Postmaturity in a genetic subtype of schizophrenia

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Abstract

Objective—To determine whether postmaturity (gestation > 41 weeks), small for gestational age (SGA), and other pregnancy and birth complications that may elevate risk for neurodevelopmental disorders, are associated with elevated risk for schizophrenia in 22q11 Deletion Syndrome (22qDS), a genetic subtype of schizophrenia.

Method—Antepartum and intrapartum features were examined in 20 adults with 22qDS-schizophrenia and three comparison groups: newborn encephalopathy ($n = 164$) and healthy newborn controls ($n = 400$) from Badawi et al.'s (*Br Med J* 1998, **317**: 1549) study, and 16 non-psychotic 22qDS adults (22qDS-NP).

Results—Postmaturity (OR 13.0, 95% CI 3.95, 42.77; $P < 0.001$) and SGA (OR 3.59, 95% CI 1.23, 10.5; $P = 0.03$) were more prevalent in 22qDS-SZ than controls. Postmaturity was non-significantly more prevalent in 22qDS-SZ than in newborn encephalopathy ($P = 0.06$) or 22qDS-NP ($P = 0.2$). SGA showed similar rates in the two 22qDS groups and newborn encephalopathy, but was more prevalent in 22qDS-NP than controls ($P = 0.05$).

Conclusion—The results suggest that postmaturity may be associated with expression of schizophrenia in a 22qDS subtype of schizophrenia. SGA may be a non-specific marker of neurodevelopmental disturbance.

Keywords

schizophrenia; DiGeorge syndrome; chromosome disorders; pregnancy complications; prolonged pregnancy

Introduction

The pathogenesis of schizophrenia is hypothesized to involve abnormal neurodevelopment (1, 2). Associations of antepartum and intrapartum features with other neurodevelopmental disorders, such as cerebral palsy and newborn encephalopathy, replicated in large, well-

designed studies, may therefore be useful guides for selecting features for studies of schizophrenia. Factors most strongly associated with these neurodevelopmental disorders are antepartum features (3, 4) such as postmaturity (5, 6) (gestational age > 41 weeks) and intrauterine growth retardation, generally assessed by determining infants small (low birth weight) for gestational age (SGA) (7). Surprisingly, results related to these two antepartum features are rarely reported in studies of schizophrenia (8).

There is no consensus on the individual antepartum (maternal and pregnancy) or intrapartum (labor and delivery) factors, usually termed 'obstetrical complications' in the psychiatric literature, most strongly associated with schizophrenia (9, 10). Various features thought to be related to hypoxia are often cited as non-genetic factors that may be components in a causal pathway (8, 9, 11–13). However, several studies have found no significant association between schizophrenia and antepartum or intrapartum factors (14–18). Conflicting findings in this area may be due to the variable definitions and selection of antepartum and intrapartum factors for study (8, 10), selection of controls (14, 19), and heterogeneity of the schizophrenia samples used (20). The possible interaction between genetic endowment and antepartum/intrapartum factors is also rarely studied (8, 13), although such interactions are widely believed to be important in the neurodevelopmental pathogenesis of schizophrenia (2).

Recently, a subtype of schizophrenia which has a relatively homogeneous genetic etiology associated with a microdeletion on chromosome 22q11.2 has been identified (21), which is present in up to 2% of individuals with schizophrenia (22). The genetic syndrome associated with this deletion, 22q11 Deletion Syndrome (22qDS), has a variable physical and neurobehavioural phenotype that includes schizophrenia in about 25% of adults (21–23). High rates of congenital dysmorphic features (24, 25), developmental structural brain abnormalities (26, 27), and cognitive dysfunction (28) in 22qDS are consistent with neurodevelopmental disturbances in this genetic syndrome, and thus with this subtype of schizophrenia representing an especially neurodevelopmental form of the illness (2, 21). The relative genetic homogeneity conferred by the 22q11.2 deletion provides an improved opportunity to detect associations with other possible risk factors such as antepartum and intrapartum features, which have not yet been studied in 22qDS. The genetic risk for schizophrenia is related to the deletion, which usually occurs as a spontaneous (*de novo*) mutation, and in the absence of a family history of psychotic illness (22, 29). The syndrome therefore provides an opportunity to investigate the possible role of antepartum and intrapartum features in developing schizophrenia in the most genetically homogeneous sample currently available, without the possible confounding influence (30) of a history of psychotic illness in the mother.

