Endocrinology, Diabetes & Metabolism CASE REPORTS

A Arefzadeh and others | 2q37 deletion syndrome: a case report and review

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Brachydactyly mental retardation syndrome with growth hormone deficiency

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Summary

Deletion of chromosome 2q37 results in a rare congenital syndrome known as brachydactyly mental retardation (BDMR) syndrome; a syndrome which has phenotypes similar to Albright hereditary osteodystrophy (AHO) syndrome. In this report, we describe a patient with AHO due to microdeletion in long arm of chromosome 2 [del(2)(q37.3)] who had growth hormone (GH) deficiency, which is a unique feature among reported BDMR cases. This case was presented with shortening of the fourth and fifth metacarpals which along with AHO phenotype, brings pseudopseudohypoparathyroidism (PPHP) and pseudohypoparathyroidism type Ia (PHP-Ia) to mind; however, a genetic study revealed del(2)(q37.3). We recommend clinicians to take BDMR in consideration when they are faced with the features of AHO; although this syndrome is a rare disease, it should be ruled out while diagnosing PPHP or PHP-Ia. Moreover, we recommend evaluation of IGF 1 level and GH stimulation test in patients with BDMR whose height is below the 3rd percentile.

Learning points:

- Clinicians must have brachydactyly mental retardation (BDMR) syndrome in consideration when they are faced with the features of Albright hereditary osteodystrophy.
- Although BDMR syndrome is a rare disease, it should be ruled out while diagnosing PPHP or PHP-Ia.
- Evaluation of IGF1 level in patients diagnosed with BDMR whose height is below the 3rd percentile is important.

Background

Deletion of chromosome 2q37 results in a rare congenital syndrome known as brachydactyly mental retardation (BDMR) syndrome (1), which presents with obesity, round face, short stature, brachydactyly type E (BDE), congenital heart defects, autism and other intellectual disabilities, mild-to-moderate mental retardation syndrome, developmental defects and seizures (2). These symptoms are similar to Albright hereditary osteodystrophy (AHO) syndrome (3).

Shortening of the fourth and fifth metacarpals is seen in various disorders in addition to BDMR; common etiologies are pseudopseudohypoparathyroidism (PPHP), pseudohypoparathyroidism type Ia (PHP-Ia), Turner syndrome and post-infection complications (e.g. osteomyelitis) (4, 5). Since PHP-Ia and PPHP have AHO phenotype (6), they are important differentials of BDMR syndrome.

In this case report, we describe a patient with AHO phenotype due to microdeletion in long arm of chromosome 2[del(2)(q37.3)] who had growth hormone deficiency.

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Case presentation

An 8-year-old girl of Iranian ethnicity was presented to us with obesity and severe short stature, with her height of 107.5 cm being 4.0 S.D. below the mean. Her important physical examination findings were obesity (BMI = 29.2), mild mental retardation, autistic features, round face, highly arched eyebrows, depressed nasal bridge, hypotonia, joint hypermobility and short fourth and fifth metacarpal and metatarsal fingers (Fig. 1).

She was born at 38th week of gestation, with a spontaneous and uncomplicated delivery. After 2 years, her parents noticed her mental retardation and autism-like features. No other points in her past medical history seemed to be of importance. Father's and mother's height were 186 cm and 169 cm respectively.

During the examinations, the patient was not cooperative with the examining physician and showed aggressive behaviors. Her thyroid was normal in size, texture, consistency and without palpable mass. Puberty staging was normal in breast, axillary and pubis at stage 1 of Tanner scale. No more abnormal findings were observed in her examinations, other than the earlier mentioned ones.

