22q13 Deletion Syndrome with Central Diabetes Insipidus: A Previously Unreported Association

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We describe a two-year-old girl with 22q13 deletion syndrome (MIM # 606232), 46, XX, de l (22) (q13.31). ish del (22) (q13.31) (TUPLE 1 +,ARSA–). The patient has hypotonia, normal growth, severe expressive language delay, mild mental retardation, and minor dysmorphic facial features. In addition, she had central diabetes insipidus that was diagnosed at age two days and resolved at age 27 months. To our knowledge, this association has not been reported previously. Infants with hypotonia, or those suspected to have this syndrome should have high-resolution chromosome analysis and fluorescent in situ hybridization (FISH) studies or molecular analysis, since the chromosomal deletion may be subtle and may go undetected on routine cytogenetic studies. The association of 22q13 deletion syndrome with central diabetes insipidus is reported for the first time. *Clin Dysmorphol* **13:000–000**

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Clinical Report

The patient is a two-year-old female who was born at 38 weeks gestation to a 32 year-old mother and 35 year-old father. The parents have two other normal boys but had one son, member of twins, who was stillborn at 28 weeks gestation. Consanguinity was denied, and there was no family history of genetic disease.

Birth weight was 3998 gm (90th percentile), length 54 cm (95th percentile), and head circumference 38 cm (95th percentile). Physical examination showed deep-set eyes, small chin and edema of the lower extremities (Figure 1a). At two days of age, the infant was noted to urinate excessively (700 ml/24 hours) despite poor feeding. Laboratory work revealed serum glucose of 27 mg/dl, sodium 150 mEq/L, serum osmolality 296 mOsm/kg water, urine osmolality 110 mOsm/kg water, and normal serum chemistries, thyroid tests and serum cortisol. Growth hormone was 49 ng/ml and antidiuretic hormone 2.0 pg/ml (normal 1–13 pg/ml). Renal ultrasound was normal. Central diabetes insipidus was diagnosed and she was started on intramuscular vasopressin. Newborn hearing screen test was normal. Chromosomal analysis showed a 46, XX complement. She was maintained on DDAVP.

Physical examination at age two years, revealed a weight of 12.5 kg (65th percentile), height 89 cm (75th percentile), and head circumference 49.5 cm (90th percentile). She had bilateral epicanthal folds with inner canthal distance of 3.5 cm (> 95th percentile) and outer canthal distance of 9.5 cm (95th percentile), flat nasal bridge, large philtrum, narrow high arched palate, central hypotonia, brisk deep tendon reflexes, normal sensory neurological examination and cranial nerves, psychomotor and speech delay (Figure 1b). Pediatric ophthalmological examination was normal. BAER revealed slight bilateral elevation in the hearing threshold. Developmental evaluation at age 27 months showed generalized hypotonia, expressive language of a six months old infant, speech skills at six to nine months, and a receptive language level of 12 months.

The diabetes insipidus resolved at age 27 months, and DDAVP treatment was discontinued. Blood count, serum chemistries, thyroid studies, and plasma aminoacids were normal. Electroencephalogram was normal. MRI of the brain performed at age six months revealed a very small or absent posterior pituitary gland, a small corpus callosum, a small volume of the white matter, and a small focus of subependymal gray matter heterotopia in the left occipital horn (Figure 2). FISH analysis revealed a deletion of the distal long arm of chromosome 22 (46, XX, de l (22) (q13.31). ish del (22) (q13.31) (TUPLE 1 + , ARSA–))(Figure 3).

