NONO-Associated Syndrome: A Rare Case Report in a 2-Month-Old Belgian Male Infant

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Keywords

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Abstract

We report the first Belgian case of *NONO*-associated syndrome, which was identified in a male infant presenting with hypotonia, macrocephaly, dysmorphic features, and severe non-compaction cardiomyopathy. A likely pathogenic *NONO* variant was identified through whole exome sequencing. While cardiac monitoring was guided by clinical findings, the genetic diagnosis allowed for personalised care and counselling. This case highlights the importance of combining phenotype recognition with molecular testing for early diagnosis. Continued case reporting is essential to improve our understanding of this rare X-linked disorder, and to guide future management and family planning strategies.

Case report

A boy born at 40 weeks of gestation was admitted to the NICU 24 hours after birth due to respiratory distress. His head circumference was 34.5 cm (−0.5 SD), his weight was 3032 g (−1.5 SD), and his length was 47.2 cm (−1.9 SD). On admission, the clinical examination revealed tachypnoea (88 breaths/min), generalized hypotonia, glandular hypospadias, and facial dysmorphism, including a broad forehead, hypertelorism, and microretrognathia (Figure 1). He was the first child of healthy, unrelated parents. Malformative assessment, including cardiac, abdominal, and transfontanellar ultrasounds, identified no major abnormalities except slight cardiac ventricular asymmetry. Genetic testing, including molecular karyotype analysis via Shallow Whole Genome Sequencing, was inconclusive. Because of the hypotonia, Prader Willi syndrome, congenital myotonic dystrophy, and spinal muscular atrophy were ruled out with dedicated tests. The patient's condition improved during hospitalization, and he was discharged on day 9 with scheduled follow-up care.

At home, persistent polypnea and hypotonia were observed, with no feeding difficulties or excessive sweating. At 2 months and 2 weeks of age, a cardiac ultrasound was performed as part of the follow-up for ventricular asymmetry. This revealed severe left ventricular enlargement and dysfunction (ejection fraction <20%, left ventricular (LV) end-diastolic diameter 37 mm (> 2 SD)) with a trabecular left ventricle and no intracardiac thrombus (Figure 2). Elevated cardiac biomarkers (troponin T: 180.8 ng/L; NT-proBNP: 17,244 ng/L) led to admission to the intensive care unit to manage congestive heart failure associated with left ventricular dilated cardiomyopathy. Treatment with an ACE inhibitor (enalapril) and fluid restriction resulted in stabilization, allowing for transfer to the paediatric unit for further evaluation.

At admission, a rapid increase in head circumference was noted, shifting from −0.5 SD to +1.28 SD. Transfontanellar ultrasound revealed a slightly increased Evans index (0.32-0.34), suggesting hydrocephalus.

During hospitalization, the patient received thiamine, riboflavin, and L-carnitine as substitute treatments while awaiting the results of metabolic investigations. Carvedilol (1 mg/day, increased to 1.5 mg/day) was introduced along with enalapril (gradually increased to a maximum of 1.5 mg/day). Fluid intake was restricted to 110 ml/kg/day. Regular cardiac monitoring confirmed the diagnosis of non-compaction cardiomyopathy (NCC). The most recent ultrasound scan revealed stable, severely impaired left ventricular function (ejection fraction (EF) 25%) and consistent dilatation (LV end-diastolic diameter 33-38 mm), as well as a reduction in NT-proBNP levels (8701 ng/L).

Axial hypotonia persisted throughout the hospitalization. After obtaining informed consent from the parents, whole exome sequencing (WES) in trio was performed, identifying a likely pathogenic variant (class 4) in the hemizygous state of the *NONO* gene (NM_007363.5, GRCh38):c.441dup p.(Ala148Cysfs*36). This de novo variant causes a premature STOP codon at exon 5/12. Loss-of-function variants in *NONO* are well-known pathogenic mechanisms responsible for X-linked syndromic intellectual developmental disorder-34 (MRXS34) (OMIM: 300967), consistent with a diagnosis of *NONO*-associated syndrome.

Given the patient's stable condition, good treatment tolerance, and overall well-being, he was discharged at 3 months and 3 weeks of age. At discharge, he was prescribed oral ACE inhibitors and beta-blockers, with plans for continued follow-up care by general paediatricians, paediatric cardiologists and a geneticist.

