

# Sleep disordered breathing in Noonan syndrome: a rare case report

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## Abstract

We report the case of a child with Noonan syndrome affected by hypertrophic cardiomyopathy and severe obstructive sleep apnea syndrome. The patient was born at 35 weeks gestational age (birth weight 3,340 g) and required mechanical ventilation. At the age of 4 years and 2 months, he was referred to our center for sleep cardiorespiratory polygraphy. His parents reported frequent obstructive sleep apnea, noisy respiration and snoring, oral breathing and falling asleep during the day. They were anxious that the child could die from asphyxiation during sleep. After the polygraph study had started, the patient began napping and immediately the polygraph showed several bouts of obstructive apnea and oxygen desaturation. He was referred for urgent adenotomy. At the age of 4 years and 5 months (3 months after surgery), the symptomatology and repeat sleep polygraph study showed a marked improvement.

In conclusion, obstructive sleep apnea is a very hazardous condition for children with Noonan syndrome. They are a population at risk because of facial problems and cardiopathy. The real global incidence of obstructive sleep apnea syndrome in these children is unknown.

## Keywords

Obstructive sleep apnea syndrome, Noonan syndrome, polygraphy, sleep study.

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## Introduction

Obstructive sleep apnea syndrome (OSAS) is a condition of recurrent upper airway obstruction that leads to intermittent hypoxia, sleep disruption, learning disabilities and decreased somatic growth [1]. Overnight polysomnography is the only reliable tool that can differentiate OSAS from primary snoring [1]. Cardiovascular consequences are frequent in patients with OSAS [2].

Noonan syndrome (NS; OMIM 163950) is a genetically transmitted autosomal dominant disorder characterized by distinctive facial deformities, short stature, chest deformity and congenital heart disease [3]. The main facial features of NS are hypertelorism with down-slanting palpebral fissures, ptosis, and low-set posteriorly rotated ears with a thickened helix. Additional features are possible, such as a webbed neck, chest deformity, mild intellectual deficit, cryptorchidism, poor feeding in infancy, bleeding tendency, and lymphatic dysplasia [4]. The cardiovascular defects usually associated with this condition are pulmonary stenosis and hypertrophic cardiomyopathy [5]. The cardiological course may be stable or progressively worsening, or it may improve. Management is similar to that for any patient with hypertrophic cardiomyopathy [3].

We report the case of a child with NS affected by hypertrophic cardiomyopathy and severe OSAS. History and clinical considerations have been included.

## Case report

The case study was based on pre-existing clinical practice, so that ethical permission and informed consent were unnecessary. The study was performed in accordance with the Declaration of Helsinki and under the terms of all relevant local

legislation. Written informed consent was obtained from the patient's parents for publication of this case report and any accompanying images.

## Patient

The case patient was born at 35 weeks gestational age (birth weight 3,340 g) and required mechanical ventilation. His mother, father, and an older brother were healthy. He showed left ventricular hypertrophy, liver and spleen hypertrophy, cryptorchidism and bifid uvula. From the age of 2 years, he suffered from persistent sleep apnea, nasal obstruction, and frequent bouts of high airway infection. At the age of 2 years and 8 months, otorhinolaryngological evaluation disclosed adenoid hypertrophy. Since he was affected by cardiopathy, the anesthesiologist postponed the surgical intervention.