Discussion

The terminal 22q13 deletion syndrome is characterized by hypotonia in 97% of patients, normal or accelerated growth in 95%, severe expressive language delay, global developmental delay, and minor dysmorphic facial features (Nesslinger *et al.*, 1994; Precht *et al.*, 1998; Prasad *et*

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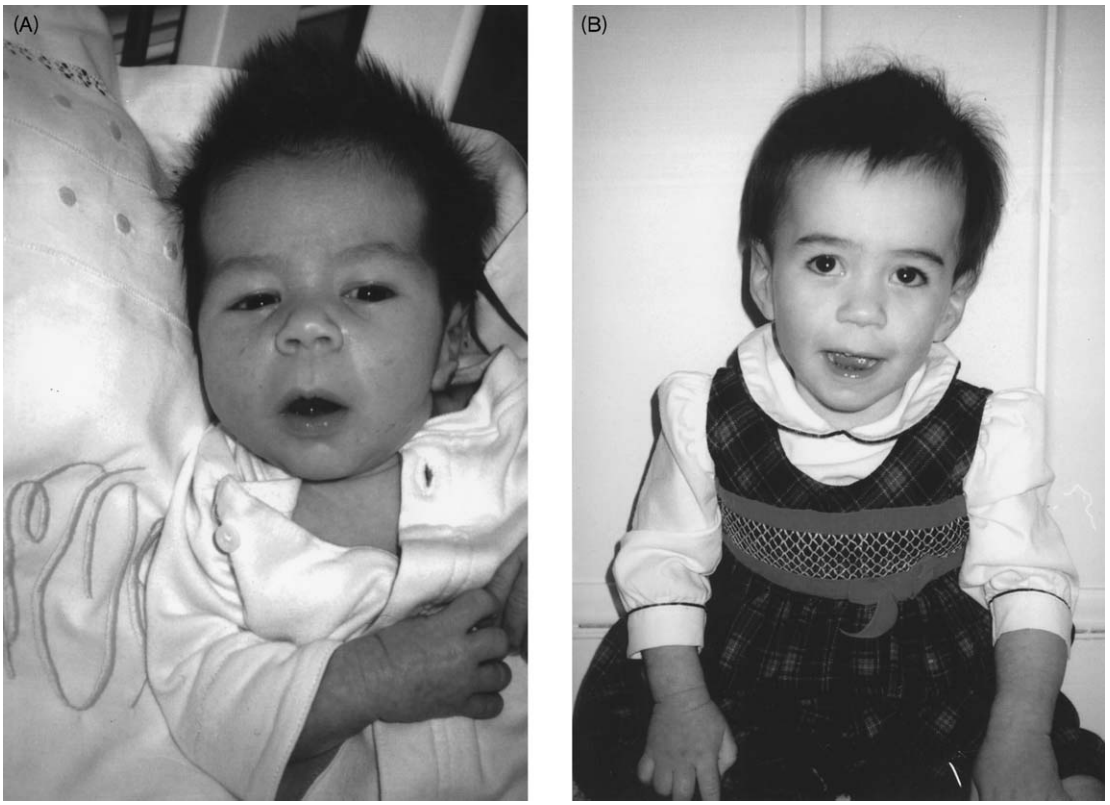
Fig. 1



