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Obstetric Factors, Neonatal Hypoxia and Congenital Heart Defects in Patients with 22q11.2 Deletion Syndrome: Effects on Developmental Delay

By

Sofia Angelica Tenorio Martinez

Master of Public Health

Epidemiology

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By

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Doctor of Medicine

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Abstract

Obstetric Factors, Neonatal Hypoxia and Congenital Heart Defects in Children with 22q11.2 Deletion Syndrome: Effects on Developmental Delay

By Sofia Angelica Tenorio Martinez

Background: 22q11.2 Deletion Syndrome (22q11.2DS) has a prevalence of 1/4000 live births and is the second most common cause of developmental delay and Congenital Heart Defects (CHD) in the US. Preterm birth and low birthweight (BW) can influence brain development and lead to adverse outcomes. However, there is a lack of prevalence data on preterm births and BW, delivery methods, neonatal hypoxia and poor respiration at birth for this population.
Hypothesis: Determine the distribution of gestational age (GA), BW, Small for Gestational Age (SGA), delivery method, neonatal hypoxia and poor respiration. Analyze the association between these factors and developmental delay domains.
Methods: Analyzed a sample of 158 participants, all with genetically confirmed 22q11DS. Data were abstracted for BW, GA, SGA, delivery method, neonatal hypoxia, poor respiration at birth and CHD presence. Use logistic regression models to assess the association between BW, GA and SGA with and developmental delay as determined by CDIP and CSBS-CP scores.
Results: Of the participants, 47 (29.75%) were delivered by C-Section. Hypoxia was reported in 18 (11.39%) children and there were 42 (26.58%) with poor respiration at birth. Most of the participants had at least one congenital heart defect (125, 79.11%). Of those labeled as Level 2 (Hypoxic CHD), the majority had Tetralogy of Fallot (30, 18.99%). Of those considered as level 1 CHD (lowest risk of hypoxia) the majority had Ventricular Septal Defects (62, 39.24%). Mean GA was 38.06 weeks (SD 1.83), BW of 2,920 grams (SD 560) and birthweight percentile of 32.07% (SD 28.61), with 33.33% meeting established criteria for SGA. Neonatal hypoxia was associated with an increased likelihood of C-Section (Prevalence Odds Ratio 3.10, p .03). CHD Hypoxia Level 1 (OR: 11.89, 1.55- 130.72, p=.03), SGA (OR: .14, .02-.73, p=.03) and CHD Hypoxia Level 2 (OR: .13, .01-.88, p=.05) were associated to domains of developmental delay.
Conclusions: Patients with 22q11.2DS have higher prevalence of GA, BW and SGA compared to the general population. SGA and CHD Hypoxia have an impact on developmental delay, albeit in opposite directions. Additional investigations are required to understand how these obstetric factors influence neurodevelopmental conditions.

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BACKGROUND

22q11.2 Deletion Syndrome Epidemiology and Clinical Presentation

22q11.2 Deletion Syndrome (22q11.2 DS), previously called Di George or Velocardiofacial Syndrome(1), is the most common microdeletion syndrome and, even though it's considered rare, it has an estimated prevalence of 1 in 4,000 live births(2). With an autosomal dominant pattern of inheritance(3), approximately 10% of the cases will be inherited from an affected parent, while the majority of the cases (around 90%) present as a de novo genetic disease(4). This deletion syndrome is considered the second most common cause of developmental delay and congenital heart defects. 2.4% of those with 22q11.2DS can present developmental disabilities, while 10-15% of patients present with Tetralogy of Fallot(5).

Around 85% of the patients with 22q11.2DS have a large deletion of approximately 3 Mb, while the rest of the patients have smaller, "nested" deletions inside the 3 Mb deletion region. When a large deletion occurs, it encompasses 45 functional genes(5). There are multiple methods used to detect 22q11.2DS; depending on the type of deletion, its size and location. Fluorescence in Situ Hybridization (FISH) can be used to detect microdeletions of the long arm of chromosome 22 and submicroscopic deletions(3, 5). More powerful techniques that can detect any size of deletions are the Array Comparative Genomic Hybridization (aCGH), Microarrays and Multiplex Ligation Dependent Probe Amplification (MLPA)(5).

22q11.2 DS has clinical heterogeneity, with a wide range of associated conditions. The classic clinical triad seen is: conotruncal cardiac anomalies, hypocalcemia and hypoplastic thymus leading to immunodeficiency. Usually patients present with two or more findings: developmental or learning disabilities, sometimes both; cardiac anomalies, immunodeficiency, hypocalcemia, characteristic facial features, palatal defects; among others(5). Some of the less common symptoms are hearing loss, renal anomalies, growth retardation, among others(2).

Almost all types of well-defined Congenital Heart Defects (CHD) are associated to 22q11.2DS. Conotruncal anomalies found in 22q11.2DS include Tetralogy of Fallot (ToF), Truncus Arteriosus (TA) and Interrupted Aortic Arch(3) (IAA); all of them usually found shortly after birth. Among them, ToF is the most frequent CHD seen(2).

As mentioned above, developmental delay is one of the main findings seen in this deletion syndrome. It occurs when a child cannot achieve developmental milestones that other children in the same age range have been able to(6). About 10-15% of children under the age of 5 have presented patterns of developmental delay(6). 22q11.2 DS children have shown greater developmental impairment in accuracy performance on various developmental domains than those non-deleted children with developmental delay and medical comorbidities(7). The main impairments in those with 22q11.2 DS are seen in face memory and social cognition, followed by language and nonverbal reasoning(7). Some of the Psychiatric disorders associated to 22q11.2DS are anxiety, Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD); schizophrenia and depression are also commonly present, but emerge in

adolescence or early adulthood(7). Patients with 22q11.2DS have a 20-25-fold increased risk of developing schizophrenia(8). Identifying the factors that can increase or influence the risk for developmental delay in 22q11.2DS is a relevant matter to study for those working with these patients and their families.

Congenital heart defects have also been associated to neurodevelopmental delay. This has been considered to be an effect of preoperative, operative and postoperative aspects that have an influence on neural development; but there is still a lot that is not understood(9). These patients can present with motor delays, learning disabilities, problems with visual-motor integration, among others(10). Neurodevelopmental delay can mostly be seen in patients with cyanotic CHD and those that required surgical intervention(11). 22q11.2DS is found in a significant proportion of patients with CHD; which in turn is associated to various neurocognitive deficits(12). A study determined that 22q11.2DS patients with CHD had reduced cortical volumes, suggesting that hemodynamic alterations can contribute to development delay in 22q11.2DS patients(13). Even though there are some studies analyzing the effect of CHD on developmental delay; there hasn't been an extensive analysis of the association of specific Congenital Heart Defects, their associated hypoxia, and developmental delay factors and scores. A study reported lower than expected development using the Bayle Scales of Infant Development in toddlers with single ventricle palliation(9). This association hasn't been analyzed in the 22q11.2DS population, where there is high prevalence of CHD and developmental delay and where early intervention might lead to better outcomes.

