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Neonatal hypocalcemia, neonatal seizures, and intellectual disability in 22q11.2 deletion syndrome

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Purpose: Hypocalcemia is a common endocrinological condition in 22q11.2 deletion syndrome. Neonatal hypocalcemia may affect neurodevelopment. We hypothesized that neonatal hypocalcemia would be associated with rare, more severe forms of intellectual disability in 22q11.2 deletion syndrome.

Methods: We used a logistic regression model to investigate potential predictors of intellectual disability severity, including neonatal hypocalcemia, neonatal seizures, and complex congenital heart disease, e.g., interrupted aortic arch, in 149 adults with 22q11.2 deletion syndrome. Ten subjects had moderate-to-severe intellectual disability.

Results: The model was highly significant ($P < 0.0001$), showing neonatal seizures ($P = 0.0018$) and neonatal hypocalcemia ($P = 0.047$) to be significant predictors of a more severe level of intellectual disability. Neonatal seizures were significantly associated with neonatal hypocalcemia in the entire sample ($P < 0.0001$), regardless of intellectual level. There was no evidence for the association of moderate-to-severe intellectual disability with other factors such as major structural brain malformations in this sample.

Conclusion: The results suggest that neonatal seizures may increase the risk for more severe intellectual deficits in 22q11.2 deletion syndrome, likely mediated by neonatal hypocalcemia. Neonatal hypocalcemia often remains unrecognized until the postseizure period, when damage to neurons may already have occurred. These findings support the importance of early recognition and treatment of neonatal hypocalcemia and potentially neonatal screening for 22q11.2 deletions.

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Key Words: 22q11 deletion syndrome; cognitive; endocrine; neonatal; outcome

INTRODUCTION

22q11.2 deletion syndrome (22q11.2DS) is a common although underrecognized genetic condition associated with congenital and later-onset features including congenital cardiac and palatal defects, and neuropsychiatric conditions such as schizophrenia and, more rarely, epilepsy.[1–3] Learning difficulties are common although only ~30–40% of individuals have mild intellectual disability (ID);[4] moderate-to-severe ID is present in <10%.[5] Endocrinological disorders are prevalent, and hypocalcemia, in particular, is a common lifetime manifestation of 22q11.2DS,[1,3] usually associated with relative or absolute hypoparathyroidism.[6] Although there are several studies and case reports about the prevalence and/or clinical presentation of hypocalcemia in children,[2,6] none to date has investigated the long-term impact of neonatal hypocalcemia on intellect in patients with 22q11.2DS.

Calcium ions are important second messengers that translate information carried by extracellular molecules to various intracellular target molecules in all cells.[7] In neurons, calcium ions regulate activity-dependent signaling and play an important role in controlling neuronal excitability. Calcium thus plays an essential role in both neuronal development and function, as well as long-term potentiation.[7] Given the pivotal role of calcium ions in neurodevelopment, we hypothesized that neonatal hypocalcemia would be associated with more severe levels of ID in 22q11.2DS.

MATERIALS AND METHODS

Subjects

In this study, 149 individuals (73 males and 76 females) from our cohort of adults with 22q11.2DS (older than 17 years) with available data were enrolled. Written informed consent was obtained, and the study was approved by local research ethics boards. The mean age, at the time of this retrospective nested case–control study, was 34.4 (SD = 11.7) years. As previously described,[8] most subjects were ascertained through adult congenital cardiac, psychiatric, and genetic services using active screening and/or clinical referrals. Deletion of 22q11.2 was confirmed in all subjects by clinical genetic testing using standard methods.[8] On the basis

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of molecular and/or clinical data,[8] 6 subjects had 22q11.2 deletions that were definitely or probably inherited from a parent; the remaining 143 had known or probable *de novo* mutations.

Evaluations

Data collection and detailed phenotyping are described elsewhere.[1,4,8,9] Briefly, we obtained lifetime medical, psychiatric, and developmental, including antenatal, birth, and neonatal, history from direct interview of parents and review of lifetime medical records. Record evaluation included birth records where available ($n = 69$); the information was largely congruent with pediatric records from a major children's hospital and history from parents.[10] The neonatal period was defined as events occurring within 2 weeks of birth.