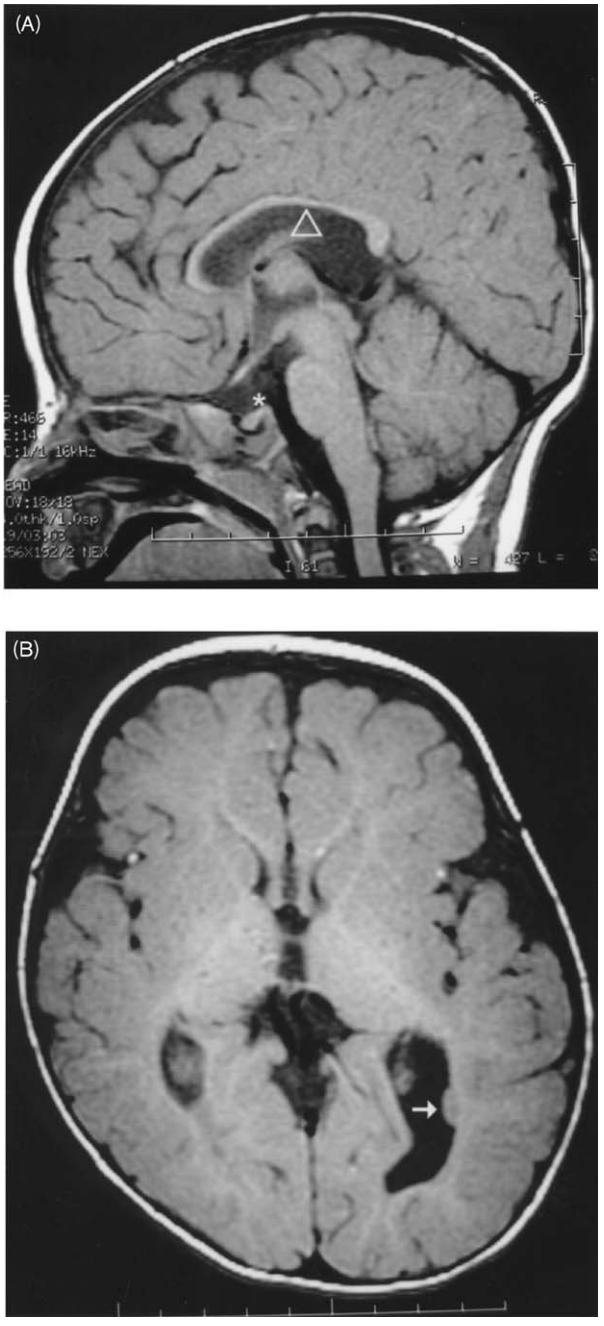
(A) Frontal view of the patient at age two months showing deep-set eyes and a small chin. (B) Frontal view of the patient at age 20 months showing mild dysmorphic facial features.

al., 2000; Bonaglia *et al.*, 2001). Other less common features include dolicocephaly, dysplastic ears, pointed chin, ptosis, epicanthic folds, saddle nose, fleshy hands, dysplastic toenails, increased tolerance to pain, chewing behavior, and tendency to overheat. The deletion typically involves the terminal band 22q13.3, and has been associated with both familial and *de-novo* translocations (Phelan *et al.*, 2001). The incidence of this syndrome is unknown. Autism has also been described to occur in patients with this deletion syndrome (Goiset *et al.*, 2000).

Fluorescent in situ hybridization (FISH) analysis in our patient using the ARSA probe revealed a deletion in the distal part of 22q (22q13.31). Deletions in this syndrome vary widely in size from 130 kb to over 9 Mb; however all 45 cases tested by Wilson *et al.* (2003) for the terminal region at the site of SHANK3 were deleted for this gene. ProSAP2 has been postulated as a potential candidate gene for this syndrome because it is preferentially expressed in the cerebral cortex and cerebellum (Bonaglia *et al.*, 2001). This gene encodes for a scaffold protein involved in the postsynaptic density of excitatory synapses haploinsufficiency of the gene SHANK3, which codes for a structural protein of the postsynaptic density. This seems to be a major causative factor in the neurological symptoms of 22q13 deletion syndrome (Wilson *et al.*, 2003). More detailed chromosomal analysis is needed to determine the minimal critical region in order to elucidate specific genes involved in different syndromes described in this deletion.