Aim of the study

The aim of the present study was to investigate postmaturity, SGA and other antepartum and intrapartum features previously validated as risk factors in term infants with newborn neurodevelopmental disorders in a 22qDS subtype of schizophrenia (22qDS-SZ), and determine whether the prevalence of postmaturity and SGA was higher in 22qDS-SZ than in

healthy controls or a genetic risk control group, but similar to that in subjects with a known neurodevelopmental disorder.

Material and methods

Selection of subjects

Twenty (nine male, 11 female) 22qDS-SZ subjects were ascertained from adults with schizophrenia who met proposed clinical screening criteria for 22qDS (21) ($n = 13$) or psychiatric referrals of individuals previously diagnosed with 22qDS ($n = 7$). Sixteen (nine male, seven female) subjects with 22qDS and no psychosis (22qDS-NP) were ascertained through an adult congenital cardiac disease clinic ($n = 13$) or community sources ($n = 3$) to serve as a genetic risk control group. All 22qDS subjects had physical congenital anomalies commonly associated with the syndrome (21, 24), and a chromosome 22q11.2 deletion confirmed by standard cytogenetic studies using fluorescence *in-situ* hybridization (FISH) and a probe from the commonly deleted 22q11.2 region (31). Sample sizes were necessarily limited, given the rarity of adults diagnosed with 22qDS (32).

To place the findings in a larger context, we used a population-based healthy control group and a sample of subjects with a neurodevelopmental disorder (newborn encephalopathy, defined as newborns with seizures, or two or more other significant neurological signs lasting > 24 h) from a recently published study by Badawi et al. (6, 33). Premature infants were excluded as the focus of this study was on features associated with encephalopathy in term infants who represent the majority of newborns. Therefore, to be comparable with the comparison groups of Badawi et al. we selected only 22qDS subjects born at 37 weeks gestation or later; five additional ascertained subjects (three 22qDS-SZ, two 22qDS-NP) with a history of prematurity were therefore not included in the current study.

Assessment

22qDS subjects were assessed for lifetime psychiatric diagnoses by research psychiatrists using the Structured Clinical Interview for DSM-IV for Axis I disorders (SCID-I) (34) by direct interview and collateral information from family members and medical records. All 22qDS-SZ subjects met DSM-IV criteria for schizophrenia or schizoaffective disorder, depressed subtype; none of the 22qDS-NP subjects had a history of any psychotic or bipolar disorder. Age at onset of psychosis, defined by age when first documented to have psychotic symptoms, was determined from interviews with subjects and collateral information from family members and medical records. Information on family history of psychotic illnesses in first-degree relatives and parental socioeconomic status (SES) was obtained from direct interview of subjects and their relatives, and from medical records. The diagnosis of mental retardation was made using DSM-IV criteria aided by estimated IQ using WAIS-R vocabulary and block design scores (35) ($n = 31$) or previous test results ($n = 2$) for those with $IQ > 50$, and from history and functional assessment of those with $IQ < 50$ ($n = 3$). Parental SES was assessed using the three categories of maternal employment used in the study by Badawi et al. Informed consent was obtained from subjects and participating relatives and the study was approved by the Research Ethics Boards of the University of

Toronto, Centre for Addiction and Mental Health, Toronto General Hospital, and Hospital for Sick Children.

For each 22qDS subject, using available medical records and/or semi-structured interviews with mothers (or fathers when mothers were unavailable), we recorded information on antepartum and intrapartum features. Both medical records and parental history were available for 30 (83%) subjects; parental history alone was used for four subjects, and medical records alone were used for two subjects. Using these data, we determined the presence or absence of 12 antepartum and intrapartum features that were identified as significant risk factors for newborn neurological sequelae (moderate to severe newborn encephalopathy) in the study by Badawi et al. that had been replicated in other studies (6, 33) (see Table 2). Two additional features, placental abnormalities and persistent occipito-posterior presentation, could not be used because consistent data were not available in our sample for these variables. The Badawi et al. study (33) used similar methods (maternal history and medical records) to obtain data on antepartum and intrapartum features as for our 22qDS sample. Similar to methods used by Badawi et al. (31) and in other studies (8, 36), postmaturity was defined as gestational age > 41 weeks and SGA (<10th percentile) was determined using standard curves (37) based on birth weight, sex, and gestational age (8, 33).