Birthweight, Gestational Age and Developmental Delay

Weeks 24-40 in gestation are relevant in the development of multiple components of the brain(14). A lot of brain growth and development occurs during the last 6 weeks of gestation. During this period, neuronal migration and differentiation occur; as well as myelination, synapse formation, etc. Therefore, births before this process is complete are particularly vulnerable to hypoxia, inflammation and free radical damage(14). There is a higher likelihood of brain injury when in neonates with low gestational age and low birthweight; the lower the weeks of gestation, the higher the risk(15). One of the consequences expected from brain injury, either primary or secondary, is impaired white matter development throughout childhood and even adolescence. Therefore, children who are preterm or with very low birthweights have lower brain volume, both for white and grey matter(14).

In general, severe outcomes in those who are very preterm or very low birthweight have decreased as interventions have improved; but the risk of overall developmental delay has remained the same in these populations(14, 16). Even those classified as late preterm have been reported to have neurologic abnormalities, behavioral problems and learning disabilities; they are 2 times more likely to present developmental delay compared to full term infants(15). In both very and moderately preterm babies, the odds of developmental delay increase around 10-14% for each week of premature gestation(17). Aside of gestational age, birthweight has been shown to have an independent effect on the risk of developmental delay. The threshold of <1,250 grams identifies children with the highest

risk of diagnosed developmental delay(18). As presented above, there is evidence that shows the possible relationship between birthweight and gestational age, and developmental delay; but it hasn't been completely explained or understood. Almost no studies have explored the effect of gestational age, at all levels of preterm and normal gestation, on specific developmental domains that have a broad impact on children and children with a well-defined genetic disorder such as 22q11DS. Most studies have focused on specific diagnoses of developmental delay or have presented inconclusive information about the risk of developmental delay with decreasing gestational age.

SGA and developmental delay

Small for gestational age (SGA) refers to a newborn that falls below the 10^{th} percentile of newborns with the same sex and gestational age(19). The prevalence of SGA is approximately 8.6%-9.6% across several countries(20), but studies have shown that children with 22q11.2DS have a higher prevalence of SGA, of up to 40%(8). The catch-up growth seen in children born SGA has been associated to cardiovascular diseases, hypertension, metabolic syndrome, among others(21). The information associating SGA and developmental delay is varied. Some studies have shown that children who were SGA can have higher levels of developmental delay compared to those born at an appropriate gestational age; while other studies have shown no relevant difference between SGA and appropriate gestational age children(22). A study on a nationally representative sample of US children showed that SGA children had worse motor and cognitive outcomes at 5 years compared to those who were not SGA(19). Increased levels of developmental delay among SGA children can be explained by the chronic nutritional

and oxygen deficits during gestation, which in turn can alter brain structure and therefore affect delay as the child grows(23). On the other hand, almost no studies have tried to establish the relationship between SGA and developmental delay in this population, 22q11.2DS children, who have a high prevalence of SGA.

CSBS-DP and CDI

There are various tests used by physicians to evaluate the general development of a child. One of them is the Communication and Symbolic Behavior Scales Developmental Profile (CSBS-DP). This is a routine screening tool for developmental delay in children 6-24 months of age, to determine the need for a communication evaluation and to monitor changes in a child's communication, symbolic behavior and expressive speech over time(24). The level of communication development can be considered one of the main indicators for developmental delay, where a delay in language development can reflect the child is not developing correctly. The CSBS-DP is designed to evaluate 7 language predictors, which are: emotion and use of eye gaze, use of gestures, use of sounds, use of objects, use of communication, use of words and understanding of words(24). If there is continuous language delay there can be long-term academic, social and psychological negative effects(25). This test consists of 3 parts: the infant-toddler checklist, the behavior sample and the caregiver questionnaire. The purpose of the infant-toddler checklist is to measure social, speech and symbolic aspects of early communication. The social portion includes indicators of communicative competence; the speech portion evaluates vowel combinations to form words and syllables. And the symbolic aspect evaluates comprehension(25). The Infant-Toddler checklist consists of 24 questions,

scored from 0-2 or 0-4. A total cut-off score is determined to identify age appropriate determinations of “concern” or “no concern”.

The Child Development Inventory (CDI) is used from ages 25-72 months old. This instrument is designed to assess language, motor, letter, number, social development; as well as self-help and the presence of behaviors problems(26). It consists of 300 questions and 8 domains. Each score then falls at 1.5 or 2.0 SD below the mean.

Public Health Relevance

The relevance of this study is to further describe the 22q11.2DS population and its characteristics regarding birthweight, gestational age, SGA, congenital heart defect, and hypoxia and respiration at birth; all of which have not completely been described in this population and which are relevant in the development of health outcomes later on in children with 22q11.2DS. It’s also one of the first studies that looks to establish the association and impact of birthweight, gestational age and SGA; with developmental delay, either influenced by heart disease or not, in those with 22q11.2DS. This is relevant because a lot of these patients are not identified as having developmental delay or psychiatric disorders until later in life; which at that point, intervention might not be as helpful. Also, because SGA has a higher prevalence in this population compared to children born with adequate gestation, it is relevant to understand how and if it affects later development in children. By determining which early risk factors might be relevant for the progress of developmental delay, there is a possibility for early identification and intervention. This is also a novel study, since the outcomes are obtained through

questionnaires and scoring methods which present details or traits of developmental delay even before a diagnosis is made.

METHODS

Hypothesis and Objectives

1. Determine the distribution of gestational age (GA), birthweight (BW), SGA, delivery method, maternal age, neonatal hypoxia and poor respiration in this population.
2. Determine if low birthweight (LBW), low gestational age and Small for Gestational age (SGA) patients with 22q11.2DS have an increased risk of developmental delay, based on the CSBS-DP and the CDI. Part of this analysis was to analyze if there is an increased risk or association of developmental delay in patients with Congenital Heart Defect-associated hypoxia, neonatal hypoxia and poor respiration at birth.

