The implications of terminal 6q deletion syndrome: determining appropriate anticipatory guidance, evaluation, and management: a case report and analysis of published literature

Abstract
Terminal 6q deletions have been infrequently described and have a variable phenotype. The constellation of symptoms described includes characteristic facies, developmental delay, growth delay, urogenital abnormalities, brain malformations, and cardiovascular malformations. Identification of a terminal 6q deletion should prompt an appropriate evaluation as well as thorough anticipatory guidance for the family. Here we describe an additional case of a terminal 6q deletion and review all previously reported cases.

Introduction
Terminal 6q deletions (those occurring from q25.0 onwards) have been infrequently described in the literature but do appear to represent a syndrome with some common phenotypic features. Recognition of terminal 6q deletion syndrome is important as this allows for proper anticipatory guidance to be provided to patients and their families, evaluation for associated abnormalities, and the implementation of appropriate management strategies. While this holds true, there is no standardized protocol for the evaluation of management of these children due to its rarity. Case reports of terminal 6q deletion syndrome exist and offer a majority of available data, demonstrating the variability not only in the phenotype of patients but also the evaluation and management of these patients. We describe here a case of a young boy noted to have a terminal 6q deletion syndrome in infancy and analyze this alongside data extracted from previous case reports of terminal 6q deletions in children and adults to describe the frequency of phenotypic characteristics, describe the most common phenotype, and determine appropriate evaluation and management strategies for those noted to have terminal 6q deletions.

Methods
A systematic review of the literature was performed to identify manuscripts describing terminal 6q deletions. This was a newly conducted review with no previous review protocol having been established for it. The aim of the study was identified as being that of describing the phenotypic characteristics of both children and adults with terminal 6q deletions and characterizing the evaluation of these patients.

Search strategy
Manuscripts were identified using electronic databases including PubMed, EMBASE, and Ovid which were queried using the following search terms: “6q deletion” and “6q monosomy”. No specific restriction on year of publication was used. Resulting studies were then screened by title and abstract with manuscripts describing terminal 6q deletions and characterizing the evaluation of these patients due to its rarity. Case reports of terminal 6q deletion syndrome exist and offer a majority of available data, demonstrating the variability not only in the phenotype of patients but also the evaluation and management of these patients. We describe here a case of a young boy noted to have a terminal 6q deletion syndrome in infancy and analyze this alongside data extracted from previous case reports of terminal 6q deletions in children and adults to describe the frequency of phenotypic characteristics, describe the most common phenotype, and determine appropriate evaluation and management strategies for those noted to have terminal 6q deletions.

Data extraction
Next, data regarding several clinical features of terminal 6q deletion were extracted from the manuscripts identified for inclusion. This data was extracted independently with use of a data collection form. Clinical features mentioned to be present or absent in the text or tables of the manuscripts were recorded as such. If no information was available about certain clinical features then this was designated separately. Authors of included studies were not contacted for additional data.

Bias analysis
Since all manuscripts identified for this study were case reports or case series no quantification of specific bias could be performed. Some studies described the same clinical features in a variety of ways and these were recorded as a single clinical feature during data extraction. For example, some studies described a “broad nasal tip” while others described a “bulbous nose”. These were both treated as representing the same clinical feature and recorded as “broad nasal tip” in this review. Similarly, some studies described “narrow palpebral fissures” while others described “short palpebral fissures” both of which were recorded as “short palpebral fissures” in this review.

Data analysis
Numerical data is presented as means with standard deviations or medians with ranges. Categorical data is presented as frequencies.
with absolute numbers as well as percentages. Analysis was begun with a Pearson correlation of all binary clinical features to determine associations between individual features. A chi-square analysis was then done to determine whether particular clinical features were more likely in males and females. An independent samples T-test was then performed to determine the effect of deletion size on particular clinical features. P-values of (insert less than or equal to sign here) 0.05 were considered statistically significant. All analysis was done using SPSS statistical software, version 20.0 (Chicago, IL).

Case report

We present the case of an infant born at 38 weeks gestation in a twin gestation to a G6P5 mother at an outside institution. The pregnancy itself was uncomplicated and the mother’s medications during pregnancy were fluodrocortisone acetate for palpitations and syncope as well as acetylsalicylic acid due to history of a previous stroke. Prenatal care was complete and prenatal ultrasounds had demonstrated what appeared to be normal fetal structures although the mother shares that there was mention of some concern of the heart but a fetal echocardiogram was not obtained. Maternal serum screening was normal. Delivery was via C-section due to transverse lie but was otherwise uncomplicated. The child was taken to the nursery where he spent a day and a half before being taken to the neonatal intensive care unit due to increased work of breathing. He was placed on supplemental oxygen and had an echocardiogram done which demonstrated a moderate sized ventricular septal defect and a patent ductus arteriosus with a small shunt. Mild mitral valve insufficiency was also present. His respiratory distress improved without additional intervention and with weans to room air and he was discharged home after 5 days.

