Neuroimaging findings in Emanuel Syndrome

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ABSTRACT

Emanuel syndrome is a rare inherited chromosomal abnormality caused by an unbalanced translocation of chromosomes 11 and 22. Clinically, Emanuel syndrome is characterized by a wide spectrum of congenital anomalies, dysmorphisms, and developmental disability often confused with other similar syndromes. Outside of genetic testing, diagnosis remains challenging and current literature on typical radiologic findings is limited. We present classic neuroimaging findings of Emanuel syndrome consistent with prior literature including microcephaly, microretrognathia, external auditory canal stenosis, and cleft palate; and also introduce the additional maxillofacial anomaly of dysplastic middle ear ossicles, to our knowledge not previously described in the literature. Recognition of findings leading to earlier diagnosis of Emanuel syndrome may improve outcomes and quality of life for patients and their families.

CASE REPORT

Our patient was diagnosed with Emanuel syndrome prenatally after genetic testing was performed for evaluation of multiple fetal anomalies. His mother had multiple prior miscarriages and was found to have a balanced translocation of chromosome 11 and 22. He was born at term via vaginal delivery without complication. Though he did not have any congenital cardiac or renal abnormalities, he was noted to have hypotonia, cleft palate, and microcephaly at birth.

Soon after birth, he was found to have bilateral Eustachian tube dysfunction with recurrent ear infections, which were treated with bilateral myringotomy and tube placement. Audiology evaluation was notable for bilateral sensorineural hearing loss. We present images from a temporal bone CT without contrast performed at 9 months of age for further evaluation. Helical CT images were obtained using a Phillips iCT 256-slice scanner (Andover, MA, USA). Coronal and sagittal reformatted images, as well as 3D volume rendering reconstructions were obtained from the axial data set.

There was decreased brain to face ratio and low fronto-occipital diameter for age, consistent with the patient’s clinically diagnosed microcephaly. There was a small mandible, with abnormal posterior positioning relative to the maxilla (Figure 1, 2). A cleft palate was also seen (Figure 3). Limited evaluation of the supratentorial compartment demonstrated mild diffuse microencephaly (Figure 4). The orbits and paranasal sinuses were normal. Trace fluid was noted in the left mastoid air cells.

Stenosis of the bilateral external auditory canals was present (Figure 5). Tympanostomy tubes were noted bilaterally. The malleus and incus were dysplastic (Figure 5); stapes was normal. The tympanic cavities including Prussak’s
space were clear bilaterally. No soft tissue mass was seen. The cochlea and vestibular labyrinth were within normal limits.

These findings were communicated with otolaryngology, who are currently managing the patient’s hearing loss conservatively. The patient is developmentally and cognitively delayed, and receiving speech therapy.

**DISCUSSION**

**Etiology & Demographics:**

Emanuel syndrome, also known as supernumerary der(22)(q11.22) syndrome (OMIM #609029), is a rare unbalanced chromosomal translocation characterized by multiple congenital anomalies, dysmorphisms, and developmental disability [1]. Balanced translocation of chromosomes 11 and 22 is the most frequent recurrent non-Robertsonian translocation in humans [2]. While carriers of this balanced translocation are typically asymptomatic, they often have infertility or recurrent miscarriages. When able to successfully bear offspring, their children are at risk of developing an unbalanced translocation from 3:1 meiotic malsegregation: a condition currently known as Emanuel syndrome [1].

Based on the frequency of the de novo chromosome 11/22 translocation in sperm from healthy men, prevalence of Emanuel Syndrome has been estimated at 1 in 110,000 [2]. However, this is much higher than the actual number of documented cases. This discrepancy may be in part due to shortcomings in clinical diagnosis.

**Clinical & Imaging Findings:**

Emanuel syndrome is characterized by several congenital abnormalities; the most common being preauricular tags or pits, ear anomalies, microcephaly, micrognathia, heart and kidney malformations, cleft palate, and genital abnormalities in males [1]. The majority of patients also have vision and hearing impairment, recurrent infections (particularly otitis media), cognitive impairment, and psychomotor delay.

Description of patterns of structural brain abnormalities in Emanuel syndrome in the current literature is limited, and largely based on parental reports rather than medical records [3]. Our case report describes classic neuroimaging findings associated with Emanuel syndrome including microcephaly, microretrognathia, external auditory canal stenosis, and cleft palate; and also introduce the novel maxillofacial anomaly of dysplastic middle ear ossicles.

**Treatment & Prognosis:**

Management of Emanuel syndrome necessitates a multidisciplinary approach focused on the abnormalities and symptoms unique to each patient. Diagnosis is confirmed via genetic detection of a duplication of 22q10-22q11 and 11q23-qter on a supernumerary derivative chromosome 22. While the precise rate of mortality of the disease is not well established, many patients with Emanuel syndrome have been able to survive to adulthood [2].

**Differential Diagnosis:**

Among previously reported cases, few were diagnosed prenatally [3]. While the majority were diagnosed within the first month of life, a significant number were diagnosed later. For those presenting with a delayed diagnosis, the disease had initially been confused with similar conditions including cat eye syndrome, Pierre Robin sequence, DiGeorge syndrome, cri du chat syndrome, and prematurity [3,4]. These findings suggest that outside of genetic testing, clinical diagnosis of Emanuel syndrome remains challenging.

While there are no necessarily distinguishing pathognomonic findings, abnormal neuroimaging can be expected in virtually all patients with Emanuel syndrome. We hope that the common characteristic findings described in this case report will aid in the diagnosis of Emanuel syndrome. The constellation of microcephaly, cleft palate, and jaw abnormalities can also be seen in cat eye syndrome, Fryns syndrome, Smith-Lemli-Opitz syndrome, and Wolf-Hirschhorn syndrome. However, none of these syndromes have previously been associated with dysplastic ossicles. Dysplasia of the inner ear has been described in Kabuki syndrome, which however can be differentiated by the presence of cerebellar/brainstem anomalies and cortical dysplasia [5]. The differences in neuroimaging findings among these similar appearing syndromes are summarized in Table 2.