Sample

CSBS-DP and CDIP Questionnaires were done from October 2006 to December 2017 at the 22q Specialty Clinic at Children's Healthcare of Atlanta, gathering a total of 158 participants. 83 were males and 75 females (53%, 47%), with ages between 5 and 60 months old. 92 participants were given the CSBS-DP test, 91 the CDI test and from those, 25 participants had both. 9 and 19 participants took the CSBS-DP and the CDIP twice, respectively.

Criteria and Instruments

At every medical visit within the 22q Specialty Clinic, caregivers are asked to complete developmental or adaptative behavior questionnaires. Afterwards, the nurse or certified genetic counselor scores them. All patients that went to the 22q11 Specialty Clinic during this time period (October 2006-December 2017) received the questionnaires appropriate to their age. The CSBS-DP is used in patients 6-24 months of age, while the CDIP is used with those 25-72 months old. No patient attending the 22q11 Specialty Clinic was excluded from receiving the questionnaires, unless they decided not to participate. Consents were obtained from caregivers of the 22q11.2 Specialty Clinic. Collection of this information and medical records information was approved by Emory University IRB.

The outcomes to analyze for the CSBS-DP test are the communication composite (including emotion & use of eye gaze, use of communication and use of gestures), the expressive speech composite (use of sounds and use of words), the symbolic composite (understanding of words and use of objects) and the total score, which is the total raw scores for all previous composites. The scores are then classified in Concern or No Concern, being classified as “Concern” if the criterion levels are set more than 1.25SD below the mean for the specific age of the child being evaluated. Based on that classification and in which composite the Concern is seen; the children are established as communicating adequately for their age or in need of referral for a developmental evaluation.

For the CDIP test, the scales to evaluate are: social (S), self-help (SH), gross motor (GM), fine motor (FM), expressive language (EL), language comprehension (LC), letters (L), numbers (N) and general development (GD), which is a summary of all the previous scales. The scores are compared to the expected scores by age in each of the scales, which are based on a sample of 568 children one to six years old. The children are categorized as "Developmentally Delayed" if their score is between 25% to 30% or below 30% the age line and "Developing as expected" if they score above 25%.

For this study, the focus will be on CSBS-DP total concern and on gross motor, fine motor, expressive language and language comprehension for CDIP. These outcomes have the highest specificity for Developmental Delay, which is why we focused only on them.

Statistical Analysis

This is a cross-sectional analysis using data from the CSBS-DP and CDIP questionnaires, and medical records information for the 22q11.2 Specialty Clinic patients. Birthweight (grams), gestational age (weeks), small for gestational age (SGA, percentage), CDIP and CSBS-DP results are the main variables of analysis. Also gathered and considered were delivery method (C-Section or Vaginal Delivery), neonatal hypoxia (dichotomous, presence or not), poor respiration at birth (dichotomous, presence or not) and congenital heart defect presence. As covariates to consider for our analysis we also gathered sex, children's and mother's race, maternal age (years) and the patient's age (months) when the questionnaires were administered.

Gestational age and birthweight were analyzed as continuous and categorical variables. Gestational age was classified as extremely preterm (<28 weeks), very preterm (28-32 weeks), moderate preterm (32-33.6 weeks), late preterm (34-36.6 weeks), early term (37-38.6 weeks), full term (39-40.6 weeks) and late term (>41 weeks). Birthweight was classified as extremely low birthweight (<1,000 grams), very low birthweight (1,000-1499 grams), low birthweight (1,500-2,499 grams) and normal birthweight (>=2,500). Birthweight percentiles were calculated based on gender, gestational age and birthweight in grams, utilizing the WHO Birthweight Percentile Calculator. Congenital Heart Defects considered for the analysis were ToF, TA, Transportation of the Great Arteries, IAA and Pulmonary Atresia (PA). Any other Congenital Heart Defects presented by the patients were labeled as Others; which included Ventricular Septal Defect (VSD), Auricular Septal Defect (ASD), Right Aortic Arch, Vascular Ring, Aortic Stenosis, Patent Ductus Arteriosus (PDA), Pulmonary Stenosis, Bicuspid Aortic Arch, Patent Foramen Ovale (PFO), Aortic Root Dilation, and Aberrant Right Subclavian Artery. All CHDs were further classified to three levels based on their severity and their possible association to neonatal hypoxia. Level 0 were those without any known Congenital Heart Defects, level 1 those with other known cardiac defects such as ASD, VSD and those defects established as “Other” in our Congenital Heart Defects classification; and level 2, those with a cardiac defect targeted for screening due to known risk of hypoxia and complications; such as PA, ToF, Transposition of the Great Arteries, TA and IAA. If a participant had criteria for both Level 1 and Level 2, then they were classified based on their most severe CHD.

For a participant to be established as having neonatal hypoxia, it had to be written in the medical records or with arterial gas results (PO2, SatO2, pH) associated with hypoxia. On the other hand, participants were categorized with poor respiration if in the medical records it was referenced or if the patient was referenced to be “blue” at delivery.

Venn Diagrams were done to analyze overlap between categories of categorical variables. Chi-square and Exact Fisher tests were done to analyze the differences between levels of fetal hypoxia based on Congenital Heart Defects, neonatal hypoxia and poor respiration; by delivery methods.

Regression models were used to assess the association between BW, GA and SGA with CDIP and CSBS-CP scores representing developmental delay. The association between CDIP and CSBS-CP outcomes with Congenital Heart Defect Hypoxia, neonatal hypoxia and poor respiration were also analyzed. An individual model was done for Total Concern based on the CSBS-CP and its association to BW, GA, SGA, CHD Hypoxia Level, Neonatal Hypoxia and Poor Respiration. Exposures were only considered individually because of possible collinearity between them. Covariates included in the model were maternal age, delivery method, sex, race and age at questionnaire.

For CDIP, individual models were run for gross motor, fine motor, expressive language and language comprehension; the exposures considered were the same ones used in the CSBS-DP analysis and the same covariates were used in this model.

Multiple imputation for each of the regression models was done to account for missing data. Imputation was done 10 times, producing parameter estimates for each imputed dataset. The overall parameter estimate is an average of the parameter estimates for each imputed dataset.

A discriminative analysis was also run, to determine which exposures better predicted and categorized the outcomes.

All statistical analysis was done with SAS 9.4.

RESULTS

Description of the population

158 children with genetically confirmed 22q11.2DS were analyzed. Of these, 92 participants were given the CSBS-DP test, 91 the CDIP test and from those, 25 participants had both. While 9 and 19 participants took the CSBS-DP and the CDIP twice, respectively, for this paper, only the first CSBS-DP and CDIP test done per person will be used.

