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First African case report of hypoparathyroidism, deafness and renal dysplasia (HDR) syndrome due to inverted duplication and deletion of chromosome 10p

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Abstract

Background Hypoparathyroidism, sensorineural deafness and renal disease (HDR) syndrome, also known as Barakat syndrome, is a rare autosomal dominant genetic disorder manifesting as a result of haploinsufficiency of the *GATA3* gene. GATA3 is a member of zinc-finger transcription factors that are responsible for the embryonic development of key organs and structures including the parathyroid glands, auditory system and kidneys. Here, we report the first African case of HDR syndrome to be confirmed by chromosomal microarray analysis (CMA).

Case presentation A 3-month-old female presented with focal seizures due to severe hypocalcaemia associated with low parathyroid hormone. The patient also had sensorineural hearing loss, global developmental delay and prominent dysmorphic features that included a tall, prominent forehead, long, curly eyelashes, a depressed nasal bridge as well as subtle skeletal abnormalities. The dysmorphic features, global developmental delay and hypoparathyroidism associated with persistent and severe hypocalcaemia led to the investigation by CMA which detected a 9.5 Mb heterozygous terminal loss of chromosome 10p15.3p14; *GATA3* is included in this region. In addition, CMA detected a 4.4 Mb heterozygous interstitial gain of chromosome 10p14p13 indicating the presence of an inverted duplication and deletion of chromosome 10p. The patient was actively treated with IVI calcium gluconate, oral calcium carbonate and alfa cholecalciferol.

Conclusion This case emphasizes that complex patients with developmental delay and multiple congenital anomalies are likely to benefit from evaluation by CMA. Indeed, this approach still has an important role to play, particularly in inadequately resourced settings such as in Africa, for the investigation of patients with complex genetic disorders associated with significant chromosome aberrations.

Keywords Hypoparathyroidism, Sensorineural deafness and renal disease syndrome, Barakat syndrome, Chromosomal microarray, *GATA3*

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Background

Genetic disorders associated with hypocalcaemia may arise from disease-causing variants in genes that regulate the development of the parathyroid glands, parathyroid hormone (PTH) synthesis or its physiological effectiveness. Familial hypoparathyroidism occurring in isolation may be inherited in an autosomal recessive, dominant or in an X-linked manner depending on the genes involved [1]. The glial cells missing transcription factor-2 gene (*GCM2*) encodes a notable nuclear transcriptional factor associated with familial hypoparathyroidism attributed to agenesis of parathyroid glands. *GCM2* expression is further controlled by other regulatory genes in the form of glutamyl amidotransferase subunit A binding protein 3 (*GATA3,* OMIM #131320). and T-box transcription factor *(TBX1);* pathogenic variants in these genes lead to hypoparathyroidism associated with other major malformations [2]. Hypoparathyroidism, sensorineural deafness and renal disease (HDR) syndrome, or Barakat syndrome as it is otherwise known, is a rare autosomal dominant genetic disorder manifesting as a result of haploinsufficiency of *GATA3*. *GATA3* is a member of zinc-finger transcription factors that are responsible for the embryonic development of key organs and structures including the parathyroid glands, auditory system and kidneys [3]. Although the global prevalence remains undetermined, a recent study reported a total of 224 known patients of various ages and ethnicities, making HDR syndrome an ultra-rare disorder [4]. We report here on a complex case of HDR syndrome confirmed by chromosomal microarray analysis (CMA). To the best of our knowledge, this is the first African case report to be published.