## Physical examination and laboratory tests

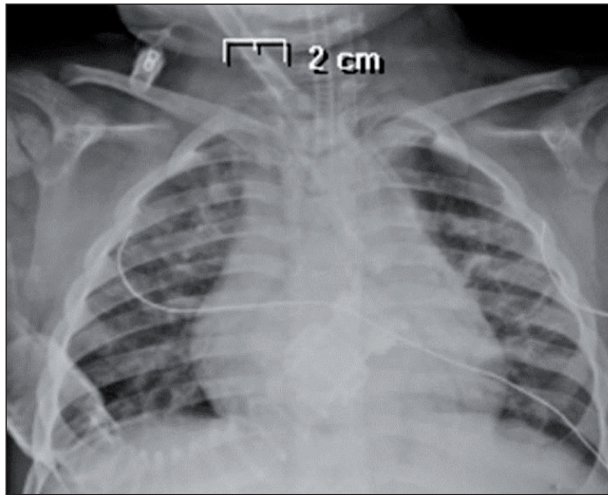
At the age of 4 years and 2 months (body weight 15 kg, length 92 cm, BSA 0.6), he was referred to our center for cardiorespiratory portable polygraphy [6]. His parents had reported frequent obstructive sleep apnea (OSA) followed by unblocking of the airway, noisy respiration and snoring, oral breathing, and falling asleep during the daytime. They were anxious that the child could die from asphyxiation during sleep. After the polygraphy had started, the child began to nap and immediately the polygraph showed several bouts of obstructive apnea and oxygen desaturation. As a result, he was hospitalized.

His blood coagulation profile was normal. A chest X-ray showed heart hypertrophy (**Fig. 1**), and the polygraph was applied that same evening again to record for a full night (**Tab. 1**, **Fig. 2A** and **Fig. 2B**). Respiratory events were inspired by the American Academy of Sleep Medicine guidelines [7]. At the same time, he showed nocturnal (during sleep) pCO<sub>2</sub> of 58 mmHg and HCO<sub>3</sub> 32 mmol/L and diurnal (wakeful) pCO<sub>2</sub> of 41 mmHg and HCO<sub>3</sub> 26 mmol/L. Otorhinolaryngological evaluation with nasal fiberoscopy confirmed severe adenoidal hypertrophy (grade IV) and bifid uvula. He was treated with C-PAP initially, and then with a high flow nasal cannula [8]. A cardiological ultrasound evaluation showed a left intraventricular gradient of 26 mmHg; left ventricle with basal hypertrophy of the septum (14 mm); systolic obstruction of the ventricular cavity; mild mitral and tricuspid

insufficiency; normal right ventricle function. He was referred for urgent adenotomy.

After surgery, the patient was extubated and awakened successfully in the Intensive Pediatric Care Unit. He showed a rapid improvement in sleep quality and sleep respiratory pattern, and was discharged.

At the age of 4 years and 5 months (3 months after surgery), a repeat sleep polygraph study