Demographics information for the complete cohort is established in Table 1. In total, 83 were males and 75 females (53%, 47%), with ages between 5 and 60 months old. Most children were White Non-Hispanic (89, 64.96%), followed by Black Non-Hispanic (37, 27.01%) and 20 Hispanic participants (20, 12.66%). Mean gestational age was 38.06 weeks (SD 1.83, 33-41), with a mean birthweight of 2,923.30 grams (SD 562.60, 1,320-4,338) and mean birthweight percentile of 32.07% (SD 28.61, 2.5-97.5). Most children were not classified as SGA (88, 66.67%, 95% CI .58-.75), but around 33% of children in the sample were SGA (44, 33%, 95% CI .25, .42) which is higher than the general population. Around 14% of the children in this sample had neonatal hypoxia (18, 14.17%, 95% CI .09-.21) and 33% had poor respiration at birth (42, 32.81%, 95% CI .25, .42). Only 11% of the of the children were labeled as having neonatal hypoxia and poor respiration at birth (14, 11.02%) (Figure 1).

A high number of participants in this study presented with at least one Congenital Heart Defect (125, 80.13%, 95% CI .73, .86). Of the cyanotic Congenital Heart Defects considered for this study, Tetralogy of Fallot is the highest prevalence (30, 18.99%, 95% CI .13, .26), followed by Interrupted Aortic Arch (24, 15.19%, 95% CI .10, .22). Both these diseases, ToF and IAA, are also the cyanotic Congenital Heart Defects s who present most with other Congenital Heart Defects, (Figure 2 and 3). As can be seen in Table 2, those that can be considered non-cyanotic were labeled as 'Others', which overall made up most of the Congenital Heart Defects (102, 64.56%, .95% .57, .72). Of those, VSD presented the highest prevalence (62, 39.24%, 95% CI .32, .47), followed by ASD (29, 18.35%, 95% CI .13, .25) and PFO (20, 12.66%, 95% CI .08, .19). As mentioned in the statistical analysis section, the Congenital Heart Defects were categorized based on the levels of hypoxia. Those Level 0 were 19.87% (31, 19.87%, 95% CI .14, .27), Level 1 65% (102, 65.38%, 95% CI .57, .73) and Level 2 15% (23, 14.74%, 95% CI .10, .21).

Mean maternal age at birth was 27.73 years (SD 5.80, 17-44) and maternal race distribution was similar to what was seen in children. Most mothers where White Non-Hispanic (85, 57.82%), followed by Black Non-Hispanic (34, 23.13%) and Hispanic (19, 12.93%). Most of the children in this cohort were delivered vaginally (77, 62.10%, 95% CI .53, .71), while around 38% were C-Sections (47, 37.90%, 95% CI .29, .47). Only 46.80% (22/47) of the children delivered by C-Section had a reason specified in their medical records (Table 3); "Repeat C-Section" being the main specified reasons (8, 36.36%), followed by "Failure to Dilate/Progress" (4, 18.18%).

BW and GA were also categorized. For this sample, no participants were in the categories of extremely preterm and very preterm for GA; and in the extremely low birthweight category for BW. Most of the participants were full term (61, 43.26%, 95% CI .35, .52), followed by early term (48, 34.04%, 95% CI .26, .42) and late preterm (16, 18.44%, 95% CI .12, .26). For birthweight, the category with the highest percentage was normal birthweight (109, 77.30%, 95% CI .70, .84), followed by low birthweight (31, 21.99%, 95% CI .15, .30).

Distribution of gestational age and birthweight

Birthweight presents a normal distribution; while gestational age and birthweight percentiles are skewed. GA is left skewed, while Birthweight Percentile is right skewed; all of these based on the histograms of the variables.

There is no difference in the distribution of gestational age by delivery method; both histograms present the highest proportion at 39.6 weeks gestation. There's a slight increase seen at 37.2 weeks in those having C-Section, but this could just be based on scheduled C-Sections.

The distribution of birthweight doesn't differ based on delivery method either. Both those with vaginal delivery and C-Sections present the highest proportion at 3,000 grams.

Delivery method's association with Neonatal Hypoxia and Poor Respiration

When analyzing the difference in Hypoxia based on CHD by delivery method, there is not a statistically significant difference between the three levels and their proportions by

delivery method. Hypoxia based on CHD is not statistically significantly associated with an increased likelihood of C-Section, either between level 1 and level 0 (POR= 1.80, 95% CI .64, 5.07, p=.32) or level 2 and level 0 (POR= 1.78, 95% CI .49, 6.50, p= .52). Poor respiration at birth and delivery method are not statistically significantly associated (POR=1.37, 95% CI .63, 2.99, p= .55). The odds of C-Section among those who have fetal hypoxia are 3.10 times the odds among those without fetal hypoxia (POR=3.10, 95% CI 1.10, 8.72, p=.03) (Table 4).

CSBS-DP and CDIP

CSBS-DP and CDIP were analyzed individually, for which the database was subdivided based on the questionnaire answered. The mean age of those taking the CSBS-DP was 14.61 months (SD 10.99, 5-108), while the mean age of those answering the CDIP was 43.88 (SD 15.29, 25-105).

CSBS-DP consists of three composites concern and scores. The mean score in the communication composite was 16.03 (SD 5.30, 4-26), the mean score in the expressive speech composite concern was 5.15 (SD 2.80, 0-13), the mean score for the symbolic composite is 6.98 (SD 3.45, 2-16) and the mean total CSBS-DP score was 28.15 (SD 10.15, 7-50). When classified based on concern, the composites with most children categorized as of concern were the Expressive Speech Composite (49 vs 42, 53.85% vs 46.15%), Symbolic Composite (47 vs 44, 51.65% vs 48.35%) and the CSBS Total Concern (48 vs 43, 52.75% vs 47.25%). The Communication Composite was not established as majority concern (35 vs 56, 38.46% vs 61.54%).

For CDIP, there are eight areas of analysis; each of them is further classified as "Developed as expected" and "Developmentally Delayed". Almost all the areas of analysis classify the participants in this study as mostly "Developmentally delayed", these areas are social (55, 60.44%), self-help (63, 69.23%), gross motor (56, 62.22%), fine motor (46, 50.55%), expressive language (58, 63.74%), language composition (55, 60.44%) and numbers (44, 48.35%). Only letters has a majority established as "Developed as expected" (61, 67.03%).

Regression Models

None of the models were analyzed using Gestational Age and Birthweight as categorical variables, because of sparse data in certain classifications. The main unadjusted, adjusted and imputed models are established in Table 5 and Table 6.