Case presentation

Clinical features and investigations

A three-month-old female presented to the emergency department with a history of focal left-sided seizures affecting the arm and face. The seizures were aborted with diazepam, and the patient was initiated on maintenance oral phenobarbital. This was the patient's first presentation to hospital with no previous medical problems. The patient is the only child to her non-consanguineous parents. She has two half-sisters (maternal and paternal) who are both well. There was no family history of epilepsy disorders, congenital anomalies (including renal anomalies), renal disease, hearing impairment or developmental/intellectual disability. The patient was born at term, via normal vaginal delivery, to a young healthy mother with no significant prenatal history. She was born with a low birth weight of 2490g [3rd centile, −1.78 standard deviations (SD)], microcephaly with a head circumference of 29cm (< 3rd centile, −3.93 SD), and her length was not documented. She had good Apgar scores, and there were no immediate neonatal complications. Upon presentation at 3 months of age, she had mild global developmental delay and was failing to thrive. She was underweight-for-age, had short stature (of unknown onset) and microcephaly (of prenatal onset). In addition to restricted growth, the patient was noted to be dysmorphic with a flat nasal bridge, epicanthic folds, micrognathia and overriding fingers. She was alert and saturating well in room air, though she had mild conjunctival pallor. She had mild subcostal recessions, and her cardiovascular system examination was normal. The abdominal examination revealed mild hepatomegaly and no splenomegaly. Biochemical investigations were as follows: creatinine 43 µmol/L [reference interval (RI) 14–34], urea 8.2 mmol/L, [RI 1.4–5.1], urine protein creatinine ratio 1.8 g/mmol [RI < 0.015], calcium 1.2 mmol/L [RI 2.2–2.6], phosphate 3.2 mmol/L (RI 1.2–2.1), PTH 0.7 pmol/L [RI 1.6–6.9] and 25 OH-vitamin D 74.4 nmol/L [RI 50–150] (Table 1). Renal ultrasound revealed no gross abnormalities and the left kidney measured 5.5 × 2.17 × 2.30 cm and right kidney measured 4.72 × 2.57 × 2.07 cm, kidney sizes were normal for her age. Audiology screening reported bilateral sensorineural hearing impairment. The patient was treated with IVI calcium gluconate, oral calcium carbonate and alfa cholecalciferol; however, serum calcium continued to be symptomatically low, requiring further calcium titration and dosing.

The dysmorphic features, global developmental delay and hypoparathyroidism associated with persistent and severe hypocalcaemia with seizures suggested a complex genetic disorder, possibly a pathogenic chromosome copy number variation, and a peripheral blood sample was taken for CMA. DNA was extracted, and comparative genomic hybridization was performed using the Agilent SurePrint G3 ISCA v2 CGH 8 × 60K microarray on the Agilent platform as per manufacturer's instructions (www.genomics.agilent.com). Agilent CytoGenomics version 5.3 was used for data analysis. Interpretation and

Table 1 Results of biochemical parameters measured

Tests	Results	Reference intervals
Creatinine	43	14–34 µmol/L
Urea	8.2	1.4–5.1 mmol/L
Urine protein creatinine ratio	1.8	< 0.015 g/mmol
Calcium	1.2	2.2–2.6 mmol/L
Phosphate	3.2	1.2–2.1 mmol/L
Parathyroid hormone	0.7	1.6–6.9 pmol/L
25 OH-vitamin D	74.4	50–150 nmol/L

reporting of the chromosomal aberrations were done by a multidisciplinary team comprising medical scientists, genetic counsellors and clinical geneticists. The results revealed a 9.5 Mb heterozygous terminal loss of chromosome 10p15.3p14, which included the *GATA3* gene. Loss-of-function pathogenic variants in *GATA3* are associated with HDR or Barakat syndrome. In addition, a 4.4 Mb heterozygous interstitial gain of chromosome 10p14p13, adjacent to the terminal loss, was detected (see Fig. 1). The terminal loss and adjacent gain are suggestive of an inverted duplication and deletion of 10p.