Statistical analysis

The analyses involved comparisons between 22qDS-SZ and each of the three comparison groups: the Badawi et al. healthy control group, the Badawi et al. newborn encephalopathy (neurodevelopmental disorder) group, and the 22qDS-NP genetic risk control group. Non-parametric Wilcoxon *z*-tests were used to analyze both ordinal and continuous variables as the latter did not have normal distributions. We used non-parametric analyses, either chi-square or Fisher's exact test (if expected frequencies were <5), to analyze categorical variables. Two-tailed tests with a *P*-value of <0.05 were used to determine statistical significance.

Results

Demographic and basic clinical features

The 22qDS-SZ, and the three comparison groups were similar on many demographic and basic clinical variables (see Table 1), including sex distribution, older maternal age, parity, and alcohol consumption during pregnancy. The two 22qDS groups did not differ in the proportion of subjects with mental retardation or history of maternal smoking during pregnancy.

Distributions of maternal SES categories were not significantly different between the two 22qDS groups, therefore these groups were combined in order to have sufficient numbers per cell to compare them with maternal SES results reported for the Badawi et al. sample (33). Proportions of mothers having professional (25.8%, 30.6%), trade or clerical (51.6%, 41.3%) and other (22.5%, 28.1%) occupations were not significantly different in the 22qDS and Badawi et al. newborn control groups, respectively ($\chi^2 = 1.25$, *df* = 2, *P* = 0.53). All

22qDS subjects were singleton births; twins comprised two (0.5%) of 400 subjects in the newborn control group and four (2.4%) of 164 subjects in the newborn encephalopathy group.

The median age of the 22qDS-SZ group was significantly older than the 22qDS-NP group (31 years, range 21–48 years vs. 23.5 years, range 20–44 years; $z = -2.92$, $P = 0.045$). None of the subjects in either of the 22qDS groups had a family history of psychosis. Median age at onset of psychosis in the 22qDS-SZ group was 20.5 years, range 14–30 years. There were no significant differences in median paternal age between the 22qDS-SZ (30 years, range 23–37 years) and 22qDS-NP groups (30.5 years, range 25–43 years; $z = 1.17$, $P = 0.24$). No 22qDS subject had breech or other malpresentation. Distributions of these variables were not available in comparable form for the Badawi et al. samples.

Postmaturity and SGA

In the 22qDS-SZ group, postmaturity (25.0%) and SGA (25.0%) were the most common features. As predicted, these features were significantly more common ($P < 0.001$ and $P = 0.029$, respectively) in the 22qDS-SZ group than in the populationbased normal control sample (6, 33) (Table 2). The respective odds ratios (OR) and 95% confidence intervals (CI) were: OR = 13.0 (95% CI 3.95, 42.77) for postmaturity and OR = 3.59 (95% CI 1.23, 10.48) for SGA. Also as hypothesized, rates for SGA were similar in both 22qDS-SZ and Badawi et al. neuroencephalopathy groups, but there was a strong trend for postmaturity to be more prevalent in 22qDS-SZ than in newborn encephalopathy (9.8%, $P = 0.058$).

Comparing the two 22qDS groups revealed a four-fold greater prevalence of postmaturity in the 22qDS-SZ group (25.0%) than in the 22qDS-NP group (6.25%), but the difference did not reach statistical significance; OR = 5.0 (95% CI 0.52, 48.07). In contrast, the proportion of subjects with SGA was equally high in both 22qDS groups (see Table 2). No feature reached statistical significance in comparison between the two 22qDS groups. The proportion of subjects with SGA was significantly higher in the 22qDS-NP group than in healthy controls [25% vs. 8.5%, $P = 0.048$; OR = 3.59 (95% CI 1.097, 11.73)], representing the only significant difference in individual antepartum and intrapartum features between these comparison groups (see Table 2). As in the 22qDS-SZ group, rates for SGA were similar in the 22qDS-NP and newborn encephalopathy groups.