For CSBS-DP Total Concern, none of the unadjusted models were statistically significant. CHD Hypoxia Levels and Poor Respiration had increased odds in the unadjusted model, but not statistically significant. Meanwhile, SGA and GA had non-statistically significant decreased odds for the outcome in the unadjusted model. We still analyzed the adjusted odds ratio, to determine the impact of the covariates on the outcome and the exposures influence on it. For CSBS Total concern unadjusted models indicated greater concern for those with level 1 or level 2 hypoxia compared to those without a CHD, but the odds ratios for these unadjusted models included 1. When performing the adjusted model, only CHD Hypoxia Level 1 presented statistically significant increased odds for CSBS Total Concern (aOR: 11.89, 95% CI 1.55, 130.72, p

.03). This particular result had a wide confidence interval, which can be explained by sparse data in that category. After adjusting with the inclusion of imputed variables, CHD Hypoxia Levels and Poor Respiration continued to have non-statistically significant increased odds; while only SGA remained as having a protective effect, although non-statistically significant. When doing imputation to account for missing variables, no association continued to be statistically significant. The change in statistical significance and decrease in odds ratios after imputation (particularly in the association between CSBS Total Concern and CHD Hypoxia Level 1); is because of the quantity of missing variables. Without imputation, the number of observations used was lower compared to the number in imputed models. Delivery method was the covariate with the highest percentage missing that was included in the models and which could cause the decrease in observations used.

In CDIP, only in the association between birthweight percentile and Fine Motor Delay was there a statistically significant association in the unadjusted model. A one unit increase in Birthweight Percentile (%) led to increased odds of 1.50 for Fine Motor Delay (uOR: 1.50, 95% CI 1.001-2.30, p-value .05). None of the other unadjusted regression models presented statistically significant associations, even though there were higher or decreased odds for certain exposures. Birthweight percentile and Poor Respiration seemed to have increased odds for all subtests of the CDIP, although not significant in most cases. In contrast, SGA presented a protective effect in all classifications, but not statistically significant. It is interesting that CHD Hypoxia Level 1 has increased odds in motor classifications (gross motor) and CHD Hypoxia Level 2 has decreased odds in

those classifications; but when analyzing language associated classifications, the odds of both CHD Hypoxia Levels are below 1. None of these associations were statistically significant. When analyzing the adjusted odds ratio, SGA has a statistically significant association with Gross Motor Delay (aOR; .14, 95% CI .02, .73, p .03); and CHD Hypoxia Level 2 had a protective statistically significant association with fine motor delay (aOR: .13, 95% CI .01-.88, p .05). None of the other models were statistically significant. There were not changes in direction from the unadjusted models to the adjusted ones, but there seemed to be a general decrease in the associations in the adjusted models. When performing the analysis through imputation, the values were similar to what was found in the adjusted models, but they all became non-significant.

DISCUSSION

In this study we found preterm birth, low birthweight and SGA prevalence to be higher in patients with 22q11.2DS to what is found in children without 22q11.2DS at the national level. It was also found that neonatal hypoxia was associated with C-Section 3.10 times (95% CI 1.10, 8.72, p=.03), compared to those without neonatal hypoxia. When analyzing score results for CSBS, the subtests with the highest proportions of concern were the expressive speech composite and the symbolic composite. A high proportion of concern was also seen in the Total CSBS score. Meanwhile in the CDIP questionnaire, the sub-classifications found to have high proportion of children classified as "Developmentally Delayed" were social, self-help, gross motor, fine motor, expressive language, language composition and numbers. A statistically significant association was found using adjusted models for CSBS Total Concern and CHD Hypoxia Level 1 suggesting that this hypoxia level is associated with worse scores on the CSBS. Conversely there was an association between Gross Motor Delay and SGA for the CDIP questionnaire, as well as between Fine Motor Delay and CHD Hypoxia Level 2. However, these associations were in the opposite direction as we had hypothesized as they would imply these obstetric adversities were protective on these developmental outcomes. It is relevant to mention, that all adjusted models became non-significant when missing variables were imputed.

SGA prevalence in high-income countries is around 10%-16%, while in low- and middle-income countries it can be up to 27% (27). What was found in our cohort was an SGA

prevalence of 33%, which almost doubles the prevalence in high-income countries and is relatively higher to what is seen in low- and middle-income countries. Our finding supports a previous finding by Van et al. in children with 22q11DS, which reported 39% children with SGA below the 10th percentile, with a statistically significant difference to the reference population(8). These results are of relevant given that children born SGA have increased odds of abnormal motor, cognitive and psychological outcomes compared to children who aren't SGA; which is have an increased prevalence among patients with 22q11.2DS. Given that this specific population has an increased risk of developmental delay and psychiatric diseases, the high prevalence of SGA among 22q11.2DS should be explored as a relevant factor that could be increasing or influencing the risk for developmental delay and other neuropsychological outcomes; more so than only focusing on birthweight and gestational age as isolated factors. However, our data did not support an increased risk of developmental problems associated with SGA in 22q11DS in this sample.

The prevalence of prematurity was 19.86% (28, 19.86%), higher than what's expected in the general population, which is around 9.8% in the US. The majority of those preterm were classified as late preterm (26, 18.44%), which are those born at gestational age 34-36.6 weeks. The same outcome has been seen in other studies with 22q11.2DS patients(8). Preterm birth has also been established as a risk factor for developmental delay and negative neuropsychologic outcomes, because of the relevance of the last 6 weeks of gestation in brain development. Interestingly, most preterm births in this cohort were late preterm; there have not been many studies focusing on the impact of late preterm births and developmental delay, as well as the difference between preterm stages

in the increase of risk for this outcome. The increased prevalence seen in this population could be explained by congenital diseases associated to this syndrome (i.e. congenital heart defects) and their effect on birth outcomes or fetal development, possibly promoting preterm births. An in-depth analysis of preterm birth prevalence and the effect of Congenital Heart Defects presence on it, might be beneficial for this population. Meanwhile, the same was seen in birthweight. Most children in this cohort were classified as low birthweight (31, 21.99%), which are those with birthweights from 1,500 to 2,499. In the US, the prevalence for low birthweight is 8.28%; therefore, the prevalence in children with 22q11.2DS is almost three times higher than the one seen in the general population. The increased prevalence of both low birthweight and preterm birth can explain the increased prevalence of SGA, or the other way around. Knowing the increased prevalence of these three risk factors in the 22q11.2DS population and the possible increased risk of neurodevelopmental delay associated to them can help health providers identify patients with the highest risks for these outcomes and possibly lead to early interventions.

