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Temtamy-like syndrome associated with translocation of 2p24 and 9q32

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We describe the phenotype of a 5 year old girl with features resembling Temtamy syndrome, including agenesis of the corpus callosum, ventriculomegaly, frontal bossing, peaked eyebrows, ptosis, malformed and low set ears, a depressed nasal bridge, a long philtrum, and iris and chorioretinal colobomas. Features unique to this child include profound mental retardation, bilateral sensorineural hearing loss, agenesis of the corpus callosum, patent ductus arteriosus, ventricular septal defect, unilateral renal agenesis, neurogenic bladder and hydronephrosis. High resolution chromosome analysis demonstrated a *de novo*, balanced translocation [46,XX,t(2;9)(p24;q32)]; and her case has some overlapping phenotypic features with cases of monosomy for 2p. This is the first documented case of Temtamy syndrome with a specific chromosomal anomaly, and will assist with the elucidation of the syndrome's underlying genetic defect. *Clin Dysmorphol* **12:175–177**

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Introduction

Temtamy *et al.* (1996) described 3 siblings with a presumed autosomal recessive entity characterized by frontal bossing, a prominent forehead, and a long philtrum in association with iris and chorioretinal colobomas, profound myopia, ventricular enlargement, aortic enlargement, skeletal anomalies, and agenesis of the corpus callosum. Chan *et al.* (2000) subsequently described a child with similar findings. We present a child with many of these characteristics but with a more severe phenotype including profound mental retardation, congenital anomalies of the renal and cardiovascular systems and bilateral sensorineural deafness. She is the first case of Temtamy-like syndrome to be reported with a chromosomal aberration; a *de novo* and cytogenetically balanced translocation of 2p and 9q. While this case report adds further definition of the Temtamy syndrome phenotype, it will also aid in the understanding of the underlying molecular defect.

Case report

This female was born at 34 weeks gestation to a 25 year old primigravida by cesarean section secondary to breech presentation. In the family history a maternal half-uncle has a cleft lip and palate. The parents are nonconsanguineous and the ancestry is mixed northern European and Native American. The pregnancy was complicated by insulin dependent diabetes, hypothyroidism, and pernicious anemia. Apgars were 3 and 8 at one and five minutes, respectively. Birth weight was 2538 g (85th centile), birth length 44 centimeters (25th centile), and birth head circumference 30 centimeters (25th centile). Hypotonia, decreased deep tendon reflexes, and dysmorphic features consisting of a prominent forehead with frontal bossing, an inferior coloboma of the left iris, bilateral chorioretinal colobomas, depressed and widened nasal bridge, long philtrum, and low set ears with an overfolded pinnae, a single palmar crease, hypoplastic nails and a right inverted nipple were noted. A brain MRI showed dilated ventricles and agenesis of the corpus callosum. An electroencephalogram suggested epileptiform activity and BAER was abnormal bilaterally. A chest X-ray showed 13 rib pairs. An echocardiogram showed multiple small muscular ventricular septal defects and a patent ductus arteriosus. Intravenous pyelography exhibited severe hypoplasia of the left kidney and hydronephrosis of the right. High resolution chromosome analysis demonstrated a *de novo*, balanced translocation [46,XX,t(2;9)(p24;q32)] and the parental karyotypes were normal.

The child has significant problems including profound mental retardation, obstructive apnea, sensorineural hearing loss, severe gastroesophageal reflux necessitating feeding through a gastrostomy tube, paroxysmal supraventricular tachycardia, left ventricular hypertrophy,

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hydronephrosis due to vesicoureteral reflux, and a neurogenic bladder. The tachycardia has not recurred, shows no evidence of accessory tract on ECG, and she remains unmedicated. Her left ventricular hypertrophy has improved, and the ventricular septal defects have closed spontaneously.

On examination at 5 years of age her length is 99 centimeters (5th centile), weight 14.6 kilograms (25th centile), and head circumference 46 centimeters (< 5th centile). Facial dysmorphism is shown in Figure 1. Brachydactyly was also noted. The child has hypotonia and cannot sit unsupported. She is nonverbal and communicates by grunting.

