Hypoventilation in a case of congenital Rett syndrome

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Abstract

Breathing disturbances are often a major clinical concern during wakefulness of classic form of Rett syndrome, but data for atypical forms are lacking. We report the case of a 20-month-old female affected by the congenital variant of Rett syndrome, that is characterized by severe hypotonia and neurodevelopment impairment. She presented hypoventilation, persistent periodic breathing and sustained desaturation during sleep time, without obstructive nor central events; pulse oximetry and capnography during wakefulness were strictly normal. To the best of our knowledge, this is the first case of Rett syndrome presenting hypoventilation. Hypotonia may play a major role in the genesis of hypoventilation and hypoxemia in our patient. Non-invasive ventilation led to quality-of-life improvements. Thus, we suggest screening patients with congenital Rett variant through transcutaneous bedtime carbon dioxide and oxygen monitoring. Moreover, in our case, assisted control mode was a breakthrough to achieve adequate ventilation.

Introduction:

Rett syndrome (RS) is a severe neurogenetic syndrome, affecting one baby every 10.000 live-born, almost exclusively female. Its congenital variant of Rett syndrome (CRS) accounts for just 5-7% of all cases, and the clinical picture is characterized by severe hypotonia, often present at birth, and neurodevelopmental delay since the very firsts few months. Classic RS leads to remarkably breathing instability, usually even more pronounced during wakefulness. We report a 20-month-old female affected by a congenital variant of Rett syndrome, how showed central apneas, periodic breathing, and persistent hypercapnia only during sleep time. Such findings were never reported before in a child affected by Rett syndrome. We present ventilatory and clinical management of this unique case.

Case report

The patient is a full-term Caucasian girl, born after an unremarkable pregnancy and with no perinatal issues. She was admitted due to an icterus and a urinary tract infection on the fifth day of life. Hypotony was remarkable, together with reduced weight gain and recurrent emesis. Fundus oculi, cranial and abdominal ultrasound were normal; cardiac ultrasound showed only the persistency of the foramen ovale. She tested negative for Angelman and Prader-Willi performed due to hypotonia. At the age of 2 months, brain magnetic resonance (MR) was reported unremarkable, and she was discharged shortly after.

She came to our attention at the age of 10 months, the psychomotor delay had become evident, and she scored <70 on the Developmental Profile-3 test. She did not properly control the head; she reached but did not grasp objects and fix her gaze just for up to three minutes. The head circumference was 44 cm

(5-10°centile). CGH-array and extensive metabolic screening, including lumbar puncture, tested negative; evoked potentials were within normal ranges. Intensive physiotherapy allowed her to eat semi-liquid foods safely, reach and grab objects with her hands and maintain ocular contact for several minutes. Despite efforts, axial hypotonia progressively worsened in the following months, and the hand's grip remained poor. At the age of 16 months, she underwent MR showing a mild bilateral ventricle and subarachnoid spaces widening; MR spectroscopy was normal. Clinical exome analysis provided a diagnosis of Rett syndrome 3-months after, identifying a de novo heterozygous mutation in MECP2 gene (c.396_397insA variant). After that, we performed polysomnography, showing a not well-organized electrical activity and diffuse irritating signals at the EEG. PSG was performed using Somtè PSG (Compumedics, Australia). Cardiorespiratory data included airflow (nasal pressure transducer and oronasal thermistor if available), body position, body movements, thoracic and abdominal movements assessed by respiratory inductance belts, SpO2, and video recording. The electroencephalographic record was based on the international 10-20 system with electrodes in positions F1-A2, F2-A1, C3-A2, C4-A1, O1-A2, O2-A1, recording of eye movements. Transcutaneous carbon dioxide pressure (PtcCO2) recordings was performed simultaneously (SenTec Digital Monitor, SenTec Inc, Therwil, Switzerland). Scoring of respiratory events was performed by an experienced reader, according to the American Academy of sleep medicine (AASM) criteria: obstructive apnea was defined as the absence of nasal airflow with continued chest movements for at least two breaths. Central apnea was defined as the absence of nasal airflow with the interruption of respiratory effort lasting more than 20 seconds or associated with arousal and/or a 3% oxygen desaturation. Periodic breathing was defined as three or more episodes of central apnea lasting $>$ 3 seconds each and separated by $<$ 20 seconds of normal breathing. She spent 55% of her total sleep time (TST) with peripheral oxygen saturation (SpO_2) <90%. Her oxygen desaturations index (ODI) was 13.9, defined as the number of desaturations >3% per hour of TST. Periodic breathing (PB) accounted for 25% of TST matching criteria for persistent periodic breathing (PPB). The mean percutaneous carbon dioxide partial pressure ($PtcCO_2$) during bedtime was 50 mmHg, and she spent 57% of the TST above this limit. Therefore, she fulfilled even the stricter paediatric criteria for hypoventilation basing on persistent overnight hypercapnia. Obstructive events were virtually absent with a 0.2 of mixed-obstructive hypopnea apnoea index (MOHAI), defined as the number of such episodes per hour of TST. Following the clinical evidence of a huge difference in breathing patterns between daytime and bedtime, we performed measurements of SpO2 and PtcCO2 during wakefulness, which were strictly normal (mean PtcCO2 35 mmHg, range 34-36 mmHg). Therefore, the increase of PtcCO2 between wakefulness and sleep is greater than 10 mmHg providing further confirmation of nocturnal hypoventilation.