Genetic assessment

Based on the results obtained from CMA, the patient was referred for assessment and genetic counselling at the Division of Human Genetics, National Health Laboratory Service and the University of the Witwatersrand in Johannesburg, South Africa. At this appointment, she was 10 months of age and presented with mild global developmental delay. She was noted to be globally growth restricted with weight 5.5 kg (< 3rd centile, −4.04 SD), length 63 cm (< 3rd centile, −3.16 SD) and head circumference 41 cm (< 3rd centile, −2.92 SD). She had significant dysmorphism, including an unusual hair distribution (a high anterior hairline, sparse hair in the frontal/parietal regions, mild hypertrichosis on the forehead and synophrys), a tall, prominent forehead, long, curly eyelashes a depressed nasal bridge, an impression of hypertelorism, a rounded nasal tip with a short columella, a tented upper lip and hypoplastic ear lobes with a right-sided preauricular ear pit (see Fig. 2). Her palate and dentition were normal. In addition to the dysmorphic facial features, she had a small, reducible umbilical hernia, hypoplastic labia majora, two small (< 1 cm x 1 cm) café-au-lait macules and subtle skeletal abnormalities (sloping shoulders, long halluces and a large gap between her 4th and 5th toes bilaterally). The patient subsequently had a formal cardiac assessment which showed no abnormalities and also had normal echocardiogram. On brief examination, her mother was noted to have similar synophrys and a left-sided preauricular ear pit. Her mother was counselled on the genetic result, the clinical features and complications associated with Barakat syndrome, the inheritance, recurrence risk and prenatal genetic testing options for future pregnancies. A medical investigation and surveillance plan were put into place for the patient, based on case studies and academic literature on Barakat syndrome. The patient's mother consented to genetic testing to aid with more accurate genetic counselling on recurrence risk for future pregnancies. Unfortunately, the mother's karyotype was unsuccessful as the blood culture did not yield sufficient metaphase cells for chromosome analysis. Microarray analysis of the mother's DNA did not reveal any clinically significant chromosome abnormalities. The patient's father was not available for genetic counselling and testing.

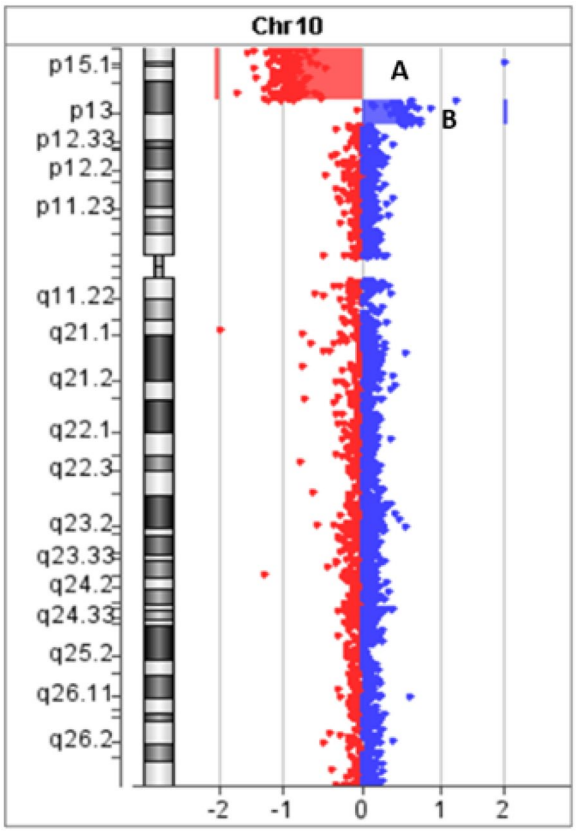

Fig. 1 Image of the terminal loss and adjacent gain on the short arm of chromosome 10, visualized using Agilent CytoGenomics software (v5.3). A: Terminal loss of chromosome 10p15.3p14; the probes at the deleted region have a $\log_2$ ratio that approaches − 1. B: Adjacent gain of chromosome 10p14p13; the probes at the duplicated region have a $\log_2$ ratio that approaches 0.58