The frequency of congenital heart defects in this sample matches what is found in the literature for the 22q11.2DS population(3, 28). In our sample, 125 children had at least one congenital heart defect (80.13%); with Tetralogy of Fallot being the most common (29, 18.35%), followed by Interrupted Aortic Arch (24, 15.19%).

Percent of all deliveries by C-Section in this study was 37.90% (47, 37.90%), 8% higher than the general population. Even though the difference is not high, an explanation for it

could be the increased prevalence of congenital diseases in this population and the possible need for planned or emergency C-Sections because of its effects. The main reason for C-Section was “Repeat C-Section” (8, 36.36%), followed by “Failure to dilate/progress” (4, 18.18%). Witt et al. found that prior C-section was the main reason for medically indicated and non-medically indicated C-Sections(29), similar to the results in this study. We did not find a difference in Gestational Age, Birthweight, CHD Hypoxia Levels and poor respiration distribution by delivery method; even though they might be possible indications for C-Section. There is a slight peak at 37.2 weeks gestation in C-Sections for this population. Considering patients with 22q11.2DS have congenital defects that can be worrisome for the gynecologist and pediatrician, physicians could suggest planned C-Sections just when the baby is at term. This could explain the slight increase at 37 weeks gestation in this population. Neonatal Hypoxia did increase the odds for C-Section, possibly because subjective indications like non-reassuring fetal status may have contributed the most to the increase in cesarean rate(30).

The developmental delay deficits distribution found in this study showed patients with 22q11.2DS having possible developmental delay or cause of concern in almost all areas of analysis, except for the communication and letters segments. The main deficits found in other studies were most pronounced in face memory and social cognition, followed by language(7). Variability in the identification of the deficits can be caused by using different methods and questionnaires, impeding the comparison between results of studies. This could be a reason to develop or improve current developmental delay

questionnaires, to promote comparison between studies and better determine specific areas of need in this population.

In our study, SGA was negatively associated to Gross Motor Delay. Contrarily, CHD Hypoxia levels 1 and 2 were positively associated to CSBS Total Concern and Fine Motor Delay, respectively. Information about SGA's impact on developmental delay is varied. Slykerman et al. found that SGA infants did not have an increased risk of developmental delay compared to adequate gestational age babies, but this lack of difference could be explained by questionnaire precision and identification differences seen in that age range(22). On the contrary, several studies found SGA is associated with lower scores on neurodevelopmental outcomes compared to adequate gestational age babies; with scored .32SD below those for normal controls(31). Interestingly, in this study, SGA seems to have a protective effect on Gross Motor delay; which is also seen in other CSBS-DP and CDIP subtests, though not statistically significant. This apparent protective effect was not anticipated. An explanation for this negative association could be increased neonatal care and awareness of possible developmental delay in this population. Parents of children with SGA and 22q11.2DS may have become aware that their child has this genetic disorder early on because of the clinical concern raised by SGA. Accordingly, both the parents in clinicians might have increased awareness that that their child had an increased risk of developmental delay, which in turn can lead to early intervention and identification of the child's needs regarding development. This population could be showing the positive effects of early identification of Developmental

Delay, where doctors and parents alike focus more on those with risk factors and where the external environment can have an impact.

Meanwhile, increased risk of Total Developmental Concern and Fine Motor Delay in those with CHD associated Hypoxia could be the result of hypoxia associated brain development alterations. Cyanotic CHD leads to neonatal hypoxia, which can affect brain development; while acyanotic CHD can lead to a slight, chronic hypoxic effect altering late brain development The first days and weeks after birth are relevant for brain development, given the changes in circulation, modulation and hemostasis that occur during that time in the baby's body. A study in 22q11.2DS patients found reduced cortical volumes in those patients with congenital heart defects(13). This suggest that alteration in hemodynamics can affect brain development in patients with 22q11.2DS and therefore lead to developmental delay. Outside of just showing the impact of Congenital Heart Defects in developmental delay by itself, our study presents how multiple levels of hypoxia associated to CHD could have an impact on brain development. Not only those with Cyanotic CHD have an increased risk, but also those that have more chronic and manageable CHD. The lack of association of CHD Hypoxia to the rest of the subtests and classifications can be a result of proper early management in CHD. The effects of hypoxia might not be seen in these population of 22q11.2DS, because they are treated in time and correctly managed to avoid consequences from their congenital disease.

Strengths

This is the largest 22q11.2DS database in the United States with information from patients across the nation and with the capacity of obtaining primary data from participants. All questionnaire information was gathered by specialists' as part of the 22q Clinic, decreasing bias and errors in collection. This is one of the largest studies regarding developmental delay outcomes in patients with 22q11.2DS. It doesn't just focus on Developmental Delay diagnosis but has information for specific areas to evaluate the possibility of Developmental Delay before diagnosis. Access to medical records for most of the 22q11.2DS database, which allowed us to gather clinical record primary information. This is one of the most extensive studies of possible factors influencing Developmental Delay, analyzing models for various possible predictors. It also analyzes the impact of decreasing gestational age in Developmental Delay outcomes, considering biological factors that could have an impact. It is one of the few studies focusing on SGA and Developmental delay in the 22q11.2DS population. For most of the predictors we analyzed, there are not studies focused on this population. It also is an extensive presentation of the demographic characteristics of the 22q11.2DS population, updating the prevalence of SGA, gestational age, birthweight, CHD and delivery methods.

Limitations

There was missing data for the covariates which introduced some bias into the ORs calculated. This was dealt with by doing imputation on all the models, but the result was a loss in significance of all the models. The loss of significance, as mentioned above, could be a result of missing data and the quantity of observations used in non-imputed

models. This loss of significance and change in odds ratios between non-imputed and imputed models is common the more missing data is found. There was loss of information variables because of incomplete medical records. Some other covariates should have been considered for the analysis, such as smoking status, parity, etc.; but could not be included because the information wasn't available in the medical records for all participants in our sample. Most of the patients are White Non-Hispanic, which could limit the generalizability of the study. Both questionnaires are based on parental perception, which could introduce bias in the results. Also, the questionnaires don't have the same specificity in all the fields that are being considered.