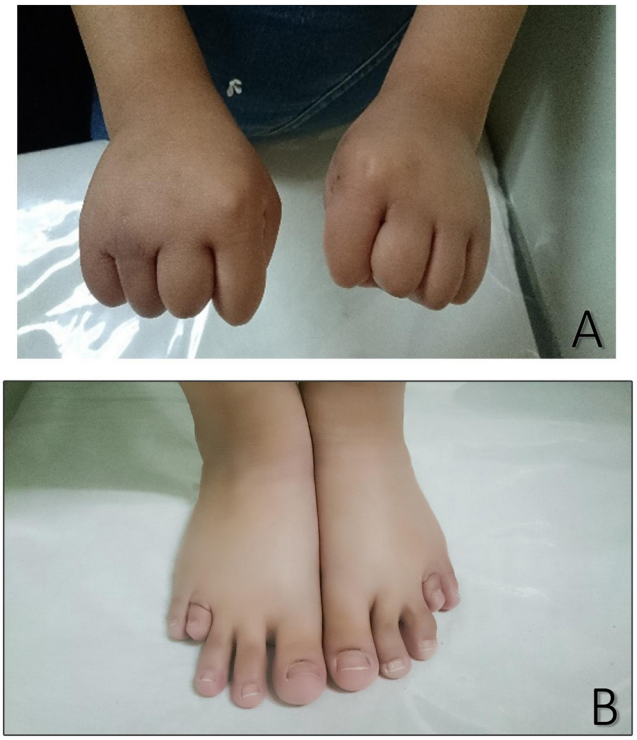

Figure 1
Apparent shortening of 4th and 5th metacarpals and metatarsals in patient's hands (A) and feet (B), respectively.

Blood panel tests were performed and findings are summarized in Table 1, of which the most important data were IGF-I value was 22 ng/mL lower than the normal age-sex specific reference ranges: (39–396 ng/mL, S.D. score = −3.14). The low IGF-1 was important result in screening for GHD. A clonidine test was performed to confirm GH deficiency with a peak GH of only 1.3 ng/mL.

Plain radiographic studies of the hands and feet showed fourth and fifth metacarpal and metatarsal shortening, and bone age of 8 years (Fig. 2).

Table 1 Patient's blood panel.

Parameters	Value	Normal range
Fasting blood sugar (mg/dL)	76.2	80–100
Uric acid (mg/dL)	5.1	3–6.4
Serum Mg (mg/dL)	2.9	1.6–3
Calcium (mg/dL)	9.6	8.4–10.4
Phosphate (mg/dL)	4.7	3.2–5.4
Intact PTH (pg/mL)	44.30	15–65
Potassium (mEq/L)	4.6	3.5–5.1
Alkaline phosphatase (IU/L)	352	180–1200
Zinc (µg/dL)	90	70–100
T3 (ng/dL)	197	80–230
T4 (µg/dL)	11.5	4.6–12
Free T4 (ng/dL)	1.15	0.7–1.9
TSH (µIU/mL)	1.030	0.3–3.5
25-Hydroxy vitamin D (ng/mL)	36.4	30–100**
Serum albumin (g/dL)	4.2	3.5–5.3
24 h urine Ph/Cr ratio	0.97	0.153–1.44
24 h urine Ca/Cr ratio	0.07	≤0.2
FSH (mIU/mL)	0.2	2.8–11.3
LH (mIU/mL)	0.1	1.1–11
Testosterone (ng/dL)	5.0	<7–20
DHEA SO_4 (µg/dL)	79.1	44–332
17 OH progesterone (ng/mL)	0.439	<2.5
Cortisol (8AM) (µg/dL)	5.539	4–25
IGF-1 (ng/mL)	22	39–396†
Insulin (µIU/mL)	10	1.4–14
Estradiol (pg/mL)	5.9	0.1–160
Progesterone (ng/mL)	0.3	0.15–1.4
GH (ng/mL)		
Basal	0.5	0.01–4
After clonidine test		
GH 30′	0.2*	
GH 60′	1.3*	
GH 90′	1.2*	
GH 120′	0.6*	
24 h urine calcium (mg/24 h)	56	50–300
24 h urine phosphorus (mg/24 h)	399	385–1300

*Deficiency: (A normal response following stimulation tests is a peak GH concentration >5 ng/mL in children and >4 ng/mL in adults. For children, some experts consider GH values between 5 ng/mL and 8 ng/mL equivocal and only GH peak values >8 ng/mL as truly normal); **sufficient range; †normal age-sex specific ranges.

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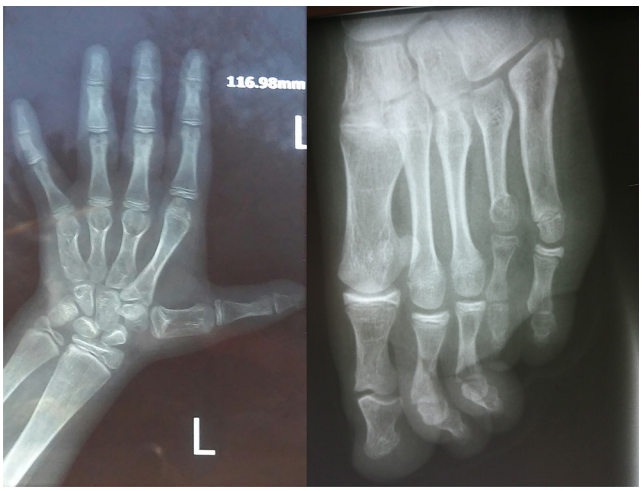

Figure 2
Plain radiograph studies of left foot and hand.