Discussion

HDR/Barakat syndrome is a rare autosomal dominant inherited condition manifesting with hypoparathyroidism, sensorineural deafness and/or renal dysfunction [5]. Here, we report on an infant with symptomatic hypocalcaemia, suppressed PTH, hearing and renal impairment as well as developmental delay and dysmorphism. There are diverse clinical features reported in 10p deletion syndromes ranging from dysmorphism to disparate cognitive, behavioural and developmental phenotypes. Moreover, 10p15 deletions are reported to be remarkably rare as an isolated finding; often complemented by duplication at a different location on the same chromosome, or a different chromosome altogether [6]. This was demonstrated in our case with both a terminal deletion and an interstitial duplication on the short arm

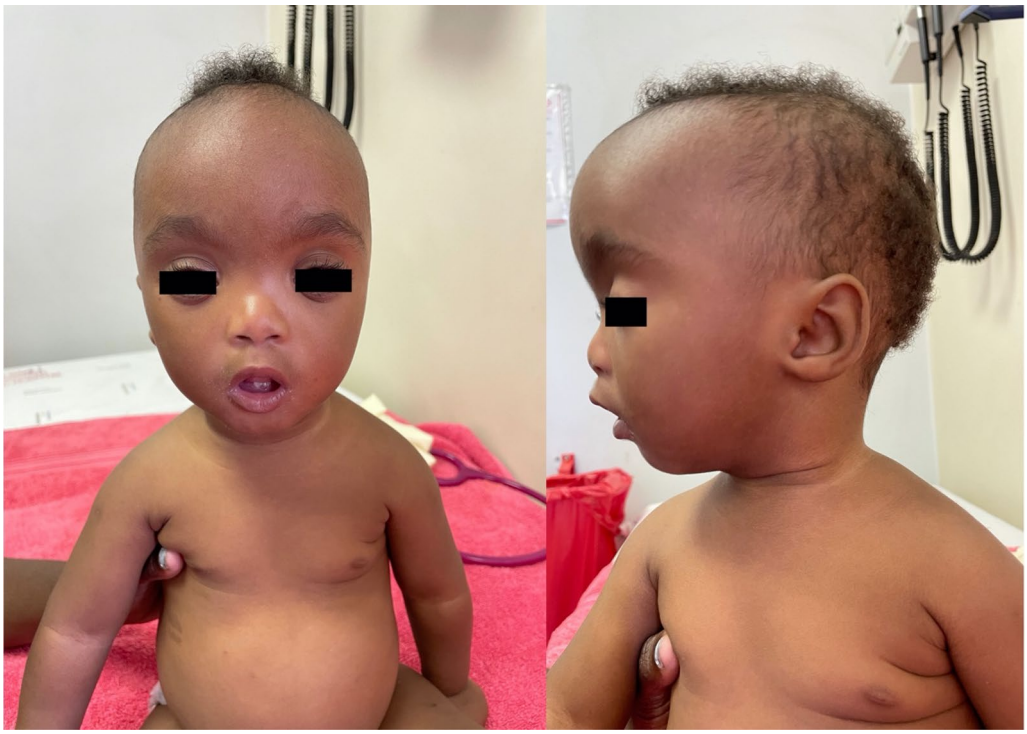

Fig. 2 A 10-month-old female patient with a 9.5 Mb heterozygous terminal loss of chromosome 10p15.3p14, encompassing *GATA3*. Haploinsufficiency of *GATA3* is associated with Barakat syndrome. Note the dysmorphic features including a tall, prominent forehead, synophrys, depressed nasal bridge and tented upper lip

of chromosome 10. Deletions of 10p15.3, the most distal segment of 10p, are associated with 10p15.3 microdeletion syndrome. Haploinsufficiency of *ZMYND11* was identified as the underlying cause of the clinical phenotype of 10p15.3 microdeletion syndrome. This syndrome is associated with developmental delay, characteristic dysmorphic features, behavioural disturbances, hypotonia, seizures, low birth weight, short stature, genitourinary malformations and recurrent infections [7].