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TABLES

Table 1. Demographics for participants with 22q11.2DS answering CSBS-DP and CDIP questionnaires, gathered from Medical Records

Variable	Mean (SD) - continuous or N (%) - categorical
Gestational Age (weeks)	38.06 (1.83)
Birthweight (grams)	2,923.30 (562.60)
Birthweight Percentile (%)	32.07 (28.61)
Child's Age at CSBS-DP (months)	14.61 (10.99)
Child's Age at CDIP (months)	43.88 (15.29)
Maternal Age at Child's Birth (years)	27.73 (5.80)
Sex	
Male	83 (52.53)
Female	75 (47.47)
Race	
White Non-Hispanic	89 (64.96)
Black Non-Hispanic	37 (27.01)
Other	11 (8.03)
Ethnicity	
Hispanic	20 (12.66)
Non-Hispanic	138 (87.34)
Delivery Method	
Vaginal	77 (62.10)
C-Section	47 (37.90)
Neonatal Hypoxia	
Yes	18 (14.17)
No	109 (85.83)
Poor Respiration	
Yes	42 (32.81)

No	86 (67.10)
Congenital Heart Defect Presence	
Yes	125 (80.13)
No	31 (19.87)
Congenital Heart Defect	
Tetralogy of Fallot	30 (18.99)
Truncus Arteriosus	13 (8.23)
Transportation of the Great Arteries	1 (.63)
Interrupted Aortic Arch	24 (15.19)
Pulmonary Atresia	16 (10.13)
Others	102 (64.56)

Table 2. Distribution of Congenital Heart Defects classified as "Other" in Congenital Heart Defect Question, obtained from Medical Records of patients with 22q11.2DS

Congenital Heart Defects (n=102)	**N (%)**
VSD	62 (39.24)
ASD	29 (18.35)
Right aortic arch	17 (10.76)
Vascular ring	11 (6.96)
Aortic stenosis	5 (3.16)
PDA	9 (5.70)
Pulmonary stenosis	14 (8.86)
Bicuspid aortic arch	10 (6.33)
PFO	20 (12.66)
Aortic root dilation	6 (3.80)
Aberrant right subclavian artery	3 (1.90)

Table 3. Reasons for C-Section Delivery established in Medical Records of patients with 22q11.2DS

Reasons for getting a C-Section (n=22)	N (%)
Failure to dilate / progress	4 (18.18)
Presentation	2 (9.09)
Repeat C-Section	8 (36.36)
Fetal distress	3 (13.63)
Preeclampsia	2 (9.09)
Meconium	2 (9.09)
Genital herpes	1 (4.54)

Table 4. Neonatal Hypoxia Comparison by Delivery Method, patients with 22q11.2DS, Chi-Square Analysis

Neonatal Hypoxia (N=116)	Vaginal Delivery (%)	C-Section (%)	p-value
Fetal Hypoxia	7 (6.03)	11 (9.48)	**.03**
No Fetal Hypoxia	65 (56.03)	33 (28.45)	

Table 5. Unadjusted, Adjusted and Imputed Odds Ratios from regression models associating CSBS-DP total concern and gestational age, birthweight, birthweight percentile, SGA, CHD Hypoxia Levels, Neonatal Hypoxia and Poor Respiration

Exposures	Unadjusted Odds Ratio (95% CI), p-value	Adjusted Odds Ratio (95% CI). P-value	Imputed adjusted Odds Ratio (95% CI), p-value
CSBS TOTAL CONCERN			
Gestational Age	.87 (.66, 1.11), .26	1.00 (.72, 1.39), .99	.99 (.93, 1.05), .64

Birthweight	1.00 (.99, 1.001), .69	1.001 (1.00, 1.002), .24	1.00 (.99, 1.00), .89
Birthweight Percentile	1.02 (.71, 1.48), .90	1.37 (.80, 2.43), .26	1.02 (.93, 1.11), .69
Small for Gestational Age	.86 (.33, 2.21), .75	.39 (.08, 1.62), .21	.94 (.76, 1.16), .55
Congenital Heart Defect Hypoxia			
Level 0 (Ref.)	1.00	1.00	1.00
Level 1	3.40 (.86, 14.69), .09	**11.89 (1.55, 130.72), .03**	1.16 (.83, 1.62), .4
Level 2	1.49 (.44, 5.47), .54	2.36 (.43, 15.57), .34	.98 (.72, 1.33), .89
Neonatal Hypoxia	1.09 (.30, 4.14), .89	.56 (.08, 3.68), .55	.98 (.73, 1.30), .88
Poor Respiration	1.68 (.63, 4.69), .31	1.14 (.33, 4.01), .83	1.07 (.84, 1.35), .59

Table 6. Unadjusted, Adjusted and Imputed Odds Ratios from regression models associating CDIP Gross Motor, Fine Motor, Expressive Language and Language Comprehension delay; and gestational age, birthweight, birthweight percentile, SGA, CHD Hypoxia Levels, Neonatal Hypoxia and Poor Respiration outcomes

Exposures	**Unadjusted Odds Ratio (95% CI), p-value**	**Adjusted Odds Ratio (95% CI), p-value**	**Imputed adjusted Odds Ratio (95% CI), p-value**
GROSS MOTOR DELAY			
Gestational Age	1.14 (.89, 1.47), .31	1.13 (.82, 1.56), .46	1.02 (.97, 1.07), .39
Birthweight	1.00 (.99, 1.001), .47	1.001 (.99, 1.002), .30	1.00 (.99, 1.00), .34
Birthweight percentile	1.35 (.88, 2.09), .16	1.63 (.93, 2.97), .09	1.00 (.97, 1.05), .74
Small for Gestational Age	.38 (.13, 1.12), .08	**.14 (.02, .73), .03**	.98 (.89, 1.08), .70
Congenital Heart Defect Hypoxia			
Level 0 (Ref.)	1.00	1.00	1.00