In accordance of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), a diagnosis of borderline, mild, moderate, or severe mental retardation, here termed ID, was determined from the level of function and IQ testing results.[4] Diagnoses of schizophrenia or schizoaffective disorder, according to the DSM-IV, were collectively termed "schizophrenia".[4] We characterized major congenital heart disease (CHD) by structural complexity[8] and considered only serious CHD, e.g., tetralogy of Fallot or interrupted aortic arch (IAA), all of which in this sample were IAA type B (IAA-B).

The focus of this study was on the clinical features predicting intellectual level, classified as average-to-borderline ($n = 79$), mild ID ($n = 60$), and moderate-to-severe ID ($n = 10$). Features were examined if they had a previously known association with ID or neonatal hypocalcemia. Documented variables considered to be related to neonatal hypocalcemia were neonatal seizures and hypoparathyroidism ($n = 2$). Serious CHDs were studied collectively, with the exception of IAA-B, due to a previously reported association of ID with 22q11.2DS in IAA.[11] We also studied neonatal cyanosis unexplained by either neonatal hypocalcemia or serious CHD. We recorded family history of ID ($n = 4$) and epilepsy ($n = 2$) in first-degree relatives of subjects, excluding relatives with proven or probable 22q11.2DS.[8] We also recorded central nervous system features, defined as structural abnormalities of the brain detected using magnetic resonance imaging or computed tomography, including atrophy and calcification, or a history of epilepsy or schizophrenia.

Statistical analyses

A logistic regression model was used to identify clinical features as predictors of intellectual level in 22q11.2DS. Only covariates that were present in ≥5 subjects were included. In addition to age and sex, these were neonatal hypocalcemia, neonatal seizures, IAA-B, other cyanotic CHDs, and unexplained neonatal cyanosis. Odds ratio and 95% confidence intervals were reported. Post hoc Fisher's exact test of significant covariates was performed. The Sobel test[12] was used to show whether neonatal seizures mediated the association between neonatal hypocalcemia and ID. The coefficient change of neonatal hypocalcemia after removing neonatal seizures from the regression model was also reported.

Among the 15 subjects with neonatal seizures or neonatal hypocalcemia, we performed χ^2 or Fisher's exact tests to compare central nervous system features of those with moderate-to-severe ID with those with borderline-to-mild ID. All statistical analyses were two tailed and performed using SAS 9.2 (SAS Institute, Cary, NC). P values < 0.05 were considered statistically significant.

RESULTS

The logistic regression model used to predict intellectual level (average-to-borderline, mild ID, and moderate-to-severe ID) in 22q11.2DS was highly significant (likelihood ratio test: $\chi^2 = 41.44$; $df = 7$; $P < 0.0001$). **Table 1** summarizes the prevalence of each predictor in each ID group. The model showed that neonatal seizures and neonatal hypocalcemia were significant independent predictors of intellectual level. No significant interaction was found between all variables tested. Post hoc analysis showed that neonatal seizures and neonatal hypocalcemia were significantly associated ($P < 0.0001$, Fisher's exact test). The degree of mediation of neonatal seizures on neonatal hypocalcemia in reference to ID level was significant ($P = 0.041$). The coefficient of neonatal hypocalcemia changed from 1.53 ± 0.35 to 0.79 ± 0.49 when controlling for the effect of neonatal seizures on ID level.

Table 2 shows details of the 15 individuals with neonatal hypocalcemia and/or neonatal seizures and of 3 patients with moderate-to-severe ID but neither neonatal hypocalcemia nor neonatal seizures. Post hoc analyses focused on other potential factors relevant to ID in the first 15 subjects. None had neonatal central nervous system infection, congenital hypothyroidism, infantile-onset epilepsy, or neonatal hypoxia requiring resuscitation. All were singleton births and only one was premature. One patient had a sibling with ID but no 22q11.2DS. Seven had both neonatal hypocalcemia and neonatal seizures; neonatal hypocalcemia was identified following neonatal seizures in five subjects. There was no documentation of other factors related to neonatal seizures, with the exception of one subject with concurrent hypoglycemia. Comparing the individuals with moderate-to-severe ID ($n = 8$) with those with borderline-to-mild ID ($n = 7$), no significant associations were found with abnormal magnetic resonance imaging/computed tomography brain scans ($P = 0.10$) or a lifetime diagnosis of epilepsy ($P = 0.28$) or schizophrenia ($P = 0.13$).

