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Dandy–Walker Malformation, Genitourinary Abnormalities, and Intellectual Disability in Two Families

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Abstract

We report on two families, each with documented consanguinity and two affected with overlapping features of Dandy-Walker malformation, genitourinary abnormalities, intellectual disability, and hearing deficit. This phenotype shares similar findings with many well-known syndromes. However, the clinical findings of this syndrome categorize this as a new syndrome as compared with the phenotype of already established syndromes. Due to parental consanguinity, occurrence in siblings of both genders and the absence of manifestations in obligate carrier parents, an autosomal recessive pattern of inheritance is more likely. The authors believe that these families suggest a novel autosomal recessive cerebello–genital syndrome. Array CGH analyses of an affected did not show pathological deletions or duplications.

Keywords

autosomal recessive; Dandy–Walker malformation; extremity abnormalities; genitourinary abnormalities; cerebello–genital syndrome

INTRODUCTION

Cerebellar anomalies and genital abnormalities are relatively common findings in the context of inherited human malformation syndromes. There are numerous syndromes that carry specific genitourinary abnormalities and cerebellar malformations together as diagnostic handles. For these group of syndromes, which we may call as cerebello–genital syndromes, the accompanying major and minor dysmorphisms point to a certain diagnosis.

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Here, we describe four patients with overlapping features of central nervous system malformations, characterized by features of Dandy-Walker malformation, hearing deficit, genitourinary abnormalities, and intellectual disability that we believe does not fit into any hitherto known syndrome.

CLINICAL REPORTS

Family 1 (927)

The proband (927-III-2) from an Egyptian family was born to a first-degree cousin marriage. Parents were healthy with normal cognitive abilities. Family history was unremarkable, except a similarly affected cousin (Fig. 1a).

The patient was a 3-year-7-month-old female born by cesarean after an uneventful pregnancy. Birth weight was 2.7 kg ($-1.1SD$), head circumference 33 cm ($-0.8SD$), and length 47cm ($-1SD$). Anal atresia, single cloacal opening, and underdeveloped labia majora were detected at birth. Because of this notable malformation, the patient was subjected to noninvasive imaging procedures to identify other congenital anomalies. The echocardiography was normal; abdominopelvic sonography showed normal but smaller than average-sized kidneys and cranial ultrasound was suggestive of Dandy-Walker malformation. At the age of 3 months, colostomy was performed. Patient was first evaluated neurologically at 9 months of age. She had global developmental delay, was only able to support the head, and recognize her mother. Anthropometric measurements showed weight 6.25 kg ($-3SD$), length 64 cm ($-2.4SD$), and head circumference 42 cm ($-1.8SD$). Facial features revealed a broad forehead, sparse eyebrows, epicanthal folds, downslanted palpebral fissures, deeply set eyes, blue sclera, under-developed ala nasi, and low-set ears, which were all not present in the parents. Bilateral single transverse palmar crease and broad halluces were noted in the extremities. General examination was unremarkable except for the exit of colostomy and hypoplastic labia majora and minora. Motor examination showed hypotonia with brisk reflexes.

Reevaluation at the age of 3 years and 7 months showed moderate intellectual delay, ability to say few words, stand, and walk supported. Height was 91 cm ($-1.6SD$), weight was 12.5 kg ($-2.5SD$), and head circumference was 47 cm ($-2SD$). Dysmorphic facial characteristics had become more prominent (Fig 2a) and hypotonia was still present. Genital examination revealed the cloacae-like single orifice (Fig. 2b).

Additional studies revealed normal hearing and vision. Dandy-Walker malformation was detected in her cranial magnetic resonance imaging (MRI), with massive cystic enlargement of the fourth ventricle, elevation of the torcula/tentorium, and hypoplastic cerebellar vermis (Fig 3a). Chromosome analysis yielded a normal female karyotype (46,XX).

Although not examined, the parents described a similarly affected deceased cousin with intellectual disability and microcephaly, born to a first-degree consanguineous marriage. Previous examination notes retrieved from this male affected also described unilateral preaxial polydactyly and arthrogryposis, but imaging studies of brain and abdomen were not available.

Family 2 (1040)

Similarly affected cousins from Jordan were born to two first-degree cousin marriages within the same family. Parents had normal phenotypes with no systemic abnormalities (Fig 1b).

Affected female was a 3.5-year old who was delivered by cesarean due to antenatal findings of a brain cyst and hydrocephalus. Her birth centiles were unknown. Following delivery, she was observed to have imperforate anus and urogenital fistula, for which she was admitted to the hospital and underwent surgery. She could sit without support at 2 years of age and at 3.5 years, she was documented to have a broad forehead, deeply set eyes, blue sclera, underdeveloped ala nasi, and overhanging nasal tip that were not present in first-degree relatives (Fig 2c). She could not walk unsupported and had no speech.

Additional investigations showed normal thyroid function and vision. Sensorineural deafness was determined after clinical suspicion. Ultrasonography revealed hypoplastic kidneys. Chromosome analysis yielded a normal female karyotype (46,XX). MRI studies revealed Dandy–Walker malformation, nearly identical in appearance to family 927, with mild ventriculomegaly (Fig 3b).