Level 1	1.53 (.41, 5.80), .52	1.10 (.16, 6.94), .92	1.05 (.41, 1.68), .60
Level 2	.71 (.21, 2.20), .57	.58 (.09, 2.99), .53	.83 (.72, 2.08), .46
Hypoxia	1.24 (.32, 6.11), .77	.93 (.14, 7.96), .94	.99 (.81, 1.21), .91
Respiration	2.28 (.81, 7.14), .13	2.16 (.64, 8.14), .23	1.10 (.91, 1.32), .32
FINE MOTOR DELAY			
Gestational Age	1.05 (.83, 1.33), .68	1.03 (.73, 1.45), .87	1.02 (.97, 1.06), .44
Birthweight	1.001 (1.00, 1.002), .09	1.00 (.99, 1.001), .68	1.00 (.99, 1.00), .39
Birthweight percentile	**1.50 (1.001, 2.30), .05**	1.52 (.84, 2.91), .18	.99 (.94, 1.04), .66
Small for Gestational Age	.43 (.15, 1.21), .11	.23 (.03, 1.35), .12	1.04 (.95, 1.15), .40
Congenital Heart Defect Hypoxia			
Level 0 (Ref.)	1.00	1.00	1.00
Level 1	1.30 (.41, 4.09), .66	.26 (.03, 1.82), .19	1.39 (.65, 1.89), .40
Level 2	.97 (.33, 2.83), .96	**.13 (.01, .88), .05**	.97 (.50, 2.72), .94
Hypoxia	.77 (.21, 2.92), .69	.17 (.02, 1.25), .10	.96 (.75, 1.23), .73
Respiration	1.10 (.43, 2.90), .84	.94 (.26, 3.56), .92	1.00 (.82, 1.22), .99
EXPRESSIVE LANGUAGE DELAY			
Gestational Age	.93 (.70, 1.20), .58	.85 (.57, 1.20), .37	1.00 (.96, 1.04), .99
Birthweight	1.00 (.99, 1.001), .43	1.00 (.99, 1.001), .72	1.00 (.99, 1.00), .81
Birthweight percentile	1.49 (.97, 2.32), .07	1.64 (.93, 3.11), .10	.99 (.95, 1.04), .89
Small for Gestational Age	.37 (.12, 1.09), .07	.23 (.04, 1.17), .08	1.02 (.93, 1.11), .75
Congenital Heart Defect Hypoxia			
Level 0 (Ref.)	1.00	1.00	1.00
Level 1	.39 (.08, 1.53), .20	.12 (.006, .97), .08	.84 (.40, 1.76), .64
Level 2	.42 (.09, 1.58), .23	.19 (.009, 1.44), .16	.76 (.40, 1.45), .41
Hypoxia	.89 (.23, 4.42), .87	.53 (.08, 3.49), .50	.93 (.76, 1.13), .45

Respiration	2.73 (.86, 10.50), .11	2.30 (.62, 10.16), .23	1.10 (.88, 1.37), .38
LANGUAGE COMPREHENSION DELAY			
Gestational Age	1.18 (.92, 1.51), .19	1.28 (.90, 1.89), .18	1.03 (.98, 1.08), .29
Birthweight	1.00 (1.00, 1.001), .36	1.001 (1.00, 1.002), .21	1.00 (.99, 1.00), .33
Birthweight percentile	1.27 (.83, 1.95), .26	1.49 (.77, 3.18), .25	.99 (.96, 1.04), .98
Small for Gestational Age	.41 (.14, 1.20), .10	.21 (.02, 1.49), .14	.99 (.89, 1.10), .79
Congenital Heart Defect Hypoxia			
Level 0 (Ref.)	1.00	1.00	1.00
Level 1	.80 (.23, 2.66), .72	.20 (.02, 1.43), .13	1.33 (.67, 2.65), .42
Level 2	.80 (.24, 2.49), .71	.15 (.01, 1.05), .08	.98 (.54, 1.79), .96
Hypoxia	2.36 (.55, 16.35), .30	1.04 (.13, 10.06), .97	1.04 (.85, 1.28), .67
Respiration	1.80 (.66, 5.33), .27	1.32 (.35, 5.20), .68	1.07 (.89, 1.29), .44

FIGURES

Figure 1. Venn Diagram for Neonatal Hypoxia and Poor Respiration information from Medical Records, of patients with 22q11.2DS

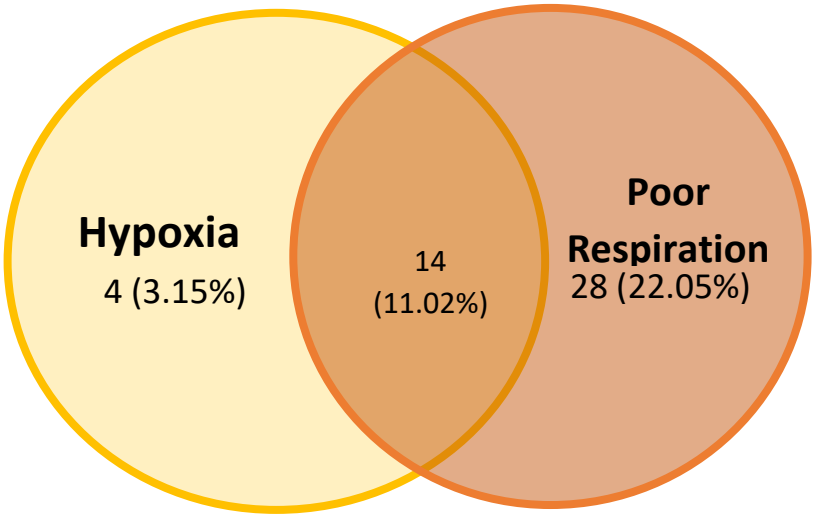

Figure 2. Venn Diagram for Tetralogy of Fallot with other Congenital Heart Defects, from Medical Records of Patients with 22q11.2DS

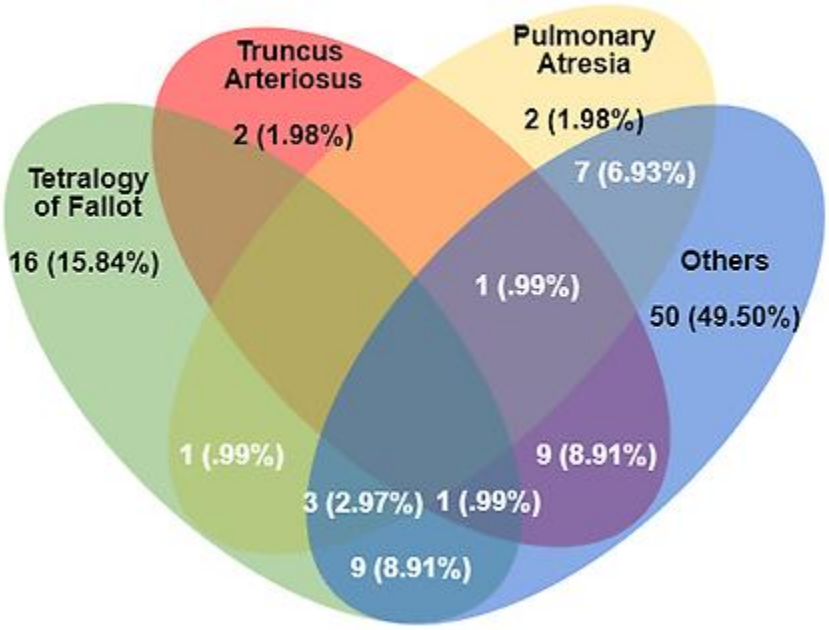

Figure 3. Venn Diagram for Interrupted Aortic Arch with other Congenital Heart Defects, from Medical Records of patients with 22q11.2DS