Case report

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Terminal deletion of chromosome 10p13 as a cause of hypoparathyroidism in a neonate

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Objective – To present a case of hypoparathyroidism that was found to be a part of a rare chromosomal syndrome and to emphasize the importance of its early diagnosis. **Case reports** – We report the case of a neonate with hypoparathyroidism and dysmorphic features. The chromosome analysis detected terminal deletion of chromosome 10p13. The diagnosis was made of HDR (hypoparathyroidism, sensorineural deafness and renal disease) syndrome due to haploinsufficiency of the *GATA-3* gene located on 10p. We searched for additional manifestations of 10p deletion and developed an early management plan in order to prevent complications and improve the prognosis. **Conclusion** – Chromosomal aberration should be suspected in any neonate with dysmorphic features and intrauterine growth retardation, but the presence of hypoparathyroidism may prompt targeted evaluation for particular chromosomal areas, including 10p.

Introduction

Hypocalcaemia is a frequently observed clinical and laboratory abnormality in neonates and, if not treated properly, it may cause serious complications and leave consequences for the child's development. Among causes of hypocalcaemia, congenital hypoparathyroidism, either permanent or transient, is rare. It may be familial or, in rare cases, occur as part of a larger genetic or chromosomal syndrome. Terminal deletion of chromosome 10p is a rare chromosomal disorder, characterized by different phenotypes, depending on the genomic position of the deletion. The combination of hypoparathyroidism, deafness and renal disease, known as HDR syndrome, was first described in a patient who had a 10p13-14 deletion (1). The causative gene, *GATA-3*, was later identified 8.1 Mb from the 10p-telomere. *GATA-3* was shown to be essential in the embryonic development of the parathyroid glands, auditory system and kidneys (2, 3, 4). Terminal deletion of 10p13-14 is also associated with congenital heart defects and thymus hypoplasia/aplasia, known as DiGeorge syndrome type 2, and its critical region has been located at 10.6-11.3 Mb from the 10p-telomere (5). Finally, deletion involving a more distal region, 10p15.3, is characterized by neurodevelopmental delay, craniofacial dysmorphism (microcephaly, frontal bossing, blepharoptosis, epicanthal folds, micrognathia, short neck etc.), brain anomalies and seizures (6, 7).

Here, we report a case of congenital hypoparathyroidism that was found to be part of a larger chromosomal syndrome, terminal deletion of chromosome 10p13.

Case report

The proband is a female neonate born to healthy non-consanguineous couple by spontaneous vaginal delivery at term (39 weeks of gestation). Birth weight was 2400 g (below 3rd percentile), birth length was 48 cm (10-25th percentile), and head circumference was 31 cm (below 3rd percentile). There was no history of prenatal complications and no relevant family history. Dysmorphic features were noted at birth, such as blepharoptosis, epicanthal folds, low set dysplastic and posteriorly rotated ears, long philtrum, thin upper lip, pointed chin and short neck. She had pale skin, weak cry and hypertonia. From the second day of life she had persistent hypocalcaemia. The lowest serum calcium was 1.36 mmol/L (normal range: 1.9-2.65 mmol/L). Serum phosphate level was high, up to 2.88 mmol/L (normal range: 1.2-2.26 mmol/L) and serum PTH was inappropriately low, 13 pg/mL (normal range: 15-65 pg/mL). There were no laboratory signs of kidney dysfunction. Maternal parathyroid status was normal. The final diagnosis of congenital hypoparathyroidism was made and the patient was managed with intravenous calcium for three days, followed by oral calcium carbonate and vitamin D3 supplementation. Her calcium levels became normal in subsequent evaluations. Her feeding problem was quite marked and during the whole neonatal period she was fed through a nasogastric tube with combination of mother's milk and high-energy infant formula. She had a urinary tract infection that was treated with intravenous antibiotic therapy. Due to her dysmorphic features, we undertook chromosome analysis that detected terminal deletion of 10p13. As the deletion included the specific loss of the *GATA-3* gene responsible for HDR syndrome, audiometric testing and kidney ultrasound were conducted. Ultrasound showed a small and dysplastic left kidney, and the hearing test showed bilateral sensorineural severe deafness. Since the deletion also involved the region associated with DiGeorge syndrome type 2, echocardiography was done and a very small foramen ovale apertum was found.

Genetic counseling was performed. The parents were advised to do chromosome analysis according to the results of which they would be given information about the recurrence risk and prenatal diagnostics in the future pregnancies. We discharged the patient from hospital at the 26th day of life with oral calcium carbonate and vitamin D3 supplementation, and advised regular check-ups by an endocrinologist, nephrologist, audiologist, clinical geneticist, and nutrition and physiotherapy specialists.

Discussion

We report a case of congenital hypoparathyroidism that was found to be a part of a larger chromosomal syndrome, terminal deletion of chromosome 10p13. When the diagnosis is made in the neonatal period, there is an opportunity to perform early investigation of particular organ systems and to develop a management plan in order to prevent complications, improve prognosis and give proper genetic counseling to the family. As many cases of deletion 10p have been reported to date, possible abnormalities are well known (5, 8, 9, 10). Hypoparathyroidism in a newborn accompanied with dysmorphic features and intrauterine growth retardation was the reason for performing chromosome analysis. Using a cytogenetic technic, we detected terminal deletion of 10p13 that allowed us to make the diagnosis of HDR syndrome due to the haploinsufficiency of the *GATA-3* gene and to search for additional manifestations of HDR syndrome and, in general, manifestations of deletion 10p.

The phenotype of HDR syndrome is highly variable. Hypoparathyroidism is probably the most specific symptom, reportedly

present in 95-97% of patients affected by a *GATA-3* mutation. Deafness is found in 95% and kidney abnormalities in 60% of these patients (10). In our case, a hearing test showed bilateral sensorineural deafness. Kidney ultrasound examination revealed a small and dysplastic left kidney. Heart conditions have been found in around half of the patients with 10p deletion, and in most of these, deletion that involved the DiGeorge 2 region. The most common is atrial septal defect, followed by ventricular septal defect and valve anomaly (8). In our case, echocardiography showed a very small foramen ovale apertum. A 10p deletion may affect the development of the thymus so that the child has an insufficient number of T-cells, leading to recurrence infections. During the first month of life our proband had a urinary tract infection, with good response to antibiotic therapy. The child was born with low weight for gestation and during the neonatal period had significant feeding problems. She did not gain sufficient weight, so she had to be fed using a nasogastric tube with a combination of high-energy infant formula and mother's milk. Based on previously reported cases, she will need assessment of early development, as well as early intervention and follow up.

Since the levels of intellectual and developmental delay are related to the size and position of the deletion, it will be useful to delineate the terminal deletions using techniques such as chromosomal microarray. This will allow us to examine more easily which genes and regulatory elements are missing and to give a more precise prognosis. Chromosomal microarray also enables detection of submicroscopic chromosome deletions in cases of characteristic phenotype but normal cytogenetic findings.

Conclusion

A chromosomal aberration should be suspected in any neonate with dysmorphic features and intrauterine growth retardation, but the presence of hypoparathyroidism may prompt targeted evaluation for particular chromosomal areas, including 10p. The identification of terminal deletion of 10p allows us to make the diagnosis of HDR syndrome due to the haploinsufficiency of the *GATA-3* gene, and also to search for additional manifestations of the deletion and develop an early management plan in order to improve prognosis.

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Conflict of interest: he authors declare that they have no conflict of interest.

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