Investigations

The patient had AHO phenotype, however, she had normal serum levels of calcium, phosphorus and parathyroid hormone; this scenario is commonly seen in PPHP. Shortening of the fourth and fifth metacarpals is seen in Turner syndrome. The patient did not have any past histories of trauma or infection of her feet and hands; therefore, post infectious complications were ruled out. Genetic studies were performed to rule out PPHP and Turner syndrome.

Karyotype and conventional cytogenetic study

Fifteen metaphase spreads from the patient were analyzed with a high-resolution 500-550 GTG banding according to standard procedures using a lithium-heparin peripheral blood sample. The test showed deletion in long arm of chromosome 2, which was occurred in all spreads [46,XX,del(2)(q37.3)]. Karyotype was 46XX and Turner syndrome was ruled out.

Fluorescence *in situ* hybridization

A fluorescence *in situ* hybridization (FISH) analysis was performed on metaphase chromosomes from peripheral blood lymphocytes. The slides were prepared according to standard cytogenetic procedures. Double-colored FISH probes including Tel 2q (Spectrum Red) and CEP 17 (Spectrum Green) as control probes, using probe direct labeled fluorescent Vysis DNA probe kit (Abbott Molecular) were applied. Thirty interphasic and metaphasic cells were screened. The result of GTG banding was approved. Deletion (2)(q37.3) was detected and the analysis showed 46,XX,del(2)(q37.3).ish del(2)(q37.3q37.3)(DS244-)[15]. nuc ish(DS2447x1)[15].

Patient's parents did not have any clinical manifestations of BDMR syndrome or PPHP and genetic studies were performed on them, which did not reveal PPHP or BDMR syndrome.

Interventions and follow-up

Since the patient had GH deficiency as well as a short stature, she was treated with biosynthetic growth hormone (Pen Nordilet 5 mg/1.5 CC) approximately with a dosage of 0.6 mg/day or 4.2 mg/weekly. Her growth velocity improved after 2 years. The patient's height increased to 122.5 cm (near 3rd percentile), and 140 cm (above the 50th percentile), respectively, 1 year and 2 years after GH therapy. The patient's weight increased from 33.8 kg before treatment to 41 kg and 49 kg, respectively, 1 year and 2 years after GH therapy. The patient's BMI decreased from 29.2 before treatment to 27.32 and 25, respectively, 1 year and 2 years after GH therapy. The chart of height and weight is demonstrated in Fig. 3.

She was referred to the psychology and speech therapy departments for treatment of behavioral and speech disorders. She was also referred to the cardiology department to assess probable cardiovascular complications; no abnormalities were found in her cardiovascular evaluation. New hormone panel tests were performed which did not show gonadal axis activity or an increase in sexual hormones; and her staging of puberty was within normal range.

Discussion

Deletions of 2q37 have been described clinically with obesity, overweight, moon face, short stature, intellectual deficiency and brachydactyly, resembling AHO syndrome; however, some features are present in this syndrome which are different from AHO, such as congenital hypotonia, cardiovascular disorders, mild-to-severe developmental delays, mental retardation, facial prominent foreheads, frontal bossing, a flat nasal bridge, small or large ears, down turned-corners of the mouth, highly arched eyebrows, depressed nasal bridge, prominent ear helix, epicanthic folds, palpebral fissure slant up, highly arched eyebrows, deep-set eyes, a thin upper lip, prominent lower lip, strabismus, gaze palsy, sparse hair and alopecia areata (7, 8, 9). Bone deformities such as brachymetaphalangism, asymmetrical legs and

