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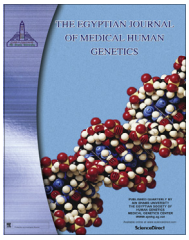

CASE REPORT

Absent abdominal muscles, nephro-urologic abnormalities, and severe neurologic damage in an infant with 3 chromosomal duplications: A novel syndrome?

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Abstract Absent abdominal muscles, cryptorchidism, and hydroureteronephrosis are known to occur in the prune belly syndrome (PBS).

We present a male with absent abdominal muscles, severe neurologic damage, with global developmental delay, hydroureteronephrosis, and cryptorchidism. The patient also had arthrogryposis multiplex congenital, low set ears, short neck, micrognathia, bilateral total ptosis, and bilateral clubfeet. Genetic testing (CGH array) revealed 3 novel duplications of unknown clinical significance at 7q11.23, 9q22.32 (PTCH 1 gene), and 12q21.32 (CEP 290 gene).

Conclusion: We feel that our patient represents a novel entity, henceforth not described in the literature.

1. Introduction

Syndromes associated with absent abdominal muscles include the prune belly syndrome (PBS), and Berdon syndrome. PBS consists of absent abdominal muscles, hydrouretero-nephrosis, and cryptorchidism [1,2].

Berdon syndrome or Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome may also be associated with

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hydrouretero-nephrosis secondary to bladder distention [3]. Urethral obstruction is one of the disorders associated with abdominal wall deficiency. Fetal bladder obstruction may result in absent abdominal muscles, cryptorchidism, and club feet [4].

Here we describe clinical and genetic features of a 25 day old boy with absent abdominal muscles, hydroureteronephrosis, neurodevelopmental delay, seizures, and carrier of microduplication in 7q11.23, 9q22.32, and 12q21.32.

2. Clinical report

A 25 day old boy was referred to our service because of hydroureteronephrosis.

The boy was born to a consanguineous first cousins coming from an extended family with inbreeding. Patient was born by cesarian section at 38 weeks of gestation. Antenatal oligohydramnios and decreased fetal movements were noted. Apgar score was 5 and 7 at 1 and 10 min respectively. Birth weight was 3.8 kg m (50th percentile). Patient spent 17 days at the neonatal intensive care unit because of respiratory distress, but he did not need mechanical ventilation. Patient had history of recurrent chocking. The mother had one abortion at 5 months. There were no similar cases in siblings.

His weight was 3.5 kg m (fifth percentile), length 48 cm (< second percentile), and head circumference 36 cm (10th percentile). Facial dysmorphism including micrognathia, bilateral total ptosis, low set ears, were noted. Patient had a short neck, high arched palate, long philtrum, pinpoint pupils, clenched hands with bilateral simian creases, contractures at elbows and knees, bilateral club feet, undescended testicles, and palpable kidneys. The patient had an absent cry and moro reflex.

Laboratory investigations: serum creatinine 0.3 mg/dl, calcium 9.2 mg/dl.

Imaging; voiding cystourethrogram revealed bilateral grade 5/5 vesicoureteral reflux with duplex ureters; renal ultrasound: bilateral hydroureteronephrosis with trabeculated urinary bladder; hearing was normal. Skeletal survey was done and showed bilateral dysplasia of the hip. An echocardiogram was normal. Patient had global developmental delay with seizures. Electroencephalogram showed burst suppression which was treated with pyridoxine. Brain magnetic resonance imaging (MRI), which was normal at 1 month, showed brain atrophy at 7 months.

The patient had recurrent urinary tract infections with urine retention, and recurrent pneumonias. The patient died at home from aspiration pneumonia at the age of 1 year.

3. Methods

Karyotyping was not done.

The patient was investigated by array comparative genomic hybridization (Array-CGH). Genetic testing was done at CGC genetics laboratory:

After DNA extraction from peripheral blood, Chromosomal Microarray Analysis was performed using Affymetrix's Cytoscan HD/750Kplatform. This array has a density of 1.953.246 oligonucleotides and 743.304 SNPs, in a total of 2.700.000 markers distributed along all genome, with a median resolution of 4–9 Kb. Hybridization results were analyzed using ChAS Software (Affymetrix), that detects genetic loss and/or gains, loss of heterozigozity (LDH) and uniparental disomy (UPD). The reference genome' annotation used was Human Genome Build hg19 (UCSC genome browser February 2009). Limitations: CGH method does not allow detection of genetic loss and gain with a resolution below the one specified, as well it does not detect balanced chromosomal rearrangements, triploidy and alterations in mosaic with less than 20% expression.

4. Results

Microarray showed 7qll.23 (74590887–75091879)x3, 9qZ2.32 (98Z29524–98234S7S)x3, 12q21.32 (88478012–88493094)xl.

The array analysis detected the-following alterations: a 500 Kbp duplication in 7q11.23 (containing the genes *GTF2lPl*, *lOC100093631*, *GATSL2*, *SPOYE8P*, *PHS2L2*, *STAG311*, *lRIM73*, *TRIH74*, *NSUN5P1* and *POH121C*), a 5 Kbp duplication in 9q22.32, containing the *PTCH1* gene and a 15 Kbp duplication in 12q21.32, containing the *CEP290* gene.

5. Discussion

Our patient had microcephaly, severe neurologic damage, seizures and central hyperthermia, in addition to arthrogryposis multiplex congenita, bilateral ptosis, miosis, and absence of the abdominal muscles. Our patient neither had PBS nor Berdon syndrome. A hugely dilated fetal bladder may result in absence of the abdominal muscles [4].

Arthrogryposis may be associated with WBS and PBS [5–7], and urinary abnormalities [8,9]. Neurogenic arthrogryposis multiplex congenita has been associated with other congenital anomalies [6] including goniodysgenesis of the eye [10], and malignant hyperthermia [11]. Decreased fetal movements lead to contractures.

Genetic testing (CGH array) revealed 3 novel microduplications at 7q11.23, 9q22.32 (PTCH 1 gene), and 12q21.32 (CEP 290 gene). Our patient had a genomic disorder consisting of microduplications in the long arms of three chromosomes, 7, 9, and 12.

Multiple contiguous gene submicroscopic deletions on the long arm of one chromosome 7 (del 7q11.23) results in the neurodevelopmental disorder, Williams Beuren syndrome (WBS) [12].

While seizures rarely occur in WBS [13], few cases with infantile spasms have been reported [14]. On the other hand, seizures are common in Williams–Beuren duplication syndrome.

WBS region duplication syndrome or chromosome 7q11.23 duplication syndrome is a multisystem neurodevelopmental disorder with severe expressive language delay, autism, hypotonia, cognitive defects, and cryptorchidism [15,16].

In general, microduplication syndromes produce the opposite clinical phenotype of microdeletion syndromes.

In addition our patient had duplications in 9q22.32 and 12q21.32. We do not know the contribution of the other microduplications at chromosomes 9 and 12 to the clinical phenotype.

Besides 7q11.23 microduplication, facial dysmorphism occurs in 9q22.32 and 12q21.32 microduplications [17,18].

Unfortunately no parental genomic testing was done, to know whether the microduplication occurred denovo or was transmitted from a parent.

These findings may be due to human genomic instability and inbreeding in the patient's family, resulting in etiologic heterogeneity.

We believe that our patient represents a novel entity, henceforth not described in the literature.

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