Examining the five 22qDS-SZ subjects with a history of postmaturity in more detail, four had other antepartum or intrapartum features: one was SGA, and three were delivered by emergency cesarian section. Other features documented in these five (four female, one male) subjects, one of whom had mental retardation, included: prolonged rupture of the membranes, meconium-stained amniotic fluid, and fetal distress; prolonged (36 h) labor; no uterine contractions following oxytocin, nulliparity, and signs of placental degeneration; prolonged (24 h) labor and nulliparity; nulliparity. There was no other antepartum or intrapartum feature in the single 22qDS-NP subject with postmaturity. The five 22qDS-SZ subjects with a history of postmaturity had no significant difference in median age at onset (21 years) compared with the 15 22qDS-SZ subjects without this feature (20 years, $z = -0.04$, $P = 0.97$). Because of small sample sizes, statistical analyses comparing postmature and normal gestation 22qDS-SZ subjects on other features were not performed.

Discussion

Consistent with our hypothesis, postmaturity and SGA were significantly more prevalent in the 22qDS-SZ group than in a healthy newborn control sample from the literature. The proportion of subjects with postmaturity was greater in 22qDS-SZ, although not significantly so, than in either subjects with another neurodevelopmental disorder (newborn encephalopathy) or those from a genetic risk control group (22qDS individuals without psychosis). In contrast, SGA was equally prevalent in the 22qDS-SZ, the 22qDS-NP and the newborn encephalopathy groups, indicating that SGA may be a feature commonly found together with neurodevelopmental disturbances. Taken together, these findings suggest that postmaturity is a feature that may be specifically associated with the expression of schizophrenia in a 22qDS subtype of the disorder.

The elevated rate of postmaturity in 22qDS-SZ in the current study does not appear to be related to other developmental anomalies. The two 22qDS groups had similar rates of mental retardation, and most 22qDS-SZ subjects with mental retardation did not have postmaturity. Rates of congenital heart defects were in fact higher in the 22qDS-NP than the 22qDS-SZ group because of differences in ascertainment. This is consistent with studies on comorbid schizophrenia and mental retardation which have reported that pregnancy and birth complications, including postmaturity, were more prevalent in subject groups with schizophrenia than those with no psychotic illness (38, 39), even when the non-psychotic group had higher rates of major congenital anomalies than the comorbid group (39). Elevated rates of congenital malformations, the majority not involving the central nervous system, have also been observed in population samples with newborn neurological sequelae (3, 6). However, these abnormalities themselves were not considered by neonatologists and geneticists to be 'causal' of the neurodevelopmental disorder (40). The postmaturity finding appears to be specific to prolonged gestation, and not just any abnormality in gestational length. Prematurity does not appear to share the same association with schizophrenia in 22qDS as postmaturity. If premature 22qDS subjects had been included in the current study, there would have been no significant difference in the proportion of 22qDS-SZ (13.0%) and 22qDS-NP (11.1%) subjects with prematurity, nor would results for SGA have changed (results not shown).

Our finding of an increased rate of postmaturity in a genetic subtype of schizophrenia is consistent with results from previous studies on schizophrenia. Several studies have found a significant association of postmaturity with schizophrenia or psychosis (8, 38, 39, 41, 42). How widespread this finding may be is difficult to determine, as relatively few studies on pregnancy and birth complications in schizophrenia have reported results relating to postmaturity as an individual risk factor (8–10). This is largely because the scale (43), most commonly used in schizophrenia studies (9), defines postmaturity stringently (>42 weeks gestation instead of >41 weeks) and combines the presence of postmaturity or prematurity in a single item. Including premature births in samples, instead of limiting births to those 37 weeks gestation, may obscure observation of important associations with postmaturity (44). Mechanisms of neurodevelopmental sequelae may be quite different in post-and pre-maturity.

The mechanism of the observed association between postmaturity and neurodevelopmental disorders in general is unknown. However, there is evidence from animal studies that the brain in fetuses in late than earlier gestation is more vulnerable to asphyxia (45). Interestingly, decreased gray matter, especially in the hippocampus, was restricted to animals with umbilical clamping applied late in gestation (45). Also, hypoxia may be an intervening pathogenetic mechanism between the occurrence of the antepartum factor and the neurodevelopmental disorder, with attendant signs including fetal distress, apnea, cyanosis, and meconium (6). Several of the 22qDS-SZ subjects with postmaturity in the current study had these features.