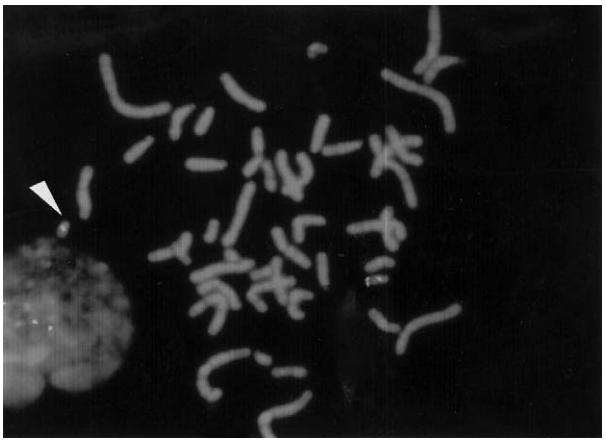
Molecular studies of seven patients with the syndrome revealed no correlation between the severity of the phenotype and the proximal extent of the deletion (Nesslinger *et al.*, 1994). The chromosomal deletion may be subtle and may go undetected on routine cytogenetic analysis, as was the case with our patient's first chromosomal study in the neonatal period. Infants with hypotonia, or those suspected to have this syndrome should have high-resolution chromosome analysis and FISH studies or molecular analysis to make the diagnosis (Phelan *et al.*, 2001). The smallest region of overlap between the 22q13.3 deletion patients (critical region) extends from below locus D22S97 proximally to below arylsulfatase A (ARSA). Since ARSA is the most distally mapped locus on chromosome 22q, it has not been possible to access the extent of the deletions below this

Fig. 2



Brain MRI at age six months: (A) Decreased signal from the region of the posterior pituitary gland (asterisk) and thin corpus callosum (arrow); (B) small subependymal gray matter heterotopia in the left occipital horn (arrow) and decreased overall white matter volume.

Fig. 3



FISH analysis of the proband with TUPLE1 showing the deleted chromosome 22 (arrow).

locus. The molecular characterization spans the terminal 130 kb of 22q (Wong *et al.*, 1997).

The patient also had central diabetes insipidus (CDI) that was diagnosed at the age of two days. The incidence of diabetes insipidus in the general population is 3 in 100,000 (Saborio *et al.*, 2000). CDI is a heterogeneous condition characterized by polyuria and polydipsea due to deficiency of the peptide hormone arginine vasopressin that is secreted by the posterior pituitary gland and regulated by paravestricular and supraoptic nuclui (Phelan *et al.*, 2001; Maghnie *et al.*, 2000).

Mutations in the arginine vasopressin-neurophysin II gene may cause autosomal dominant familial CDI by directing the production of a folding incompetent precursor that prevents the expression of the normal allele via a cytotoxic effect on the magnocellular neurons (Ritting *et al.*, 2002). The human gene for oxytocin-neurophysin I was mapped to chromosome 20p13 by in situ hybridization (Rao *et al.*, 1992). Many allelic variants of CDI have been described. CDI was also reported in a newborn with midline 46, XY, del (7) (pter→q34) and craniofacial defects (Ng *et al.*, 1997).

CDI is very rare in the neonates (Fenton and Kleinman, 1974; Stapleton and DiGeronimo, 2000; Fjellestad-Paulsen *et al.*, 1998). Spontaneous remission of CDI may occur (Fenton and Kleinman, 1974; Nagae *et al.*, 1994; Martini *et al.*, 1998). Transient diabetes insipidus has been reported in a newborn that recovered by age five months (Fenton and Kleinman, 1974). Chronic CDI has remitted spontaneously despite persistent deficiency of vasopressin (Saborio *et al.*, 2000). The mechanism of remission is not known. Anterior pituitary failure has been described in a 19-year-old patient with a balanced translocation between 11q24 and 22q13 (Yang *et al.*, 2001). The etiology of the reversible central diabetes insipidus in this patient is still unexplained.

We report a child with 46, XX, de l (*22*) (q13.31). ish del (*22*) (q13.31) (TUPLE 1 + , ARSA–) and reversible central diabetes insipidus. To our knowledge, this association has not been reported previously. Infants with hypotonia, or those suspected to have this syndrome should have high-resolution chromosome analysis and fluorescent in situ hybridization (FISH) studies or molecular analysis, since the chromosomal deletion may be subtle and may go undetected on routine cytogenetic studies. The association of *22*q13 deletion syndrome with central diabetes insipidus is reported for the first time.

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