Earlier diagnosis can accelerate timely identification of particular manifestations that may contribute to morbidity and mortality such as structural anomalies of the heart, kidneys, or gastrointestinal tract. Genetic counselling may help identify at risk relatives and assist with reproductive planning. Finally, timely evaluation by physical, occupational, speech, and developmental therapists can potentially improve quality of life for these patients and their families.

**TEACHING POINT**

Emanuel syndrome is an inherited chromosomal disorder that can be clinically challenging to diagnose. Previously described neuroimaging findings include microcephaly, micrognathia, retrognathia, cleft palate, cerebral volume loss, and external auditory canal atresia. We describe a case of a patient who presented with all these classic findings. In addition, neuroimaging depicted dysplasia of the bilateral middle ear ossicles, to our knowledge a novel finding not previously described in the literature. Familiarity with these neuroimaging findings can contribute to earlier diagnosis and, potentially, improved outcomes for these patients and their families.
REFERENCES


FIGURES

Figure 1: 9 month old male with Emanuel syndrome presenting with hearing loss.

FINDINGS: Sagittal CT image through the midline demonstrates microretrognathia with posterior displacement of the mandibular incisors by approximately 6 mm relative to the maxillary incisors (arrows).

TECHNIQUE: Non-contrast CT examination of the temporal bone, sagittal reformation, 1 mm slice thickness, 120 kV, 125 mAs, using Phillips iCT 256-slice scanner.

Figure 2: 9 month old male with Emanuel syndrome presenting with hearing loss.

FINDINGS: 3D volume rendering reconstruction of the maxillofacial skeleton shows relative dorsal displacement of the mandible relative to the maxilla.

TECHNIQUE: Non-contrast CT examination of the temporal bone, 3D reformation, using Phillips iCT 256-slice scanner.

Figure 3: 9 month old male with Emanuel syndrome presenting with hearing loss.

FINDINGS: Coronal CT image through the soft palate demonstrates a cleft palate 6 mm in width (arrow).

TECHNIQUE: Non-contrast CT examination of the temporal bone, coronal reformation, 3 mm slice thickness, 120 kV, 125 mAs, using Phillips iCT 256-slice scanner.
**Figure 4 (left):** 9 month old male with Emanuel syndrome presenting with hearing loss.

FINDINGS: Limited evaluation of the intracranial compartment in this temporal bone CT reveals prominent subarachnoid spaces (arrows) and ventriculomegaly (asterisk), in keeping with the given history of microcephaly.

TECHNIQUE: Non-contrast CT examination of the temporal bone, axial reformation, 0.67 mm slice thickness, 120 kV, 125 mAs, using Phillips iCT 256-slice scanner.

**Figure 5:** 9 month old male with Emanuel syndrome presenting with hearing loss.

FINDINGS: Side-by-side comparison, coronal CT image at the level of the middle ears demonstrate stenosis of the external auditory canals (asterisks), as well as bilateral dysplasia of the incus and malleolus (arrows).

TECHNIQUE: Non-contrast CT examination of the temporal bone, coronal reformation, 1 mm slice thickness, 120 kV, 125 mAs, using Phillips iCT 256-slice scanner.
Etiology | Unbalanced translocation of chromosomes 11 and 12 resulting from 3:1 meiotic malsegregation from a balanced carrier.
---|---
Incidence | Unknown; theoretically estimated at 1:110,000.
Gender ratio | 1:1
Age predilection | Congenital
Risk factors | Parent with balanced translocation; may manifest as parent with infertility or recurrent miscarriage.
Treatment | Multidisciplinary focused on the abnormalities and symptoms unique to each patient.
Prognosis | Unknown; many cases have survived into adulthood.
Imaging findings | Neuroimaging may show microcephaly, micrognathia, retrognathia, cleft palate, external auditory canal atresia, and dysplastic ossicles.

Table 1: Summary table for Emanuel syndrome

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Neuroimaging findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emanuel syndrome</td>
<td>Microcephaly, micrognathia, retrognathia, cleft palate, external auditory canal atresia, and dysplastic ossicles.</td>
</tr>
<tr>
<td>Cat eye syndrome</td>
<td>Coloboma of iris/choroid/optic nerve, microphthalmia, cleft palate, external auditory canal atresia.</td>
</tr>
<tr>
<td>Fryns syndrome</td>
<td>Micrognathia, retrognathia, cleft palate, hydrocephalus, Dandy-Walker malformation, corpus callosum agenesis.</td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome</td>
<td>Microcephaly, cerebellar hypoplasia, cleft palate, micrognathia, retrognathia.</td>
</tr>
<tr>
<td>Wolf-Hirschhorn syndrome</td>
<td>Microcephaly, cleft palate, corpus callosum dysgenesis, hydrocephalus.</td>
</tr>
<tr>
<td>Kabuki syndrome</td>
<td>Cerebellar and brainstem anomalies, cortical dysplasia, dysplasia of the inner ear.</td>
</tr>
</tbody>
</table>

Table 2: Differential diagnosis table for Emanuel syndrome

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Neuroimaging findings</th>
</tr>
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ABBREVIATIONS

CT = computed tomography
derr(22) = derivative chromosome 22
t(11;22) = chromosome 11 and 12 translocation

KEYWORDS

Emanuel syndrome; Supernumerary der(22)t(11;22) syndrome; Chromosome 11/22 translocation; Hearing loss; CT; Neuroimaging

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