Although IAA-B was not significant in the regression model, the odds ratio (3.80) prompted further examination. Of the seven subjects with IAA-B in the overall sample, corrective surgery was performed within 8 days of birth for six subjects and at the age of 3 months for one subject. Of the three subjects with IAA-B and moderate-to-severe ID (cases 12, 14, and 15, **Table 2**), all had neonatal seizures for which the timing had suggested an association with neonatal cardiac surgery and, when tested, with hypocalcemia. Scrutiny of records for the remaining four with better neurocognitive outcomes revealed no evidence of either perioperative seizures or neonatal hypocalcemia.

Table 1 Intellectual outcome and predictor neonatal features in 149 adults with 22q11.2 deletion syndrome

		Distribution of features by intellectual level									
	Subjects with features	Average-to-borderline		Mild ID		Moderate-to-severe ID		Logistic regression analysis			
		n = 79		*n* = 60		*n* = 10					
Clinical predictor features	***n***	***n***	**%**	***n***	**%**	***n***	**%**	**OR**	**95% Wald confidence limits**		***P***
Neonatal hypocalcemia	13	2	2.53	5	8.33	6	60.00	4.93	1.02	23.69	**0.047**
Neonatal seizures[a]	9	0	0.00	3	5.00	6	60.00	27.97	3.46	226.11	**0.0018**
Interrupted aortic arch type B	7	1	1.27	3	5.00	3	33.33	3.80	0.53	27.23	0.18
Other cyanotic CHD[b]	59	34	43.04	21	35.00	4	40.00	0.53	0.25	1.11	0.093
Unexplained neonatal cyanosis[c]	8	5	6.33	2	3.33	1	10.00	0.22	0.22	4.12	0.96
Female sex	76	42	53.16	29	48.33	5	50.00	0.60	0.30	1.19	0.14
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**OR**	**95% Wald confidence limits**		***P***
Age (years)		35.03	11.33	33.95	12.48	32.03	10.86	1.02	0.99	1.05	0.32

CHD, congenital heart disease; ID, intellectual disability; OR, odds ratio.

Bold values indicate statistical significance ($P < 0.05$).

[a]Seven of these nine subjects overlap with subjects with neonatal hypocalcemia. [b]Patients with complex CHD who did not have interrupted aortic arch type B (e.g., with tetralogy of Fallot, truncus arteriosus, or transposition of great vessels). [c]Infants who were cyanotic but without documented neonatal hypocalcemia or complex CHD.

DISCUSSION

Severe levels of ID are uncommon in 22q11.2DS.[4,13] The results of this study showed that neonatal hypocalcemia and neonatal seizures were significantly associated with more severe ID, and the effect of neonatal hypocalcemia was likely mediated by neonatal seizures. The results further suggest that IAA-B may have an indirect association with more severe ID. Of note, we found no evidence that other factors such as neonatal central nervous system infections, inherited 22q.11.2 deletions, or family history of ID or epilepsy were major contributing factors in the moderate-to-severe ID outcome in this sample.[14,15]

Several studies have shown that neonatal seizures are associated with long-term neurodevelopmental delay in the general population but that metabolic disturbances are now rarely part of this association (2–3%).[14–16] Poorer neurodevelopmental outcome has been associated with greater number of seizures per day but usually in the presence of severe neuroanatomical findings.[17] By contrast, in our study, neonatal seizures were usually single events and independent of underlying major structural brain pathology.

Potential mechanism

How could "neonatal hypocalcemia," a 22q11.2DS feature usually regarded as self-resolving and transient,[3] be associated with more severe ID? We propose a mechanism that may explain the observations. In the general population, studies have shown that decreasing the availability of calcium ions blocks the induction of long-term potentiation that underlies learning and memory.[18] It may be that patients with more severe neonatal hypocalcemia had suppression of long-term potentiation and thus an increased likelihood of severe ID. Furthermore, those who developed neonatal seizures might also as a result have impaired cerebral energy metabolism.[19]

In 22q11.2DS, proneness to seizures, perhaps related to aberrant neurodevelopment, appears to be relatively prevalent.[1] Patients with more severe neonatal hypocalcemia and/or those exposed to events that further lower the seizure threshold, such as surgery, in the neonatal period may be at increased risk of poor intellectual outcomes. In our sample, the presence of neonatal hypocalcemia was often discovered only after a neonatal seizure, and thus neuronal damage may already have occurred. We recognize that not every individual with moderate-to-severe ID had documented neonatal seizures and/or hypocalcemia. In addition to issues related to inadequate information, one could speculate that some individuals may have functional brain changes that may not lead to a seizure and would not be detectable on structural brain imaging.