GATA3 is a transcription factor consisting of conserved binary zinc-finger domains which plays an integral role in the development of parathyroid glands, kidneys and the auditory system, including the inner ears [8]. *GATA3*, the causal link to HDR syndrome, maps to 10p14-15 [9]. Two patients with Barakat syndrome were identified by deletion mapping studies which identified the critical 200-kb region that comprises *GATA3* [3]. CMA is a high-resolution technique capable of detecting chromosomal aberrations as small as 50 kb. It is a relatively affordable diagnostic tool for whole genome analysis and is the recommended first-tier test for the investigation of suspected microdeletion/duplication syndromes, neurodevelopmental delay and intellectual disability [10]. The analysis is superior to conventional cytogenetics, making it valuable in low-resource settings with limited access to advanced diagnostic technologies [11, 12]. This is a rare case of HDR syndrome diagnosed on CMA as a 10p15 deletion; and to our knowledge, is the first published case of an African patient. We know of two case reports of HDR syndrome diagnosed by CMA; the one patient had monosomy of 10p15.3p13, while the other had a pathogenic deletion of 10p15.3p14 [13, 14]. The 10p deletion was associated with duplication of different chromosomes, namely 20p13p12.3 and 12p13.33p13.33, respectively. In addition to the clinical features of Barakat syndrome, these patients presented with dysmorphic features and developmental delay resembling our case presentation.

Cases of inverted duplication and deletion of chromosome 10p have been rarely reported in the literature and differ with regard to chromosome breakpoints [15, 16]. Chromosome rearrangements resulting in a terminal deletion and adjacent inverted interstitial duplication have been reported to occur on most chromosomes. The most common mechanism resulting in this rearrangement is U-type exchange between sister chromatids. Recombination events resulting from the presence of inverted low copy repeats, or having one parent carry a paracentric inversion, can also lead to this type of rearrangement. The latter two mechanisms typically result

in a region of normal copy number between the deletion and inverted duplication. High resolution microarray with sufficient probe coverage can be used to distinguish between these mechanisms [17]. This is important to clarify recurrence risks for future pregnancies.

The interstitial gain of chromosome 10p14p13 with CNV size of approximately 4.4 Mb detected in our case is noteworthy. One patient with a duplication in this region presented with autistic features and global developmental delay (DECIPHER; 301137).

Bernandini et al. reported a case of HDR syndrome with 10p15.3p15.1 deletion as well as 10p15.1p14 duplication. Interestingly, follow up with a real-time PCR assay confirmed the increased *GATA3* gene expression leading to Barakat syndrome [16]. Kim et al. published a neonate with the largest deletion reported to date, spanning 16 Mb on chromosome 10p. As expected, the clinical presentation was extensive, with major congenital abnormalities and features of HDR syndrome [18]. The two published cases are presented in Table 2 alongside the present case, highlighting shared clinical features across the three patients. Differences in phenotype may be ascribed to the varying sizes of the CNVs in each patient and their precise breakpoints.

HDR syndrome is marked by a genetic and clinical heterogeneity with only some clinical manifestations notable in affected patients. This remarkable heterogeneity is attributed to the incomplete penetrance and variable expression as it pertains to the age of onset, severity and extent of the manifested abnormalities. Bilateral sensorineural deafness is reported as the most consistent symptom that is encountered early in the disease, while the presence of hypoparathyroidism and renal diseases is highly variable [19]. The renal complications may be subtle and functional with no renal structural abnormalities, as demonstrated by mild renal impairment and proteinuria in our patient. The renal structural abnormalities are variable and may be asymmetrical, ranging from hypoplastic to cystic kidneys and pelvicalyceal anomaly. The mild renal involvement may infer favourable outcomes for this patient because the prognosis of HDR is dependent on the severity of the kidney disease.

