CASE REPORT

Isolated brachydactyly type E and idiopathic pancreatitis in a patient presenting to a lipid disorders clinic

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Accepted 15 March 2017

SUMMARY

An 18-year-old female tertiary student was referred to a lipid clinic with hypertriglyceridaemia discovered after presentation with acute pancreatitis. The patient's only medication was l-thyroxine for treatment of hypothyroidism. She was overweight, normotensive, with unremarkable facies. However, she had hypermobile hand joints and brachydactyly resulting in loss of left 3–5 and right 4 and 5 knuckle definitions. Radiography revealed shortening of metacarpals 3–5 on the left and 4 and 5 on the right. Her mother had similar skeletal changes, consistent with a dominant mode of inheritance. Abnormally short digits involving the metacarpals, classified as brachydactyly type E, can be isolated or occur as part of a syndrome. Turner syndrome, Albright hereditary osteodystrophy, hypertension with brachydactyly, chromosome 2q37 microdeletion and *PTHLH* mutations were excluded following clinical, biochemical and genetic testing. No specific treatment was required. Genetic testing for isolated and syndromic forms of brachydactyly facilitates family screening and pre-pregnancy counselling.

BACKGROUND

Brachydactyly is characterised by shortening of the digits, which can occur as an isolated malformation or as part of a syndrome.¹ The various forms of brachydactyly can be differentiated from each other and classified on an anatomical basis.² Brachydactyly type E (BDE; OMIM 113300) is a rare finding, characterised by variable shortening of the metacarpals, metatarsals and phalanges, and has been reported as part of several genetic syndromes.³ We describe the clinical findings of a case of isolated BDE found incidentally in a patient referred to a lipid disorders clinic.

CASE PRESENTATION

An 18-year-old phenotypic woman was referred to the lipid disorders clinic after two hospital admissions due to presumed idiopathic acute pancreatitis, with mild hypertriglyceridaemia (4.2 mmol/L) documented during one of those admissions. Her medical history included primary hypothyroidism treated with l-thyroxine, mannose-binding lectin deficiency, severe otitis media and asthma in childhood. The patient was a university student with no apparent learning difficulties. Her father had hypercholesterolaemia identified at the age of 28 years without genetic evidence of familial hypercholesterolaemia.

On examination, she was 1.61 m in height, 76.8 kg in weight, with a body mass index of 29.6 kg/m² and normotensive. There were no peripheral stigmata of dyslipidaemia or facial dysmorphism. However, there was hypermobility of her hand joints with shortening of digits (brachydactyly) (figure 1A) resulting in loss of left 3–5 and right 4 and 5 knuckle definitions (figure 1B).

INVESTIGATIONS

Radiography of both hands revealed shortening of metacarpals 3–5 on the left and 4 and 5 on the right (figure 1C). Biochemical investigations were unremarkable (table 1) apart from a mildly increased serum ionised calcium concentration with a normal parathyroid hormone (PTH) level and low urine calcium excretion. PTH-dependent hypercalcaemia was excluded on subsequent repeat testing. Genetic testing for isolated and syndromic causes of brachydactyly was unremarkable (table 1), with the exception of a possible copy number variation at Xp22.31, with a gain of approximately 0.14 Mb and a copy neutral loss of heterozygosity at Xq27.3q28

Figure 1 Photographs of the patient's hands showing digital shortening (panel A) and demonstrating loss of definition of left 3–5 and right 4 and 5 knuckles (panel B). Hand radiography confirmed metacarpal shortening (panel C).

To cite: Page MM, Hooper AJ, Glendenning P, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2016-218825

Table 1 Biochemistry and molecular genetic results

Test	Result (reference interval/limit where applicable)
Sodium	142 mmol/L (134–146)
Potassium	3.9 mmol/L (3.4–5.0)
Bicarbonate	27 mmol/L (22–32)
Urea	4.1 mmol/L (3.0–8.0)
Creatinine	59 µmol/L (45–90)
Glucose	5.8 mmol/L (3.0–5.4)
Albumin	41 g/L (35–50)
Bilirubin	4 µmol/L (<20)
Alanine aminotransferase	14 U/L (<35)
Alkaline phosphatase	82 U/L (40–135)
Gamma glutamyltransferase	15 U/L (<40)
Calcium (total)	2.48 mmol/L (2.15–2.6)
Calcium (total, corrected for albumin)	2.46 mmol/L (2.15–2.6)
Calcium (ionised)	1.38 mmol/L* (1.12–1.32)
Calcium (ionised, corrected for pH)	1.34 mmol/L* (1.12–1.32)
Phosphate	1.31 mmol/L (0.8–1.5)
25-Hydroxy vitamin D	97 nmol/L (>50)
Parathyroid hormone	5.2 pmol/L (0.7–7.0)
Calcium/creatinine (urine)	0.13 mmol/mmol (0.1–0.58)
Renal phosphate threshold	1.37 mmol/L glomerular filtrate (0.75–1.35)
N-telopeptide/creatinine (urine)	90 nmol bone collagen equivalents (BCE)/mmol (<100)
Total cholesterol	6.5 mmol/L (<5.5)
HDL-cholesterol	1.0 mmol/L (>1.0)
LDL-cholesterol	4.7 mmol/L (<3.0)
Triglyceride	1.8 mmol/L (<1.7)
Karyotype	46,XX
F analysis	No deletion of either chromosome at 2q37.3
Microarray analysis for copy number variants	Xp22.31 gain of ~0.14 Mb Xq27.3q28 loss of heterozygosity of ~4.2 Mb
HOXD13 sequencing	No mutation identified
PTH1H sequencing	No mutation identified

All biochemistry results are plasma or serum concentrations or activities, unless otherwise stated.