Data from the small subset of patients with IAA-B provide further support for this proposed mechanism. Our results indicate that an observed association of IAA-B and ID in 22q11.2DS[11] may be mediated by neonatal seizures and/or (undetected) hypocalcemia. Both the aortic arch and parathyroid glands originate developmentally from the third and fourth pharyngeal pouches.[20] There may be an increased risk for hypocalcemia in IAA-B due to coincident maldevelopment of the parathyroid glands. The resulting risk for hypocalcemic neonatal seizures could then be exacerbated by the physiological stress of corrective neonatal surgery. Hypocalcemia would therefore be a potentially targetable factor with respect to ameliorating risk of more severe ID outcomes.

Advantages and limitations

To our knowledge, this is the first report of the association between long-term intellectual outcome and neonatal hypocalcemia and/or seizures in 22q11.2DS. As more patients live to adulthood,[9] understanding factors affecting the intellectual

Table 2 Clinical details by intellectual level of 15 patients with 22q11.2 deletion syndrome and documented neonatal hypocalcemia (n = 13) and/or neonatal seizures (n = 9) and of three patients with moderate-to-severe ID but with neither neonatal hypocalcemia nor neonatal seizure history

Intellect	Case	Gestational weeks	Neonatal: Hypocalcemia	Neonatal: Seizures	Neonatal: Cyanosis	Serious CHD (age at intracardiac repair)	Epilepsy (onset in years)[a]	Schizophrenia	CNS anatomy (investigation, age)	Duration of calcium treatment in infancy[b]
Patients with neonatal hypocalcemia or neonatal seizures (n = 15)										
Borderline	1[c]	38	Day 5	No	Yes	No	Yes (11)	Yes	• Cystic lesions in gray and white matter (MRI, 11 years) • No change in the size or extent of cystic lesions (MRI, 14 years)	Treated and monitored for 2 months
	2	36	Day 10	No	No	No	No	Yes	• Small lacunar infarct (CT, 24 years) • Focal area of tissue loss in the left caudate head (MRI, 27 years) • Lentiform nucleus calcification (MRI, 37 years)	Unknown duration
Mild	3[d]	38	Day 6	Day 6	Yes	TOF (5 years)	No	Yes	• Calcifications (CT, 20 years)	5 years and restarted at 14 years of age
	4	40	Day 10	Days 8 and 9	No	No	No	Yes	• Normal (CT, 52 years)	Unknown duration
	5	40	Day 1	No	No	TOF (1 year)	No	Yes	• Normal (MRI, 23 years)	Few days
	6	38	Day 2	No	Yes	TOF (5 years)	No	No	• Normal (MRI, 17 years)	Few days
	7	41	Day UK	No	Yes	Truncus arteriosus type I (3 weeks)	No	No	• White matter unidentified bright spots (CT, 1 year)	Unknown duration
	8	40	No	Day 14	No	No	No	Yes	• Mild cerebral atrophy consistent with age (CT, 56 years)	—
Moderate/ severe	9	40	Day 2	Day UK[e]	Yes	TOF (3 years 9 months)	No	No	• Never performed	Few weeks, then restarted at 3 years 9 months of age
	10[d]	40	Day 4	Day 4	Yes	TOF (9 years)	Yes (9)	No	• Increased density in temporal and parietal lobes suggesting mild degree of anoxia (CT, 2 months)	1 year
	11	39	Day 4	No	Yes	No	Yes (30)	Yes	• Temporal lobe atrophy and calcification (CT, 18 years) • Normal (MRI, 38 years)	No evidence of any treatment
	12	40	Day 8	Day 8[f]	No (pale)	IAA-B, VSD (day 7)	No	No	• Normal (MRI, 13 years)	2 months
	13	39	Day 14	Day UK[e]	No	VSD, PVS, BHPA (inoperable)	Yes (28)	No	• Ill-defined peripheral increase of radionucleotide in all views, suggesting anoxia during neonatal seizure (radionucleotide scan, 2 weeks) • Normal (CT, 5 years)	2 years, but serum calcium level was poorly controlled
	14	40	Day UK	Day UK	No	IAA-B, VSD, ASD, PAS, BAV (day 4)	No	No	• Normal (MRI, 16 years)	No evidence of any treatment
	15	38	No	Day 10[e,f,g]	Yes	IAA-B, VSD, BAV (day 8)	No	Yes	• Area of asymmetry in the left parietal area consistent with possible atrophy (CT, 1 month) • Left hemisphere smaller than right; thickening of the gray matter in left parietal region (MRI, 16 years) • Chronic periventricular leukomalacia (CT, 26 years)	—
Patients with moderate-severe ID but without neonatal hypocalcemia or neonatal seizures (n = 3)										
	16	33	No	No	Yes	No	Yes (22)	Yes	• Never performed	—
	17[h]	42	No	No	No	No	No	Yes	• Normal (MRI, 27 years)	—
	18[h]	40	No	No	No	TOF (2 years)	No	No	• Never performed	—

