Congenital Central Hypoventilation Syndrome Caused by A *de novo* RET Pathogenic Variant

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Case report

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Abstract

Introduction: Congenital central hypoventilation syndrome (CCHS) is a rare life-threatening disorder characterized by a failure in physiologic autonomic control of breathing resulting in apnoea, hypoxemia, and hypoventilation episodes, associated to a large spectrum of autonomic nervous system dysfunctions. Despite this condition is most likely caused by mutations in the PHOX2B gene, other genes have been found responsible for CCHS in rare cases.

Case report: We report a 15-month-old toddler presenting episodes of central and obstructive apnoea with cyanosis, hypertonia, hypercapnia, and cyanotic breath-holding spells. The CCHS diagnosis was supported by central desaturating apnoea/hypopneas episodes during rapid eye movement sleep and obstructive apnoea in polysomnography, as well as by the presence of hypoxia and hypercapnia in arterial blood gas during critical episodes. Autonomic dysregulation with sporadic profuse sweating and gastrointestinal dysmotility resulting in gastro-oesophageal reflux and chronic constipation were also associated. Next Generation Sequencing revealed the missense variant p.Met918Thr in the RET gene.

Conclusion: This case, identifying a de novo pathogenic variant in the RET gene, highlights the importance of using clinical exome sequencing or a panel of genes associated with the specific disease, rather than looking for mutations in the single most frequently correlated gene.

Introduction

Congenital central hypoventilation syndrome (CCHS) is a genetic disorder characterised by an idiopathic failure of the autonomic control of breathing resulting in hypoventilation, impaired ventilatory response to hypercapnia and hypoxemia episodes, more severe during sleep (1–2). CCHS has been associated to a large spectrum of autonomic nervous system dysfunctions (2). It is considered a rare syndrome affecting approximately 1:200,000 live births, and it is usually diagnosed in the newborn period or in infancy, more rarely in childhood or adulthood (3). Many studies have reported that mutations in the PHOX2B gene represent the genetic cause in 90% of CCHS cases (2). Mutations of other genes involved in the development of neural crest cells, such as RET, GDNF, ASCL1 and EDN3 were identified in rare cases of CCHS (2–4).

Here, we report on the case of a 15-month-old toddler presenting with CCHS features, caused by a de novo missense variant in the RET gene.

Patient Information

A 15-month-old boy was admitted to the Pediatric Oncology Unit in January 2020 for several episodes of brief respiratory arrest characterized by cyanosis, limb hypertonia, fixed gaze, altered level of responsiveness and resolution after strong stimulation manoeuvres. The symptoms were noticed by parents one month before the admission, more frequently during sleep. Parents referred also sporadic profuse sweating, and chronic constipation. When the patient was 3-month-old, he was diagnosed with

cyanotic breath-holding spells. The mother told us that, after an uncomplicated pregnancy, a Caesarean section was performed due to obstetric problems. Birth weight was 2,750 g. The newborn physical examination revealed monolateral clubfoot, surgically treated in the early months of life.

Clinical Findings

Physical examination upon admission to our unit revealed mild hypotonia. Vital parameters monitoring (heart rate, respiratory rate, blood pressure and oxyhaemoglobin saturation [SO₂]) showed apnoeas and desaturation episodes (from 1 to 10 episodes per day) more frequently during sleep (SO₂ of 88–89% in ambient air), but also during wakefulness.

Timeline

December, 2019	First episode of respiratory arrest
January 3 rd , 2020	Hospitalization and diagnostic assessment
February 27 th , 2020	Transfer to Bronchopneumology Unit

Diagnostic assessment

During the respiratory arrests, arterial blood gas (ABG) showed hypoxia and hypercapnia. Blood exams including haematological, liver, pancreatic, thyroid, and renal functional index were unremarkable. Infectious disease tests were negative. Prolonged 8 hours electroencephalography during wakefulness and sleep revealed a diffuse slow pattern that might evoke a reflex anoxic epileptic pattern. Chest X-ray and cardiological evaluation, with electrocardiography, echocardiogram, and 24-hour Holter-ECG revealed no abnormal findings. Brain magnetic resonance imaging showed no abnormalities. Metabolic workup including plasma amino acids and urine organic acids were unremarkable. In order to exclude child abuse, a urine drug test was performed, with negative results. Otorhinolaryngologic evaluation revealed no abnormalities. A 24-hour pH multichannel intraluminal impedance testing showed gastro-esophageal reflux episodes that were not related to the desaturation episodes. Bronchoscopy was performed and revealed an extrinsic compression of the left posterolateral wall of trachea under cricoid narrowing. Chest/neck computed tomography angiography was performed, exhibiting a bovine aortic arch, described as an anatomic variant of human aortic branching without any pathological meaning. Polysomnography (PSG) was performed in order to establish the presence of hypoventilation and sleep-related breathing disorder. It showed rare obstructive apnoeas (obstructive apnoea index, 0.4) and central desaturating apnoeas/hypopneas in rapid eye movement (REM) sleep (central apnoea index 2.7). This evaluation excluded primary pulmonary, cardiac, neurological/oncological, gastroenterological, and metabolic causes of respiratory episodes. After genetic counseling, Chromosomal Microarray Analysis (CMA) and PHOX2B molecular analysis were requested. CMA was normal and PHOX2B analysis did not detect any

