13–17 year	183 (21.48%)
Adulthood	389 (45.66%)
Ethnicity	
Caucasian	675 (79.20%)
African American	81 (9.50%)
Hispanic	40 (4.69%)
Other	56 (6.57%)
Genotype	
A-D deletion	798 (93.66%)
Atypical nested deletion (e.g. LCR22A-LCR22B; LCR22A-LCR22C; LCR22B-LCR22D; LCR22C-LCR22D;	54 (6.34%)
Congenital heart disease	550 (64.55%)

TABLE 2

Comparing deletion and hypocalcemia

Deletion size	Hypocalcemia	Normocalcemia
LCR22A-LCR22D ($n = 798$)	442	356
LCR22A-LCR22B ($n = 27$)	14	13
LCR22A-LCR22C ($n = 6$)	5	1
LCR22B-LCR22D ($n = 13$)	2	11
LCR22C-LCR22D ($n = 6$)	3	3
LCR22C-LCR22E ($n = 1$)	0	1
LCR22D-LCR22E ($n = 1$)	0	1

TABLE 3

Age at first documented hypocalcemia

Age range	No. patients (<i>n</i> = 466)	Percentage (%)
Neonatal period (0–1 month old)	197	42.27
Infancy (1 month–1 year old)	84	18.03
Childhood (1–12 year old)	97	20.82
Adolescence (13–17 year old)	33	7.08
Adulthood (older than 17 year)	32	6.87
Unknown	23	4.94

TABLE 4**CHD type versus hypocalcemia**

CHD type	Hypocalcemia	Normocalcemia
	<i>N</i>	<i>N</i>
Tetralogy of Fallot (includes those with other cardiac lesions) (137)	103 (75%)	34 (25%)
Ventricular septal defect as primary cardiac lesion (113)	53 (47%)	60 (53%)
Interrupted aortic arch (includes those with multiple cardiac lesions) (84)	65 (77%)	19 (23%)
Aortic arch abnormality as primary cardiac lesion (RAA, LAA, DAA) (75)	35 (47%)	40 (53%)
Truncus arteriosus as primary cardiac lesion (44)	38 (86%)	6 (14%)
Atrial septal defect as primary cardiac lesion (38)	16 (42%)	22 (58%)
PDA (16)	7 (44%)	9 (56%)
Other (PS, PA, PFO, bicuspid aortic valve) (43)	26 (60%)	17 (40%)

Severe CHD = Tetralogy of Fallot, interrupted aortic arch, or truncus arteriosus. Mild CHD = any other CHD. All categories included (severe CHD vs. mild) = Pearson's chi-squared test $\chi^2 = 51.487$, $p < .0001$.

TABLE 5

Comparing hypocalcemia age of onset with congenital heart defects

Hypocalcemia age of onset	CHD grade (<i>n</i> = 343) Severe CHD	Mild CHD	None (<i>n</i> = 123)
Neonatal period (<i>n</i> = 197) (0–1 month old)	113 (57.36%)	45 (22.84%)	39 (19.80%)
Infancy (<i>n</i> = 84) (up to 1 year old)	36 (42.86%)	34 (40.48%)	14 (16.67%)
Childhood (<i>n</i> = 97) (1–12 year old)	28 (28.87%)	32 (32.99%)	37 (38.14%)
Adolescence (<i>n</i> = 33) (13–17 year old)	12 (36.36%)	9 (27.27%)	12 (36.36%)
Adulthood (<i>n</i> = 32) (older than 17 year)	10 (31.25%)	8 (25.00%)	14 (43.75%)
Unknown (<i>n</i> = 23)	9 (39.13%)	7 (30.43%)	7 (30.43%)

Severe CHD = Tetralogy of Fallot, interrupted aortic arch, or truncus arteriosus. Mild CHD = any other CHD. Pearson's chi-squared test, $\chi^2 = 37.8$, $p < .0001$.