ASD, atrial septal defect; BAV, bicuspid aortic valve; BHPA, bilateral hypoplastic pulmonary artery; CHD, congenital heart disease; CNS, central nervous system; CT, computed tomography; IAA-B, interrupted aortic arch type B; ID, intellectual disability; MRI, magnetic resonance imaging; PAS, pulmonary artery stenosis; PVS, pulmonary valve stenosis; TOF, tetralogy of Fallot; UK, specific timing unknown; VSD, ventricular septal defect.

[a]All five patients with epilepsy were treated with standard anticonvulsants. [b]Treatment for hypocalcemia: i.v. calcium gluconate, calcitriol, or calcium/vitamin D. [c]Early death at 18 years of age. [d]Patient also had documented neonatal hypoparathyroidism. [e]Neonatal seizures treated with phenobarbital. [f]Postoperative seizures. [g]Laboratory data showed no calcium test done. [h]No available birth or neonatal pediatric records to confirm maternal history.

outcome is of particular importance. Studying adults provided the opportunity to study the long-term intellectual outcome. Furthermore, our ascertainment strategies allowed us to avoid oversampling transmitting parents, who are likely to have milder expression, or offspring of transmitting parents who may have somewhat worse intellectual outcomes.[5]

The main limitations of the current study are the retrospective design and unavoidable restrictions on available data. Only a prospective study design, with neonatal screening for 22q11.2 deletions in all live births followed by longitudinal follow-up, could ensure documentation of all predictor and outcome variables. Younger subjects may have had more data available; however, age was a nonsignificant factor in the regression model. Nevertheless, we recognize that missing data may lead to information bias. The study design, intellectual outcomes, and the 22q11.2 deletion status would have been unknown at the time of documentation of neonatal events;, thus the available data were unlikely to have been systematically biased. However, there could still be misclassification bias. Other unmeasured factors, such as educational supports and family situations, may play a role in intellect. We note, however, that expression of moderate-to-severe ID is largely determined by genetic factors.[5] Consequently, we focused on selected physiological influences on ID.

Clinical implications

Our results suggest that neonatal hypocalcemia and neonatal seizures may be associated with moderate-to-severe ID in 22q11.2DS. Although prospective studies are needed, neonatal seizures appeared to be largely related to neonatal hypocalcemia. It is therefore possible that early recognition and treatment of hypocalcemia in infants with 22q11.2DS could help decrease the prevalence of moderate-to-severe ID. At present, most infants with 22q11.2DS remain unrecognized in the neonatal period. It may be possible to implement measures that could help to prevent hypocalcemia and thus related seizures in a clinical setting that facilitates the availability of genetic test results for 22q11.2 deletion within 5–7 days of life, such as with systematic neonatal screening. In the absence of such test results, neonatal hypocalcemia and/or seizures in any infant should prompt consideration of genetic testing for 22q11.2 deletion. Such measures could prompt meaningful anticipatory care and help improve long-term outcome in this common genetic condition.[3]

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DISCLOSURE

The authors declare no conflict of interest.

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