At approximately 10 days of life, the baby began to have decreased oral intake, decreased urine output, and tachypnea. At 11 days of life he was brought to the emergency department at our institution where he was found to be mildly dehydrated and with signs and symptoms consistent with heart failure secondary to pulmonary overcirculation. On physical examination he was noted to have a widened nasal bridge, a broad nasal tip, low-set ears, bilateral preauricular pits, and cryptorchidism. Weight was 2.50kg (2nd percentile). He was started on anticongestive therapy including diuretics, and was given fluodrocortisone acetate for palpitations and syncope as well as acetylsalicylic acid (aspirin) due to history of a previous stroke. Prenatal care was complete and prenatal ultrasounds had not demonstrated any concerns. The mother shares that there was mention of some concern of the heart but a fetal echocardiogram was not obtained. Maternal serum screening was normal. Delivery was via C-section due to transverse lie but was otherwise uncomplicated. The child was taken to the nursery where he spent a day and a half before being taken to the neonatal intensive care unit due to increased work of breathing. He was placed on supplemental oxygen and had an echocardiogram done which demonstrated a moderate sized ventricular septal defect and a patent ductus arteriosus with a small shunt. Mild mitral valve insufficiency was also present. His respiratory distress improved without additional intervention and with weans to room air and he was discharged home after 5 days.

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Approximately 5 months of age the patient began developing periods of unresponsiveness and hypoxia which were thought to be concerning for seizures. He also had an episode of uncontrolled jerking of all his extremities with concomitant hypoxia. Although EEGs were obtained and were normal the child was started on levetiracetam with improvement in his brain natriuretic peptide values from approximately 1120 on initial evaluation in the emergency room to 60 after approximately one month of treatment. The ventricular septal defect closed spontaneously by 1 year of age. At approximately 5 months of age the patient began developing periods of unresponsiveness and hypoxia which were thought to be concerning for seizures. He also had an episode of uncontrolled jerking of all his extremities with concomitant hypoxia. Although EEGs were obtained and were normal the child was started on levetiracetam with improvement in his brain natriuretic peptide values from approximately 1120 on initial evaluation in the emergency room to 60 after approximately one month of treatment. The ventricular septal defect closed spontaneously by 1 year of age.

Results

A total of 683 unique manuscripts were identified by initial electronic search using the databases identified above. Of these, 119 were deemed relevant after review of titles and abstracts with full text manuscripts obtained for 102 of these. After review of the full text manuscripts, 35 studies were identified for inclusion in the review. This resulted in 72 cases reported in the literature that when combined with the case presented below leads to 73 cases presented in this review. Of those in this cohort, 7% were prenatally diagnosed. The median age of prenatal diagnosis was 14 months with a range of 0.5 to 444 months. Over half of the cohort (51%) was male. De novo deletions were found in 85% of cases with a median deletion size of 8 megabase pairs with a range of 0.3 to 203.4. Deletions were detected by fluorescence in situ hybridization (FISH) in 57% cases, karyotype in 22%, and array in 21%. Parental consanguinity was present in 5% of cases.

Facial dysmorphism included, but were not limited to, the following: short palpebral fissures in 24%, prominent nasal bridge in 69%, broad nasal tip in 59%, downturned corners of the mouth in 14%, and ear abnormalities in 78%. Eye or vision abnormalities were noted in 58%. Just a little of a third of the cohort (34%) had a short neck and nearly half (46%) had microcephaly. Cranial suture abnormalities were documented in 20% of patients. Other malformations included urogenital abnormalities in 27% and extremity abnormalities in 55%.

Developmental delay of some variety was noted in almost all patients. An overwhelming majority (90%) of those in the cohort were found to have a degree of intellectual disability. Motor delay was noted in 97% and speech delay in 68%. Motor delay was present in 97%. Seizures were noted in 57%. Brain imaging was obtained for 78% of patients with magnetic resonance imaging making up 79% of these tests. Brain imaging demonstrated hydrocephalus (33%), a pons abnormality in 5%, grey/white matter abnormalities in 9%, corpus callosum abnormalities in 46% of patients.