Discussion

Apparently *de novo*, balanced reciprocal translocations carry a 6% risk of serious malformations, presumably due to a submicroscopic genetic defect most likely leading to loss of function of a gene or genes (Warburton, 1991). Chromosomal translocations can provide valuable information in the cloning of disease genes (Ledbetter *et al.*, 1989; European Polycystic Kidney Disease Consortium, 1994).

Our patient has some similarities with the phenotypes associated with monosomy of chromosome 2. A *de novo*, interstitial deletion of chromosome 2p24 has been reported in two patients (Neidich *et al.*, 1987; Penchaszadeh *et al.*, 1987). Common features included failure to thrive, mental retardation, seizures, microcephaly, a high forehead with frontal bossing, ptosis, a broad nasal bridge, a long philtrum, a bow-shaped mouth, and brachydactyly. One additionally had hypotonia, a ventricular septal defect and intermittent esotropia. Kroes *et al.* (1994) reported a case of chromosome 9 deletion (q22q32) in a boy with dilated cerebral ventricles, severe mental retardation, hypotonia, short stature, microcephaly, and frontal bossing and reviewed six other cases. Farrell *et al.* (1991) reported three cases of deletion 9q22–q34 and reviewed the literature. Both authors concluded that monosomy 9q is rare with no consistent reported features. While neither monosomy is classically associated with colobomas, the phenotype of this child overall resembles the previously reported cases of interstitial deletion of chromosome 2p24.

Our case has many features consistent with reported cases of Temtamy syndrome including the dysmorphic features, agenesis of the corpus callosum, ventricular enlargement, and iris and retinal colobomas. However, her phenotype is discordant given her profound mental retardation, renal anomalies, bilateral sensorineural hearing loss, lack of aortic enlargement, a beaked nose, and short upper lip (Table 1). Also Temtamy's report of 3 siblings is suggestive of autosomal recessive inheritance, however a dominant mode of inheritance cannot be excluded. We hypothesize that genes disrupted at one or both the breakpoints have resulted in Temtamy-like syndrome. Physical mapping of the translocation breakpoint by FISH and PCR analysis led to the identification of two novel, ubiquitously expressed, zinc-finger-encoding transcripts that are disrupted in this patient. Both genes now represent candidate genes for her constellation of congenital anomalies (Ramocki *et al.*, 2003).

All cases reported by Temtamy, *et al.* (1996) had borderline to normal I.Q. scores (75, 95, and 84). At 17 months of age, the child reported by Chan *et al.* (2000)

Fig. 1

Present case at 5 years of age. (a). Frontal view. Note ptosis, downslanting palpebral fissures, broad and depressed nasal bridge, long philtrum, wide and downturned mouth. (b). Lateral view. Note the frontal bossing and low set ears.

Table 1 Defining features of Temtamy syndrome.

Author	Temtamy *et al.* (1996)			Chan *et al.* (2000)	Current case
	Case 1	Case 2	Case 3		
Gender	Female	Female	Male	Male	Female
Development	I.Q. 75 at 21 yrs	I.Q. 95 at 9 yrs	I.Q. 84 at 8 yrs.	Mild gross motor delay at 17 months	Profound mental retardation
Dysmorphic features					
Frontal bossing	+	+	+	+	+
Depressed nasal bridge	+	+	+	+	+
Low set ears	+	+	+	–	+
Long philtrum	+	+	+	+	+
Elongated face	+	+	+	–	–
Beaked nose	+	+	+	–	–
Hypertelorism	+	+	+	+	+
Ocular features					
Iris colobomas	+	+	+	+	+
Chorioretinal colobomas	+	+	+	+	+
Myopia	+	+	+	–	+
Deafness	–	–	–	–	Bilateral sensorineural
Renal agenesis	–	–	–	–	Unilateral
CNS structural defects					
Agenesis of corpus Callosum	+	+	+	+	+
Ventriculomegaly	+	+	+	–	+
Cardiovascular					
VSD	–	–	–	–	+
Aortic root ectasia	+	–	+	–	–

Table adapted from Chan *et al.* (2000).

had mild gross motor delay, however cognitive functioning was still within normal limits. Our case is functioning in the profound mental retardation range. Two of the cases presented by Temtamy had aortic root dilatation however the other 3 reported cases did not have this association.

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