*Subsequent biochemical testing repeatedly demonstrated normal markers of calcium homeostasis.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

of approximately 4.2Mb; the significance of these findings was uncertain.

Of note, her mother had similar skeletal changes, involving metacarpals 4 and 5 on the left and 5 on the right, consistent with a dominant mode of inheritance. Microarray analysis failed to find the copy number variants present in her daughter. Her mother was 1.62 m in height and was found to have PTH-dependent hypercalcaemia with elevated urinary calcium excretion (serum PTH: 11 pmol/L (0.7–7); ionised calcium, corrected for pH: 1.34 mmol/L (1.12–1.32); urine calcium to creatinine ratio: 0.68 (0.1–0.58)). CT and ultrasound imaging revealed a likely parathyroid adenoma at the lower pole of the right thyroid, confirmed on surgical resection with consequent biochemical cure of PTH-dependent hypercalcaemia.

DIFFERENTIAL DIAGNOSIS

BDE may be isolated or associated with a range of syndromes, which are described in table 2.³ These were excluded on clinical, biochemical and molecular grounds, as described above.

TREATMENT

No specific treatment was required.

Table 2 Syndromic causes of BDE³

Condition	Molecular basis	Heritability	Clinical features
Pseudohypoparathyroidism ^{5,6} (OMIM 103580, 603233, 612462, 203330)	<i>GNAS</i>	Autosomal dominant (maternal)	AHO phenotype: BDE, small stature, obesity, subcutaneous calcifications and intellectual disability. Variable resistance to PTH, TSH and gonadotropins.
Pseudopseudohypoparathyroidism ⁵ (OMIM 612463)	<i>GNAS</i>	Autosomal dominant (paternal)	AHO phenotype, without hormone resistance
Acrolystosis 1, with or without hormone resistance ⁷ (OMIM 101800)	<i>PRKARIA</i>	Autosomal dominant	Marked shortening of phalanges and metacarpals 2–5. Short stature, stenosis of lumbar spine, nasal hypoplasia and flat nasal bridge. Variable resistance to PTH, TSH and rarely gonadotropins.
Acrolystosis 2, with or without hormone resistance ⁷ (OMIM 614613)	<i>PDE4D</i>	Autosomal dominant	Clinically similar to acrolystosis 1
BDE with short stature, PTH-like hormone type ^{8,9} (OMIM 613382)	<i>PTH1H</i> , or <i>t(8;12)(q13;p11.2)</i> chromosomal translocation, affecting <i>PTH1H</i> expression	Autosomal dominant	Variable shortening of metacarpals 3–5, and sometimes the phalanges. May be associated with intellectual disability.
AHO-like syndrome ^{3,10} (OMIM 600430)	Deletions in 2q37.3, with the exact causative gene in some dispute	Autosomal dominant	Short stature, obesity, developmental delay and other craniofacial and skeletal abnormalities. Brachydactyly is variable, not fully penetrant and affects metacarpals 2–5.
Trichorhinophalangeal syndrome ¹¹ (OMIM 190350)	<i>TRPS1</i>	Autosomal dominant	Abnormalities of scalp hair, eyebrows and facial features with short stature, BDE and hip malformations, sometimes with intellectual disability
Bliginturan brachydactyly ^{12,13} (OMIM 112410)	<i>PDE3A</i>	Autosomal dominant	Hypertension, BDE and intellectual disability
Turner syndrome ³	Complete or partial monosomy of the X chromosome	Autosomal dominant	Short stature, malformations of cardiovascular, genitourinary and neurological systems. BDE is a frequent feature, typically with shortened metacarpal 4.

AHO, Albright hereditary osteodystrophy; BDE, brachydactyly type E; PTH, parathyroid hormone; TSH, thyroid stimulating hormone.

Learning points

- ▶ Brachydactyly can be isolated or occur as part of a syndrome.
- ▶ An incidental finding of brachydactyly necessitates extensive clinical workup to exclude syndromic causes.
- ▶ Genetic testing for isolated and syndromic forms of brachydactyly is possible and facilitates family screening and pre-pregnancy counselling when the underlying molecular basis is identified.

DISCUSSION

BDE principally describes shortened metacarpals with normal phalanx length, occasionally also involves the metatarsals and may be isolated or associated with a range of syndromes.³ Each of these syndromes, except Turner syndrome, which is due to complete or partial monosomy of the X chromosome, is characterised by autosomal dominant inheritance with clinical features and penetrance varying between individuals and generations. The prognosis of syndromic BDE is often dependent on the clinical characteristics of the other abnormalities present.

Although many cases of isolated BDE are of unknown genetic basis, sporadic cases have been reported with mutations in *HOXD13*, although the mechanisms for inducing embryonic malformation have not been elucidated.⁴ Mutations in *HOXD13* are autosomal dominant with variable penetrance and involvement of metacarpals and metatarsals is variable and may be asymmetric.

Owing to the variable clinical features and penetrance that characterise these syndromes, they should be carefully considered in any patient presenting with BDE because of the potential implications for family screening, family planning and pre-pregnancy counselling. Progress in molecular diagnostic research and clinical application has allowed clearer definition and delineation of many of these conditions and provided insights into their mechanistic origins.

In conclusion, we describe the clinical findings in a case of isolated BDE that necessitated extensive genetic workup to exclude important familial syndromes. Identification of

these syndromes may offer early detection and screening of affected index cases and family members harbouring the same mutation.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review JRB and PG were involved in the conception of the case report; AJH was involved in the genetic analysis; MMP was involved in drafting the manuscript; AJH, PG and JRB were involved in the critical revision of the manuscript for important intellectual content; all the authors were involved in the final approval of the version to be published and were also involved in the agreement to be accountable for all aspects of the work.

Provenance and peer review Not commissioned; externally peer reviewed.

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