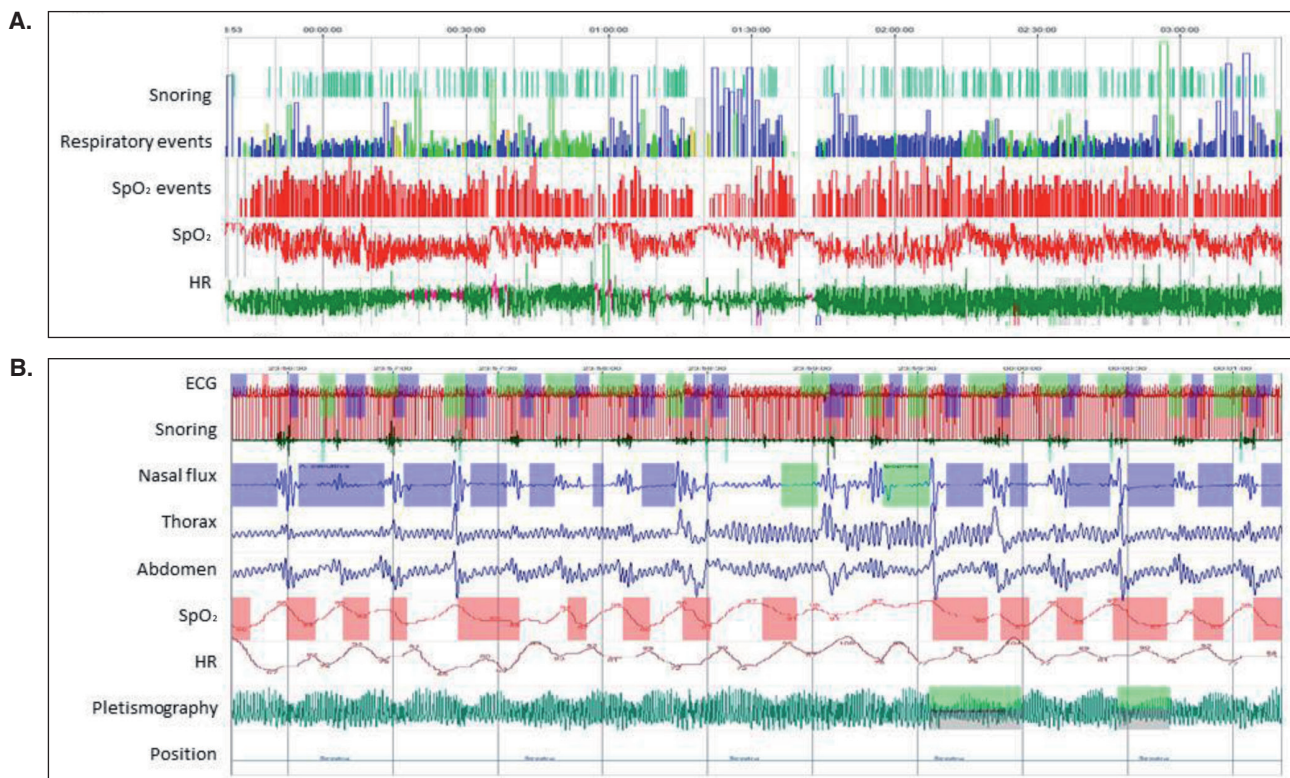
**Figure 1.** Chest X-ray showing hypertrophic cardiomyopathy.

showed a significant improvement (**Fig. 3A** and **Fig. 3B**). Thyroid function was normal; screening for celiac disease was negative. Bone age evaluation