The patient was reevaluated at 8 years of age. Her height was 104 cm (−4/−5 SD); weight was 15 kg (−4/−5 SD), and head circumference was 48 cm (−4 SD). Dysmorphic features of the face had become more evident with age. She still could not walk unsupported and did not have any speech development.

Her similarly affected cousin was examined at 5 months of age. His measurements were not available. He had similar periorbital and perioral findings as the other two patients (Fig 2d). Head control was not achieved. In his medical history, it was documented that he had surgery for imperforated anus. Additional investigations revealed sensorineural deafness, hypothyroidism, and a single kidney. MRI revealed a hypoplastic and downwardly displaced vermis, elongated fourth ventricle, mega cisterna magna, but no evidence of torcular/tentorium elevation, and thus did not meet criteria for Dandy–Walker malformation, but was within the same spectrum (Fig 3c).

Array-CGH analysis of the patient DWM-1040-3-2 showed six copy number variants (CNVs). None of the CNVs overlapped with a polymorphism listed in the database of genomic variants (DGV) (<http://projects.tcag.ca>) for healthy individuals and were judged likely to be non-pathogenic. Further molecular testing is planned in both families to unravel the underlying molecular pathology.

DISCUSSION

Clinical findings in the patients are summarized in Table I and compared to syndromes that bear some resemblance. Prominent findings in our patients were Dandy–Walker malformation, genitourinary abnormalities, intellectual disability, and hearing loss.

The association of anal and thumb (preaxial polydactyly, triphalangeal thumb) anomalies accompanied by structural and functional renal anomalies, hearing loss, and hypothyroidism

in our patients suggests a picture similar to autosomal dominant Townes–Brocks syndrome (TBS). Nearly 25% of patients with TBS have developmental delay and 10% have intellectual disability [Botzenhart et al., 2007; Miller et al., 2012]. The only central nervous system abnormalities reported, thus far have been Arnold–Chiari malformation type I, cranial palsies of nerves VI and VII, and hypoplasia of the dorsal part of corpus callosum observed in just a few patients [Cameron et al., 1991; Botzenhart et al., 2005; Harrison et al., 2012]. However, neurological abnormalities seem to be a constant feature of the phenotype of our patient group and no TBS patients with Dandy–Walker malformation have been reported so far. The clear autosomal recessive inheritance model in our families (similarly affected cousins of both genders and healthy related parents) and the presence of various severe CNS abnormalities exclude TBS.

Nevertheless, the *SALL1* gene was sequenced in patients 1 and 2, considering the probability of de novo mutations and these genes were excluded as the cause of this particular phenotype.

Radial ray abnormality, deafness, imperforate anus, and renal anomalies are features present both in our group of patients and in patients with Duane–Radial Ray syndrome (DRRS, OMIM # 607323) [Aalfs et al., 1996]. However, the absence of intellectual disability, specific eye findings and central nervous system abnormalities, and the dominant mode of inheritance in DRRS argue against this syndrome. We have sequenced the *SALL4* gene that is responsible for this phenotype and found no deleterious changes.

Another probable diagnosis for our patients may be Smith–Lemli–Opitz syndrome (SLO, OMIM # 270400). Though not common, holoprosencephaly, preaxial polydactyly, renal anomalies are features of SLO. Genital changes in males with SLO range from ambiguous genitalia to male pseudohermaphroditism, and females have hypoplastic labia [Kelley and Hennekam, 2000]. Our only male patient had normal external male genitalia. Moreover, imperforated anus, which is a constant feature in our patients, is not a feature of SLO. Cholesterol and 7-dehydrocholesterol values were tested and found to be within normal limits. Sequencing of *DHCR7* gene did not reveal any deleterious mutations.

Patients with VATER association (OMIM # 192350) also have clinical features of anal atresia, renal abnormalities, and preaxial polydactyly [Solomon et al., 2012]. However, the presence of Dandy–Walker abnormality, hearing deficit, moderate-to-severe intellectual disability, and the recessive inheritance pattern in our patients make VATER association an unlikely diagnosis.

CHARGE syndrome (OMIM # 214800) is another recessive condition that has some overlaps with our set of patients. Though deafness, intellectual disability, and imperforate anus are present in our patients as well, the fact that our patients have central nervous system abnormality types, which are not typically encountered in CHARGE syndrome and the extremity anomalies in CHARGE being almost always of the ulnar side, sets this condition apart from CHARGE syndrome [Tellier et al., 1998]. We have sequenced the *CHD7* gene that is responsible for this phenotype and found no deleterious changes.

We conclude that the present constellation of signs and symptoms in our four patients have not been reported previously. Occurrence in cousins of both sexes and the absence of symptoms in parents support the notion of recessive inheritance.

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FIG. 1. Pedigrees of the two families showing double first cousin consanguinity and affecteds of both sexes suggests a classical autosomal recessive inheritance.