Non-invasive positive pressure ventilation (NIV) was started during bedtime. We set spontaneous timed ventilation with shrink spam to enhance adaptation inspiratory positive airway pressure (IPAP) 8 cmH_2O, expiratory positive airway pressure (EPAP) 4 cmH_2O, with a respiratory frequency of 23 breaths per minute (very close to the patient one). Such setting normalized SpO_2 values with minimum SpO_2 92% and an improvement of ODI to 7.2 events/hour. Carbon dioxide even worsened with a mean $PtcCO_2$ of 51.7 mmHg, and 100% of TST spent above 50 mmHg. The first attempt was to increase IPAP to 14, reaching a partial improvement of $PtcCO_2$, lowering the percentage spent above 50 mmHg to 29% of TST. At the same time, ODI was reduced to 0.5 events/hour. Shifting ventilation mode to adaptive pressure controlled (APC) mode and slightly increasing IPAP to 16 cmH_2O, we finally obtained $PtcCO_2$normalization (peak 49 mmHg). In the few following days, a slight improvement of the hypotonia and social interaction with the caregiver was noticed. Due to hypotonia, we performed an x-ray of the column, revealing extremely precocious scoliosis (T4-L1 Cobb angle 26°).

Discussion:

Rett syndrome-related breathing features, like hyperpnoea followed by breath-holding, Valsalva efforts, and periodic breathing, are easily identifiable during wakefulness. Such symptoms usually reduce or even abruptly disappear at sleep onset[1]. Among the patients with Rett syndrome with pathological polygraph, nearly all present obstructive events during sleep, with a thin minority of central events associated with severe obstructive ones[2]. Remarkably, no patient with RS showed hypoventilation or hypercapnia[2]. MECP2 gene plays an important role in autonomic system regulation [3]. Animal models showed an important role of MECP2

in breathing centres sensitivity to CO2, and its mutations may lead to the typical respiratory instability of RS[4]. To the best of our knowledge, this is the first case reporting hypoxemia and hypoventilation in a patient affected by RS. No articles perform an in-depth analysis of breathing patterns of RS variants, in particular during sleep-time. Patients with CRS are a peculiar cohort; they will never walk autonomously and may acquire the ability to articulate few simple words at best, usually show severe mental retardation since the very first's months of life. At the diagnosis, only a few cases present epilepsy (the landmark of the classic form), but electrical activity alterations are nearly always identified at the EEG[5], [6].

As previously stressed, the congenital variant is deeply impacted by hypotonia that is as severe as to cause scoliosis within the very first years of life[7]. Therefore, in CRS, hypotony maybe, per se, cause desaturation and hypoventilation as for other neuromuscular diseases in children[8], suggesting different pathogenesis than for classic form of RS. The normality of PtcCO2 during waketime (when muscle strength is relatively increased) supports this suggestion. Of particular interest is the persistent periodic breathing of this patient. Breathing centres homeostasis is very fragile in RS due to MECP2mutation[4], with a consequent high gain loop causing periodic breathing. Such events may be boosted by repeated desaturations caused by CRS-related hypotonia[9], [10]. Therefore, although a ST mode of ventilation is usually preferred to maximize patient comfort, an assisted pressure-controlled mode could be necessary to overcome the lack of appropriate respiratory centres control. Providing an adequate ventilation in such patients could contribute to the daytime quality of life and hypotonia improvement, as already reported for other hypotonic diseases[8].

In conclusion, we think that this single case suggests the need for a very early polygraph or at least pulse oximetry plus capnography in each patient affected by the congenital variant of Rett syndrome. Broadly speaking, we suggest considering a diagnosis of congenital Rett syndrome patients with hypotonia without a diagnosis.

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