The combination of genetic susceptibility to schizophrenia and an antepartum feature such as postmaturity may make the fetal brain more vulnerable to other factors, such as hypoxia (8, 13), in a pathogenetic pathway. This is consistent with a multifactorial model of schizophrenia, with postmaturity being neither necessary nor sufficient to actually cause the illness. The majority of 22qDS-SZ subjects did not have postmaturity, supporting conclusions of other schizophrenia studies (30) that the bulk of the risk for schizophrenia is likely to be associated with genetic predisposition, in this case conferred by a 22q11.2 deletion. Postmaturity may be an additional insult that increases the chance of expressing schizophrenia. Once researchers have identified and characterized schizophrenia susceptibility genes and delineated pathogenetic pathways to symptom expression, the role of non-genetic factors, such as postmaturity and other antepartum features, should become clearer (2, 46).

The high rates of SGA in both the 22qDS-SZ and 22qDS-NP groups, and in the newborn encephalopathy group, suggest that SGA may be more generally associated with neurodevelopmental disturbances than with the expression of schizophrenia in 22qDS. These elevated rates of SGA are similar to those found in other genetic syndromes (47, 48). Thus, a possible association of SGA with schizophrenia, found in other studies (8, 12, 49), may be obscured in 22qDS. Rates of SGA were significantly different between 22qDS-SZ and Badawi et al. controls in the current study, consistent with results from these other studies of schizophrenia. This is also consistent with the study by Badawi et al. which found rates for SGA to be significantly higher in infants with newborn encephalopathy compared with healthy newborn controls (6, 33).

Advantages and limitations

The current study has some advantages over others. The etiology of schizophrenia in 22qDS is likely to be genetic with a greater degree of homogeneity than other samples used in studies of antepartum and intrapartum features in schizophrenia. Only term births were included, and comprehensive and well-validated risk factors were investigated on an individual basis. Individual antepartum and intrapartum factors are not equivalent in terms of risk (6, 33), and therefore results commonly reported in the schizophrenia literature, of the presence of any one of several pregnancy and birth complications have questionable meaning (30), and were not included in the current study. Our findings were not related to other features such as advanced maternal age, mother with psychotic illness, SES, malpresentation, multiple births, or nulliparity. The study used several comparison groups.

Others have pointed out that the selection of control samples may have important effects on results (14, 19). The population-based comparison samples provided approximate expected values for both general population controls and newborns with a neurodevelopmental disorder, allowing the evaluation of the proportion of 22qDS-SZ subjects with selected antepartum features in a greater context.

Results from this study may not be generalizable to other forms of schizophrenia, including other genetic or familial subtypes (50). However, other studies of schizophrenia have reported similar results with respect to postmaturity (8, 38, 39, 41, 42), supporting the likelihood that a 22qDS subtype of schizophrenia shares similar general characteristics and pathogenetic pathway for illness expression with non-22qDS schizophrenia. We have found similar structural brain abnormalities in 22qDS-SZ as those commonly observed in schizophrenia (51), further supporting such a possibility.

The comparison samples also presented limitations. The 22qDS samples used in the current study were Canadians born in the 1950–1980s, whereas the newborn cases and controls in the study by Badawi et al. were Australians born between 1993 and 1995 (6, 33). Obstetric practices would be expected to be different in these two time periods, if not these two countries, as there is evidence of changing obstetric practice within Canada over the past 15 years, with postmaturity rates decreasing from 5.4% in 1985–1987 to 3.5% in 1992–1994 (52). However, even if the rate of postmaturity in the Badawi et al. newborn controls (6, 31) were as high as that in Canada in the 1980s, results would not be expected to change significantly. There are also ascertainment and age differences between the two 22qDS groups. However, similarities in other demographic and clinical variables between the 22qDS groups and the newborn comparison groups from the literature support the use of these comparison groups in the study as reasonable. Clearly the ideal comparison groups would comprise similarly ascertained cohorts followed closely during antepartum, intrapartum, and newborn periods, systematically assessed for individual risk factors and newborn outcomes including 22qDS and any other genetic syndromes or neurodevelopmental disorders, and then followed over four or more decades for expression of schizophrenia or other sequelae. An ideal study would also control for the precise length of the 22q11.2 deletion which may vary, although these variations have never been associated with any particular phenotype (53, 54).