pathogenic variant. Next Generation Sequencing performed in trio using the Twist Custom Panel (clinical exome – Twist Bioscience), revealed the de novo missense (NM_020630.4:c.2753T>C; NP_066124:p.Met918Thr; rs74799832) variant in the RET gene (Rearranged During Transfection Protooncogene, chr10:43,077,068-43,130,350; GRCh37/hg19, MIM *164761). Heterozygous RET pathogenic variants are associated to Central Hypoventilation Syndrome (MIM # 209880), Medullary thyroid carcinoma (MIM # 155240), multiple endocrine neoplasia IIA (MIM # 171400) and IIB (MIM # 162300) and pheochromocytoma (MIM # 171300). The p.Met918Thr variant can be classified as “Pathogenic” according to the ACMG guidelines assessed with Intervar and Varsome. Considering the correlations between RET mutations and neuroendocrine neoplasia, we performed abdominal ultrasound and neuroendocrine oncological markers resulting normal.

Therapeutic Intervention

The patient started proton pump inhibitor therapy (Lansoprazole 1 mg/kg/die) for one month without significant clinical improvement.

Follow-up and Outcomes

The child was moved to a specialised Bronchopneumology Unit in order to receive the best respiratory care.

Discussion

CCHS represents a rare disorder characterized by abnormal control of respiration in the absence of neuromuscular, lung or cardiac disease, or an identifiable brainstem lesion. Although CCHS patients usually present apnoeas or breath holding spells since neonatal period (5), milder respiratory disorders might be detected in childhood or adulthood as late-onset CCHS, during sedation, anaesthesia, respiratory infection or sleep apnoea (2). The typical alveolar hypoventilation leads to a period of cyanosis during sleep induction, a decrease in SO₂ and increase in the partial pressure of CO₂ in arterial blood, with no physiological respiratory response or arousal reflex (6). Hypoventilation usually occurs during non-rapid eye movement (NREM) sleep, but it can also be present during REM sleep and wakefulness (1). Affected children may present neurocognitive decline related to the recurrent hypoxemia/hypercapnia episodes (7), tumours derived from neural crest cells (neuroblastoma, ganglioneuroma, and ganglioneuroblastoma), Hirschsprung’s disease (HSCR), autonomic nervous system dysregulation with oesophageal dysmotility, constipation, cardiovascular and temperature regulation abnormalities. CCHS requires an early diagnosis in order to establish adequate ventilator management and to minimise neurocognitive defects related to the repeated hypoxia and hypercapnia episodes. CCHS represents a complex diagnosis due to the rarity and the phenotypic variability of this entity. CCHS diagnosis has to be suspected when children present with hypoventilation episodes, worsening during sleep, without primary pulmonary, metabolic, neurologic, cardiac disease, or brainstem lesions (8). In the present case, episodes of central and obstructive apnoea with cyanosis, hypertonia, hypercapnia, and cyanotic breath-holding spells were considered as features of CCHS (9). The diagnosis of CCHS was supported by central desaturating apnoea/hypopneas episodes

during REM sleep and obstructive apnoea in PSG, as well as hypoxia and hypercapnia in ABG during critical episodes. Sporadic profuse sweating and gastrointestinal dysmotility resulting in gastro-oesophageal reflux and chronic constipation were considered as further features of CCHS. Despite pathogenic variants in PHOX2B usually represent the cause of CCHS, some papers highlighted that RET-GDNF signalling and/or EDN3-endothelin receptor-B signalling pathways play a significant role in the development of the respiratory centre and could be associated with the pathophysiology of CCHS (3). CCHS patients present Hirschsprung's disease (HSCR) in 16–20% of cases. HSCR is a congenital absence of ganglion cells in the myenteric and submucosal plexuses of bowel. Pathogenic variants in the RET gene have been associated with up to 50% of familial and 35% of sporadic cases of HSCR (10–11). The reported association of CCHS with HSCR in humans, and a similar phenotype observed in RET knockout mice, supports that RET is a candidate gene for CCHS (6). NGS performed in this patient revealed the de novo p.Met918Thr heterozygous missense variant in the RET gene, whose allelic frequency accounts 0.00000398. As RET mutations correlate with HSCR, multiple endocrine neoplasia IIA and IIB, pheochromocytoma, and medullary thyroid carcinoma, we performed chest, neck and abdominal radiological examinations, serum tumour markers, and we recommended a close follow-up for the late-onset occurrence of tumours. This case, identifying a de novo pathogenic variant in the RET gene, highlights the importance of using clinical exome sequencing or a panel of genes associated with the specific disease rather than looking for mutations in the single most frequently correlated gene.

Patient Perspective

Parents were informed about clinical features of disease and they agreed with management.

Informed Consent

Parents gave informed consent for the composition of case report.

Declarations

Ethics approval and consent to participate achieved

Consent for publication achieved

Authors' contributions: Drs Silvestri, Dr Rinaldi, Drs Giansanti and Drs Russo conceptualized and designed the case report, drafted the initial manuscript and reviewed and revised the manuscript.

Dr Spalice and Dr Pizzuti contributed to conception and design of the manuscript, carried out the initial analyses, analysed and interpreted data, supervised and coordinated the manuscript and reviewed and revised it.

Drs Schiavetti designed the data collection instruments, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

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