FIG. 2.

a and c: Triangular face, broad forehead, low set ears, laterally extended and highly arched eyebrows, deeply set eyes, underdeveloped ala nasi, and broad columella are observed. b: Cloaca-like single opening in the patient. (d) Mild features evident during infancy.

FIG. 3.

a: Large posterior fossa cyst elevating the torcular herophili and sinus rectus (arrowhead). The hypoplastic vermis is everted over the cyst [white arrow]. Thinned occipital squama is also seen [white longer arrows]. b: Elevated torcular herophili is seen [arrowhead]. c: Mildly superiorly rotated hypoplastic vermis [arrowhead] and thin corpus callosum is noted. No other abnormalities were present in all of the images from these three patients.

TABLE I

Clinical Features of Similar Syndromes and Our Patients

	Townes-Brocks syndrome	Duane–Radial Ray syndrome	Smith–Lemli–Opitz syndrome	VATER association	CHARGE syndrome	DWM-927-3-2	DWM-927-3-4	DWM-1040-3-2	DWM-1040-3-4
Mode of inheritance	AD	AD	AR	Isolated cases	AD	AR	AR	AR	AR
Microcephaly	+	–	+	–	+	+	+	+	N/A
Ear malformations	+	+	+	–	+	+	–	+	+
Hearing loss	+ [Sensorineural]	+ [Sensorineural]	–	–	+ [Sensorineural or mixed]	–	N/A	+ [Sensorineural]	+ [Sensorineural]
Eye anomalies	+	+	+	–	+	–	–	–	–
Cardiovascular findings									
Septal defect	+ [Ventricular]	+ [Ventricular, Septal]	+ [Ventricular, Septal]	+ [Ventricular]	+ [Ventricular, septal]	–	N/A	–	–
Tetralogy of Fallot	+	–	–	+	+	–	N/A	–	–
Patent ductus arteriosus	–	–	+	+	+	–	N/A	–	–
Gastrointestinal findings									
Anal stenosis	+	+	–	–	+	–	–	–	–
Imperforate anus	+	+	–	+	+	+	–	+	+
Anterior placement of anus	+	–	–	–	–	–	–	–	–
Fistula	+ [Rectovaginal/perineal]	–	–	+ [Tracheoesophageal]	+ [Tracheoesophageal]	–	–	–	+ [Urogenital]
Esophageal atresia	–	–	–	+	+	–	–	–	–
Pyloric stenosis	–	–	+	–	–	–	–	–	–
Genitourinary findings									
Hypoplastic kidneys	+	+	–	–	–	+	N/A	–	+
Dysplastic kidneys	+	–	–	+	+	–	N/A	–	–
Renal agenesis	–	+	+	+	–	–	N/A	+	–
Micropenis	–	–	+	–	+	–	N/A	–	–
Hypospadias	+	–	+	+	–	–	N/A	–	–
Bifid scrotum	+	–	+	–	–	–	N/A	–	–
Cryptorchidism	+	–	+	–	–	–	N/A	–	–
Bifid uterus	+	–	–	–	–	–	N/A	–	–

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	Townes-Brocks syndrome	Duane-Radial Ray syndrome	Smith-Lemli-Opitz syndrome	VATER association	CHARGE syndrome	DWM-927-3-2	DWM-927-3-4	DWM-1040-3-2	DWM-1040-3-4
Skeletal findings									
Vertebral anomalies	-	+	-	+	-	-	-	-	-
Scoliosis	-	+	-	+	-	-	-	-	-
Radial ray anomalies	+	+	-	+	-	+	-	-	-
Ulnar ray anomalies	-	-	-	-	+	-	-	-	-
Thumb anomalies	+ [Triphalangeal, bifid, broad]	+ [Triphalangeal, absent, hypoplastic]	+ [short, proximally placed]	+ [Triphalangeal, hypoplastic]	-	-	-	-	-
Polydactyly	+ [Preaxial]	+ [Preaxial]	+ [Postaxial]	+ [Preaxial]	-	-	+ [Preaxial]	-	-
Syndactyly	+ [2-3f, 3-4f,t]	+	+ [2-3t]	+	-	-	-	-	-
Endocrine features									
Hypothyroidism	+ [rare]	-	-	-	+	-	N/A	-	+
Neurological findings									
Intellectual disability	+ [rare]	-	+	-	+	+	+	+	+
Seizures	-	-	+	-	-	-	-	-	-
Hypotonia	-	-	+	-	-	+	+	+	+
Behavioral manifestations	-	-	+ [Self injurious, aggressive]	-	+ [Autistic]	-	-	-	-
MRI findings	Arnold-Chiari malformation type I, cranial palsies of nerves VI and VII, hypoplasia of the dorsal part of corpus callosum	-	Frontal lobe hypoplasia, periventricular gray matter heterotopias	-	-	Dandy-Walker malformation	N/A	Dandy-Walker malformation	Hypoplastic vermis

AD, autosomal dominant; AR, autosomal recessive; f, finger; N/A, not available; t, toe.