As demonstrated in our case, severe hypocalcaemia with seizures is often the reason that affected patients present to health care facilities for urgent medical care. Initially, the refractory hypocalcaemia could not be corrected with intravenous and oral calcium along with active vitamin D supplementation. Recombinant PTH replacement therapy is recommended in instances of unresponsive hypocalcaemia [20]; this treatment option was not available in our setting. There are no current guidelines on long-term surveillance of patients; however, frequent serum calcium monitoring is recommended until stabilized, to be followed by 2–3 monthly monitoring as an outpatient. Close monitoring of the renal function test is paramount in anticipation of nephrocalcinosis due to calcium over-supplementation [21]. Genetic counselling is a critical part of the patient's management and should be considered routine care for patients diagnosed with chromosomal anomalies. Genetic counsellors can explain the diagnosis to parents and families, discuss recurrence risks and further genetic testing recommendations and provide psychosocial support to families.

Table 2 Comparison of the patient's phenotype with the two published cases with inverted duplication and deletion of chromosome 10p

Clinical features	Index case Del. 10p15.3p14 (9.5 Mb) Dup. 10p14p13 (4.4 Mb)	Chen et al. [15] Del. 10p15.3 (0.31 Mb) Dup. 10p15.3p12.1 (24.9 Mb)	Bernardini et al. [16] Del. 10p15.3p15.1 (6.5Mb) Dup. 10p15.1p14 (1.9 Mb)
Low set ears	+	+	
Hypertelorism	+	+	+
Frontal bossing	+	+	
Large nose		+	
Rounded nasal tip	+		
Flat nasal bridge	+		
Epicanthic folds	+		
Micrognathia	+		
Wide mouth		+	
Cleft lip and palate			+
Microcephaly	+		+
Unusual hair distribution	+		
Long curly eye lashes	+		
High arched eyebrows	+		+
Upslanting palpebral fissures			+
Overriding fingers	+		+
Syndactyly			+
Umbilical hernia	+		
Café-au-lait macules	+		
Hypoplastic labia majora	+		
Hearing loss	+		
Psychomotor delay	+		+
Seizures	+		
Failure to thrive	+		

Conclusion

HDR/Barakat syndrome is a heterogeneous and ultra-rare autosomal dominant disorder with variable clinical expression. Globally, more than 200 cases have been reported thus far. We have reported on the first African case of HDR syndrome due to a terminal deletion of chromosome 10p detected by microarray analysis. This case emphasizes that complex patients with developmental delay and multiple congenital anomalies in low-resourced settings are likely to benefit from evaluation by CMA. The CMA is a high-resolution technique capable of detection approximately 50 Kb chromosome aberrations. Indeed, the CMA still has an important role to play, particularly in inadequately resourced settings such as in Africa, for the investigations of patients with complex genetic disorders associated with significant chromosome aberrations. High index of suspicion is required for prompt diagnoses of rare diseases such as Barakat syndrome. Appropriate genetic testing should be considered in patients with unexplained sensorineural deafness or renal disease with persistent hypocalcaemia with low PTH.

Abbreviations

HDR	Hypoparathyroidism, sensorineural deafness and renal disease
GATA3	Glutamyl amidotransferase subunit A binding protein 3
PTH	Parathyroid hormone
GCM2	Glial cells missing transcription factor-2 gene
TBX1	T-box transcription factor
CGH	Comparative genomic hybridization
SD	Standard deviation
RI	Reference interval

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Author contributions

Case report conceptualization and preparation of manuscript were performed by T Satekge and G Rikhotso. Case presentation was performed by G Rikhotso, B Rossouw and B Dillon. Results interpretation was done by T Satekge, F Baine-Savanhu and B Rossouw. Drafting of manuscript and review and approval of manuscript were done by all authors.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

Ethics clearance was obtained from the Polokwane Mankweng Research Ethics Committee (PMREC) (REC 300408-006).

Consent for publication

All consent for publications was taken before submission of manuscript.

Competing interests

The authors declare that there are no competing interests regarding the publication of this article.

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