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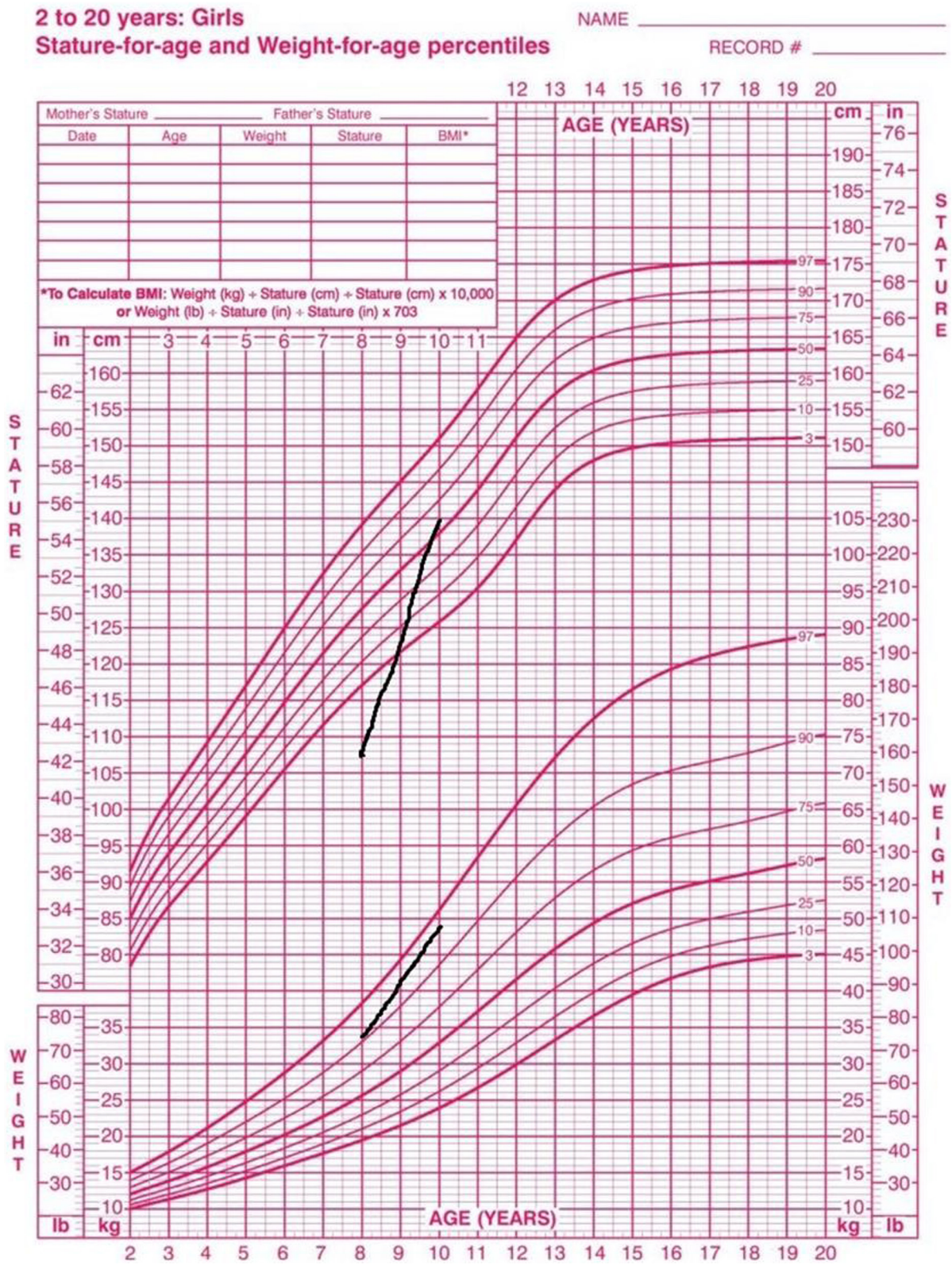

Figure 3
Growth and weight chart.

broad halluces have also been described (8). A study by Casas *et al*. (13) showed that more than 40% of patients were obese or overweight and obesity was seen more commonly in the elderly and subjects with large deletions (13). Hydrocephalus, microcephaly, dilated ventricles and seizures have also been reported in BDMR (14).

Alanine glyoxylate aminotransferase (*AGXT*) gene, is located on chromosome 2q37; and its deletion in BDMR leads to excess excretion of oxalate or primary hyperoxaluria type 1, which results in accumulation of calcium oxalate in the kidney and leads to progressive loss of renal function (15). HDAC4 haploinsufficiency causes psychomotor and behavioral disorders such as self-injuries, aggressive behavior, autistic disorders and developmental delay (16).

Paternal or maternal imprinting

Most patients with the 2q37 microdeletion have a *de novo* chromosome deletion and their parents have normal karyotypes (17). Leroy *et al*. showed that the deletion of 2q37 region was of maternal origin whereas the 2q polymorphism was found in the father (8). In a case series by Leroy *et al*., a paternal origin of the 2q37 deletion was seen in five patients and a maternal origin was seen in four (8). Deletion or mutation of HDAC4 may be inherited in an autosomal dominant manner but is more commonly *de novo* (14, 16).