**Table 1.** Summary of actigraphy and echocardiography findings before and after adenotomy.

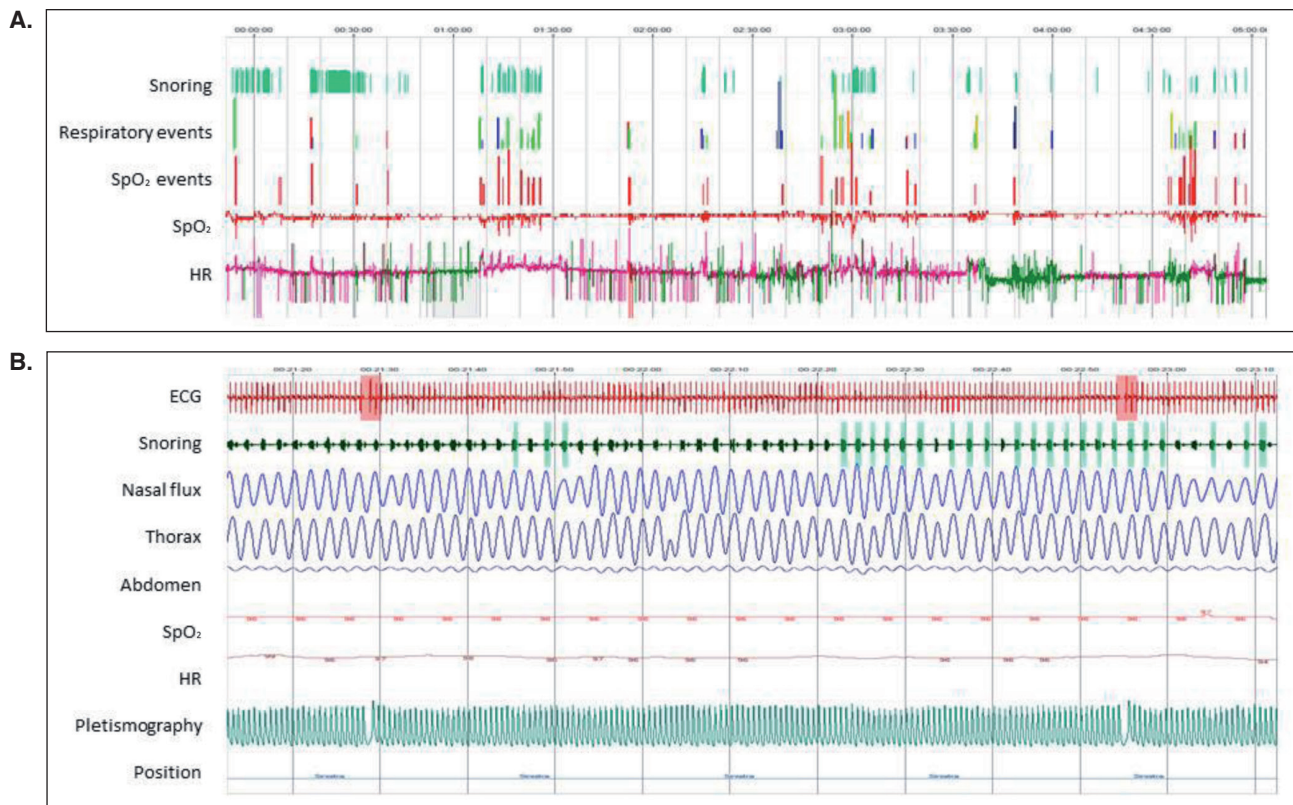
	Before surgery (T = 0)	Three months after surgery
<b>Sleep actigraphy recording</b>		
AHI (events/h)	114	9
OA (events/h)	85	3
ODI (events/h)	101	8
Mean SpO <sub>2</sub> (%)	93	96
Min SpO <sub>2</sub> (%)	79	86
SpO <sub>2</sub> < 90% (%)	21.3	0.4
Sleep pCO <sub>2</sub> (mmHg)	58	41
<b>Echocardiography</b>		
EDV (mL)	18	Unchanged
ESV (mL)	4	-
EF (%)	78	-
EDV (mL/mq)	30	-
ESV (mL/mq)	7	-
TAPSE (mm)	23	-

AHI: apnea-hypopnea index; OA: obstructive apnea; ODI: oxygen desaturation index; EDV: end-diastolic volume; ESV: end-systolic volume; EF: ejection fraction; TAPSE: tricuspid annular plane systolic excursion.



**Figure 2. A.** Four-hour cardiorespiratory polygraphy during sleep before surgery (from 11:50 PM to 3:30 AM). The graphic shows continuous respiratory events (blue = obstructive apneas, green = hypopneas) and desaturation (SpO<sub>2</sub> events; red colors). **B.** Three-minute cardiorespiratory polygraphy during sleep before surgery. The graphic shows respiratory events (nasal flux; blue = obstructive apneas, green = hypopneas) and desaturations (SpO<sub>2</sub> events; pink colors).





**Figure 3. A.** Four-hour cardiorespiratory polygraphy during sleep 3 months after surgery (from 11:45 PM to 5:15 AM). The graphic shows significant improvement with regard to both respiratory events (blue = obstructive apneas, green = hypopneas) and desaturation. **B.** Three-minute cardiorespiratory polygraphy during sleep 3 months after surgery.

(right arm X-ray) showed a delay of skeletal growth with an age of 3 years. The cardiological evaluation showed the persistence of the intraventricular gradient, unchanged from that performed before surgery. Finally, his parents were now satisfied with how he slept.

## Discussion

This is the second reported case of childhood NS showing severe OSAS and sleep hypercapnia which benefited from adenoidectomy. Previously, Khirani et al. [9] reported a 15-month-old boy with OSAS and moderate hypertrophic cardiomyopathy initially treated with beta-blockers (stopped 6 months after birth because of an improvement on ultrasonographic examination). In that case, because of important oxygen desaturation events during daytime napping, he was hospitalized, and his sleep pattern was assessed by overnight actigraphy. After surgery, he showed complete actigraphic recovery. Four months later, polysomnography during daytime napping confirmed the recovery [9]. In our case, clinical improvement was also excellent. Polygraphy, performed 3 months after surgery,

although much improved, showed that the problem was not completely resolved. In many children with craniofacial disorders, soft tissue correction, for example by adenoidectomy, does not always fully remedy the airway obstruction [10], as in our case. Further assessment and longer follow-up are mandatory.