Also, although our 22qDS-SZ sample is larger than any previously reported (23), 22qDS sample sizes remain restricted because of the relative rarity of this special patient population. This limited our ability to detect statistically significant differences despite a four-fold difference in the rates of postmaturity between the 22qDS samples. We therefore cannot rule out the possibility that, similar to SGA, the postmaturity rate in 22qDS as a whole may be elevated because of the chromosomal deletion or that differences between the two 22qDS groups may be related to ascertainment. There is also the possibility of a misclassification bias, making it more difficult to detect true differences between the two 22qDS study groups. Most of the 22qDS-NP subjects were not past the general age range for maximal risk for schizophrenia; however only two subjects were younger than the median age at onset in the 22qDS-SZ group, making the potential misclassification of eventual 22qDS-SZ subjects as 22qDSNP in the current study unlikely to significantly affect the results.

Potential implications

Results from this study and others (8, 10) suggest that using individual features more directly linked to abnormal neurodevelopment, such as antepartum and intrapartum features validated to be associated with neurodevelopmental sequelae (6, 33), may be more informative than non-specific ‘obstetrical complications’ in research on the relationship between pregnancy and birth events and schizophrenia. In particular, as others have suggested (6, 8, 33), more attention needs to be paid to well-defined antepartum factors, such as postmaturity and intrauterine growth retardation (SGA).

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Table 1

Demographic and clinical characteristics of samples studied: 22q11 Deletion Syndrome (22qDS) with schizophrenia (22qDS-SZ), 22qDS with no psychosis (22qDS-NP) and two comparison groups from a population-based study (6, 31)

Demographic & clinical characteristics	Sample group 22qDS SZ (n = 20) n (%)	Genetic risk comparison group 22qDS-NP (n = 16) n (%)	Newborn comparison groups from Badawi et al. study (31)		
			Controls* (n = 400) n (%)	NE Cases† (n = 164) n (%)	Statistics χ^2 , df, P
Sex					
Male	9 (45.0)	9 (56.3)	197 (49.3)	94 (57.3)	3.52, 3, 0.32
Female	11 (55.0)	7 (43.7)	203 (50.7)	70 (42.7)	
Ethnicity					
Caucasian	20 (100)	16 (100)	372 (93.0)	142 (86.6)	9.75, 2, 0.008‡
Non-Caucasian	0 (0)	0 (0)	28 (7.0)	22 (13.4)	
Maternal age					
34 years	20 (100)	14 (87.5)	329 (82.2)	138 (84.1)	3.63, 2, 0.16‡
>34 years	0 (0)	2 (12.5)	71 (17.8)	26 (15.9)	
Parity					
Nulliparous	8 (40.0)	8 (50.0)	168 (42.0)	76 (46.3)	1.27, 3, 0.74
Multiparous	12 (60.0)	8 (50.0)	232 (58.0)	88 (53.7)	
Alcohol consumption¶					
No alcohol	13 (72.2)	11 (73.3)	228 (62.8)	102 (69.4)	2.88, 3, 0.41
Some alcohol	5 (27.8)	4 (26.7)	135 (37.2)	45 (30.6)	
Nicotine consumption¶					
None	12 (70.6)	13 (86.7)	—	—	0.40§
Any	5 (29.4)	2 (13.3)	—	—	
Intellectual level					
IQ 70	12 (60.0)	10 (62.5)	—	—	1.00§
Mental retardation (IQ < 70)	8 (40.0)	6 (37.5)	—	—	
Congenital anomalies					
Congenital heart defects	8 (40.0)	14 (87.5)	—	—	0.006§
Palatal defects**	12 (60.0)	9 (56.3)	—	—	1.00§
Renal anomalies¶¶	2 (10.5)	1 (7.7)	—	—	1.00§

* Controls from Badawi et al. (6, 31) case-control study of 164 term (37 weeks gestation) infants with newborn encephalopathy (cases) and 400 randomly selected term infants (controls).

[†] Newborn encephalopathy cases from Badawi et al. (6, 31) case-control study.

[‡] Analysis using 22qDS groups combined as one sample.

[§] Two-way Fisher's exact test.

[¶] Data not available for all subjects.

** Palatal defects comprised velopharyngeal insufficiency ($n = 9$), submucous cleft palate ($n = 10$) and overt cleft palate ($n = 2$).