PHP-Ia and PPHP patients compared to BDMR, have mutations in the GNAS1 gene located on chromosome 20q13.11, which encodes adenylate-cyclase-stimulating G-alpha-protein causing both syndromes to develop AHO syndrome's phenotype. PHP-Ia is caused due to maternal imprinting, while PPHP is caused due to paternal imprinting of the mutation (10).

Risk of cancer

Sakai *et al*. have reported a 2-year-old boy with BDMR, who developed a sex cord-stromal tumor at 3 months of age. Their study showed that haploinsufficiency of the genes at 2q37, rather than segmental duplications of 1p36 or 20p12, has dominant effects on phenotype presentation (18). Drake *et al*. studied a series of sporadic Wilms tumors and found evidence of a tumor suppressor role for a 360-kb critical region at 2q37 encompassing the DIS3 mitotic control homolog (*Saccharomyces cerevisiae*)-like 2 (DIS3L2) locus. Their study showed that loss of heterozygosity at 2q37 was in at least 4% of population with sporadic Wilms' tumors (19).

BDMR with GH deficiency

GH deficiency has been reported in PPHP and PHP-I patients before (20); however, it is not common in BDMR. Cho *et al*. have reported the patient with BDMR, growth retardation and partial GH deficiency that responded well to GH therapy (21). Kitsiou-Tzeli *et al*. have described a 13-year-old girl with BDMR and GH deficiency and compensate hypothyroidism (22). To date, there have been only three reports of GH deficiency in patients with BDMR (21, 22, 23).

Clinicians generally have good knowledge about AHO syndrome; nonetheless, BDMR is a rare genetic disorder that practitioners do not usually face in routine practice. Thus, some BDMR patients may get referred to endocrinologists and get mistakenly diagnosed with PPHP or PHP-Ia. PHP-Ia patients have loss-of-function mutations of the GNAS1 gene, which leads to inability of adenyl cyclase activation when PTH binds to its receptor. However, PPHP patients have normal serum calcium concentrations and no renal tubular resistance to PTH (10).

On the other hand, BDMR patients have normal calcium, phosphorus and parathyroid hormone levels, which result in the characteristic osteodystrophy with normal renal response to the parathyroid hormone and preserved calcium homeostasis. These patients have normal urinary CAMP response to PTH and normal urinary PO4 response to PTH, as observed in our case (4, 11). Shortening of the fourth and fifth metacarpals and metatarsals (brachymetaphalangism) is typically seen in both PPHP and BDMR patients (12).

Management and treatment

Multidisciplinary approach including genetic study, speech therapy, physical therapy, child development, cardiology, neurology, gastroenterology, nutrition/feeding, ophthalmology and audiology disorders are recommended in BDMR patients (14).

Periodic routine primary care and reevaluation by a medical geneticist, periodic management of behavioral and cognitive problems, screening for renal cysts at age of 4 and at puberty are suggested. Moreover, screening for Wilms tumor should be considered in young cases (14).

Clinicians should consider BDMR syndrome in differential diagnosis of patients with AHO phenotype especially when calcium, phosphorous and PTH are normal (PPHP) (3, 11).

We suggest clinicians screen for GH deficiency with an IGF-1 level in patients with BDMR, whose height is

below the 3rd percentile. Although this deficiency has been reported in PPHP and PHP-I patients before (20). To date, there have been only three reports of GH deficiency in patients with BDMR (21, 22, 23). Further studies are required to determine the prevalence and also the etiology of this phenomenon.

Conclusions

We recommend clinicians to take brachydactyly mental retardation syndrome in consideration when they are faced with the features of AHO; although this syndrome is a rare disease, it should be ruled out while diagnosing PPHP or PHP-Ia. Moreover, we recommend evaluation of IGF1 level in patients diagnosed with BDMR whose height is below than 3rd percentile.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
A written signed informed consent was obtained from the patient's parents for publication of the submitted article and accompanying images.

Author contribution statement
Pooyan Khalighinejad gathered the case's information and records and drafted the manuscript. Bahar Ataeinia and Pegah Parvar completed the manuscript drafting and finalized the manuscript. The whole process was under supervision and guidance of Alireza Arefzadeh. He also revised the final version of the manuscript. All the authors read and approved the final version before submission.

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