Clinical management of NS focuses on cardiological treatment and follow-up, monitoring of growth and development, and symptomatic intervention when required [11]. About 25% of patients die because of heart failure in the first year [5]. The potential for airway difficulties exists in NS due to aberrations in the airway such as a high palatal arch, dental malocclusion, and micrognathia in children [3]. Unfortunately, no data exist about the frequency of sleep respiratory disorders in these children. Therefore, polysomnography is indicated in children with congenital heart disease or craniofacial anomalies, such as in NS, with adenotonsillectomy as a possible option to treat OSAS [12].

The risk of complications due to the presence of severe OSA in patients with NS affected by cardiopathy outweighs the risk of perioperative and/or postoperative management. In general,

OSAS negatively affects growth, neurocognitive function, and cardiovascular physiology [13], with higher pulmonary artery pressure and impaired right ventricular function [14]. The presence of hypertrophic obstructive cardiomyopathy renders these children susceptible to acute congestive heart failure due to hemodynamic fluctuations [15].

This study reports the first application of sleep respiratory polygraphy in a child with NS affected by OSAS and cardiopathy. In this case, previous anesthesiological evaluation indicated that surgery was necessary, but the polygraphic evaluation made surgical intervention mandatory. Polysomnography should be performed in children with cardiopathy, such as those with NS, to provide a full assessment of the sleep respiratory status before surgery. The cardiovascular consequences of OSAS and the congenital cardiopathy amplified each other and resulted in both short- and long-term adverse cardiovascular outcomes. A limitation of this study is the failure of the full polysomnography recording (with EEG).

OSAS is prevalent in two peak periods. The first occurs in children from 2 to 8 years of age, with the presence of an enlarged adenoid and/or tonsils. Approximately 0.5-1% of all children will have clinically relevant OSA [16]. Moreover, NS has an estimated prevalence of 1 in 1,000 to 2,500 live births [3]. In Italy, there were 474,000 live births in 2016. If the two events are independent of each other, and if the incidence of OSAS in NS is the same as in the general population, 1-2 NS neonates per year in Italy will develop OSAS.

## Conclusion

OSA must be treated promptly in children with NS. They are a population at risk because of facial problems and cardiopathy. The clinical situation significantly improved with adenotomy, but the patient requires strict follow-up after surgery. The real global incidence of OSAS in these children is unknown.

## Abbreviations

NS: Noonan syndrome

OSA: obstructive sleep apnea

OSAS: obstructive sleep apnea syndrome

## Declaration of interest

The Authors declare that there is no conflict of interest.