Cardiac abnormalities were noted in 30% of patients. Atrial septal defect was the most common, being found in 36% of patients with a cardiac abnormality. Ventricular septal defect was found in 23%. Other cardiac lesions noted included Tetralogy of Fallot, atrioventricular septal defect, and cor triatriatum. Also worth mention are cyanotic spells that were noted in 15% of this cohort. These did not demonstrate any statistically significant association with the presence of cardiac abnormalities or seizures. There are very few differences noted in phenotype between males and females. Males were more likely to have de novo mutations (p=0.021) while females were more likely to have de novo mutations (p=0.021) while females were more likely to have downturned corners of the mouth (p=0.036).

Deletion size does seem to impact the phenotypic expression. Larger deletions were found in those with prominent nasal bridge (p=0.025), ear abnormalities (p=0.038), and corpus callosum abnormalities (p=0.007). Those with Cranial suture abnormalities tended to have smaller deletions than those without (p=0.009). Not enough data was present to compare deletion size in those with mental retardation, speech delay, or motor delay. Correlation analysis run between all the studied characteristics determined the following phenotype to be the most common: broad nasal bridge, ear abnormalities, broad nasal tip, microcephaly, mental retardation, motor delay, and urogenital abnormalities.

Discussion

Terminal 6q deletions are relatively infrequent and thus there is limited data available. Additionally, there seems to be significant phenotypic variability which further complicates characterizing this group of patients. This poses difficulty to those providing care for these patients as there is a lack of guidance regarding what abnormalities patients should be evaluated for and what anticipatory guidance patients and other care providers should provide. Facial dysmorphism in terminal 6q deletion syndrome consist of short and downsloping palpebral fissures, flat and broad nasal bridge, broad nasal tip, and downturned corners of the mouth. Ear abnormalities are not infrequent and include low-set, posteriorly rotated ears.
Many patients have also been reported to have preauricular pits. Eye abnormalities, other than those pertaining to the palpebral fissures, include strabismus and corneal abnormalities. Cranial malformations common in those with terminal 6q deletion syndrome and include overriding sutures, widened anterior fontanel, and microcephaly. Brain abnormalities are also frequently encountered and include hydrocephalus, pons abnormalities, grey/white matter abnormalities, and corpus callosum abnormalities. The spectrum of corpus callosum abnormalities is quite vast from mild dysgenesis to complete agenesis.

Seizures are also frequently noted in children with terminal 6q deletion syndrome. These may or may not be associated with abnormalities noted on brain imaging. Perhaps more interesting is that some cases have described seizure like episodes that are not associated with EEG abnormalities. In some of these cases the children were started on antiepileptic drugs with improvement in their symptoms while others were followed and some eventually had EEG changes and were started on antiepileptic drugs. Seizures can be very frequent, particularly in early childhood, with patients having 4-5 seizures a day. Seizures refractory to single agent therapy also appear to be common. Developmental delay is almost uniformly present. Intellectual disability is not uncommon but appears to be mild to moderate in most cases. Speech delay is also present with most cases being worse from an expressive rather than receptive nature. Growth delay with poor weight gain is also noted in early childhood. These delays may or may not be associated with hyponatia. Cardiac abnormalities are variable and most commonly consist of septal defects. Of interest are cyanotic episodes that occur in children with terminal 6q deletion which in the setting of cardiac abnormalities may be attributed to these abnormalities. In reality, however, most of these lesions are septal defects in the setting of systemic right ventricular pressures such that these would not have a reason to lead to right to left shunting and cyanosis. Thus, cyanotic episodes must not be automatically attributed to cardiac pathology. Other etiologies such as normal changes in vasomotor reactivity to environmental stresses, reflux, seizures, and upper respiratory infections should not be ignored.

The most frequent phenotype consists of broad nasal bridge, ear abnormalities, broad nasal tip, microcephaly, intellectual disability, motor delay, and urogenital abnormalities. This constellation of symptoms should thus raise suspicion for terminal 6q deletions and evaluation by microarray or FISH. If a terminal 6q deletion is noted the child should undergo an ophthalmologic examination and also have brain imaging, preferably magnetic resonance imaging. A thorough genital examination should be done as well and if testicles cannot be palpated in the scrotal sacs of males then abdominal ultrasonography should be obtained to identify their location. There must always be vigilance for seizures. Abnormal limb movements or repetitive, acute changes in interaction should raise suspicion for terminal 6q deletions to define genotype/phenotype correlations. Clin genet. 2005;67(5):396–403.


**References**

**Conflict of interest**

None.

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Author declares that there is no conflict of interest.
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