## References

1. Kaditis AG, Alonso Alvarez ML, Boudewyns A, Alexopoulos EI, Ersu R, Joosten K, Larramona H, Miano S, Narang I, Trang H, Tsaoussoglou M, Vandenbussche N, Villa MP, Van Waardenburg D, Weber S, Verhulst S. Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. *Eur Respir J*. 2016;47(1):69-94.
2. Bhattacharjee R, Kheirandish-Gozal L, Pillar G, Gozal D. Cardiovascular complications of obstructive sleep apnea syndrome: evidence from children. *Prog Cardiovasc Dis*. 2009;51(5):416-33.
3. Romano AA, Allanson JE, Dahlgren J, Gelb BD, Hall B, Pierpont ME, Roberts AE, Robinson W, Takemoto CM, Noonan JA. Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics*. 2010;126(4):746-59.
4. Kruszka P, Porras AR, Addissie YA, Moresco A, Medrano S, Mok GTK, Leung GKC, Tekendo-Ngongang C, Uwineza A, Thong MK, Muthukumarasamy P, Honey E, Ekure EN, Sokunbi OJ, Kalu N, Jones KL, Kaplan JD, Abdul-Rahman OA, Vincent LM, Love A, Belhassan K, Ouldin K, El Bouchikhi I, Shukla A, Girisha KM, Patil SJ, Sirisena ND, Dissanayake VHW, Paththinige CS, Mishra R, Klein-Zigheboim E, Gallardo Jugo BE, Chávez Pastor M, Abarca-Barriga HH, Skinner SA, Prijoles EJ, Badoe E, Gill AD, Shotelersuk V, Smpokou P, Kisling MS, Ferreira CR, Mutesa L, Megarbane A, Kline AD, Kimball A, Okello E, Lwabi P, Aliku T, Tenywa E, Boonchooduang N, Tanpaiboon P, Richieri-Costa A, Wonkam A, Chung BHY, Stevenson RE, Summar M, Mandal K, Phadke SR, Obregon MG, Linguraru MG, Muenke M. Noonan syndrome in diverse populations. *Am J Med Genet A*. 2017;173(9):2323-34.
5. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. *Lancet*. 2013;381(9863):333-42.
6. Zaffanello M, Gasperi E, Tenero L, Piazza M, Pietrobelli A, Sacchetto L, Antoniazzi F, Piacentini G. Sleep-Disordered Breathing in Children with Recurrent Wheeze/Asthma: A Single Centre Study. *Children (Basel)*. 2017;4(11):E97.
7. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, Marcus CL, Mehra R, Parthasarathy S, Quan SF, Redline S, Strohl KP, Davidson Ward SL, Tangredi MM; American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med*. 2012;8(5):597-619.
8. Hawkins S, Huston S, Campbell K, Halbower A. High-Flow, Heated, Humidified Air Via Nasal Cannula Treats CPAP-Intolerant Children With Obstructive Sleep Apnea. *J Clin Sleep Med*. 2017;13(8):981-9.
9. Khirani S, Lebourlangier N, Ramirez A, Fauroux B. Life-threatening obstructive sleep apnea caused by adenoid hypertrophy in an infant with Noonan syndrome. *Case Rep Pediatr*. 2012;2012:514514.
10. Garg RK, Afifi AM, Garland CB, Sanchez R, Mount DL. Pediatric Obstructive Sleep Apnea: Consensus, Controversy, and Craniofacial Considerations. *Plast Reconstr Surg*. 2017;140(5):987-97.

11. Tartaglia M, Gelb BD, Zenker M. Noonan syndrome and clinically related disorders. *Best Pract Res Clin Endocrinol Metab.* 2011;25(1):161-79.
12. Aurora RN, Zak RS, Karippot A, Lamm CI, Morgenthaler TI, Auerbach SH, Bista SR, Casey KR, Chowdhuri S, Kristo DA, Ramar K; American Academy of Sleep Medicine. Practice parameters for the respiratory indications for polysomnography in children. *Sleep.* 2011;34(3):379-88.
13. Li Z, Celestin J, Lockey RF. Pediatric Sleep Apnea Syndrome: An Update. *J Allergy Clin Immunol Pract.* 2016;4(5):852-61.
14. Cincin A, Sakalli E, Bakirci EM, Dizman R. Relationship between obstructive sleep apnea-specific symptoms and cardiac function before and after adenotonsillectomy in children with adenotonsillar hypertrophy. *Int J Pediatr Otorhinolaryngol.* 2014;78(8):1281-7.
15. Aggarwal V, Malik V, Kapoor PM, Kiran U. Noonan syndrome: an anesthesiologist's perspective. *Ann Card Anaesth.* 2011;14(3):214-7.
16. Dayyat E, Kheirandish-Gozal L, Gozal D. Childhood Obstructive Sleep Apnea: One or Two Distinct Disease Entities? *Sleep Med Clin.* 2007;2(3):433-44.