Discussion

Left ventricular non-compaction cardiomyopathy (LVNC) is a rare congenital heart disease characterized by prominent trabeculations and deep intertrabecular recesses in the left ventricle, resulting from arrested myocardial compaction during embryogenesis. In paediatric populations, LVNC ranks as the third most prevalent cardiomyopathy after dilated and hypertrophic cardiomyopathy. Its clinical presentation in children varies widely, ranging from asymptomatic cases to severe heart failure, arrhythmias, and thromboembolic events. Notably, LVNC in children is more frequently associated with genetic syndromes, neuromuscular disorders, and other congenital anomalies compared to adults. Genetic factors play a significant role in paediatric LVNC, with up to 41% of cases attributed to genetic mutations (1) Most familial cases follow an autosomal dominant inheritance, often involving mutations in sarcomeric protein genes (e.g., *MYH7*, *MYBPC3*, *TNNT2*). X-linked forms are also known – for example, mutations in the *TAZ* gene on the X chromosome cause Barth syndrome, a metabolic disorder that includes LVNC as a feature (2).

Among these, loss-of-function variants in the *NONO* gene have been identified as a cause of X-linked syndromic intellectual developmental disorder-34 (MRXS34), which includes features such as developmental delay, intellectual disability, hypotonia, macrocephaly, and LVNC.

The *NONO* gene, located at Xq13.1, consists of 13 exons and encodes the non-POU domain-containing octamer-binding protein *NONO* (also known as p54NRB). This protein belongs to the DBHS (Drosophila behaviour/human splicing) family and plays a crucial role in gene expression by regulating transcription, RNA processing, transport, and DNA repair (3). It also actively regulates synaptic transcript expression across a substantial number of connections within the central nervous system (4). In 2015, a study by Mircsof et al. first implicated *NONO* in cognitive impairment by showing that *NONO*-deficient mice exhibited impaired neuronal connectivity (5). The protein's deficiency disrupts GABA-ergic inhibitory synapses, potentially contributing to the cognitive deficits.

Loss-of-function variants in *NONO* are responsible for X-linked syndromic intellectual developmental disorder-34 (MRXS34; OMIM: 300967), a rare condition that predominantly affects males. This condition is marked by haploinsufficiency due to hemizygous loss-of-function variants in the *NONO* gene. It is characterized by developmental delay, intellectual disability, macrocephaly, anomalies of the corpus callosum, and left ventricular non-compaction cardiomyopathy (LVNC).

Over the past decade, 27 cases of *NONO*-associated syndrome have been reported, contributing to a better delineation of its phenotypic spectrum (6-8). Consequently, our case represents the 28th reported in the literature and the first in Belgium.

Among this limited cohort, 7 prenatal cases were reported, all diagnosed due to cardiac malformations. All patients were male, aged between 78 days and 29 years, with an average age of 9 years.

Individuals with *NONO*-associated syndrome exhibit a broad range of phenotypes, summarized in Table 1. All surviving patients presented with neurodevelopmental delay (27/27), with 23 experiencing moderate to severe intellectual disability. Cerebellar structural abnormalities were reported in 20/23 cases, most frequently involving abnormal corpus callosum development (17/22) (4,6,9).

Cardiac anomalies were identified in 22/26 patients, primarily non-compaction cardiomyopathy (18/22) (6,7). 7 patients showed prenatal cardiopathies (7/7), including 5 cases of left ventricular non-compaction (LVNC) (10). The incidence of LVNC in patients with pathogenic *NONO* variants is significantly higher than in the general population (4,9,11). Indeed, LVNC is considered a rare form of non-compaction cardiomyopathy, with a prevalence of less than 1% among young individuals. This rarity underscores its potential as an early diagnostic indicator of *NONO*-associated syndrome (7). Other cardiac anomalies are also frequent in patients with pathogenic *NONO* variants, including ventricular and atrial septal defects. In 2023, in vitro studies demonstrated that the *NONO*-knockout H9c2 cell line exhibited reduced proliferation and adhesion capacity, along with impaired mitochondrial function and altered energy metabolism. This condition may adversely affect cardiomyocyte development in rodent models (12).

The most common musculoskeletal feature was muscle hypotonia, observed in 19/25 cases. Nearly half of the patients experienced failure to thrive associated with feeding difficulties. Regarding craniofacial features, macrocephaly was the most prevalent (24/27), followed by a prominent forehead and abnormalities of the eyes, nasal tip, or external ear. Additional features include cryptorchidism and strabismus or more rarely, renal anomalies and haematological issues such as thrombocytopenia (9,13).

FIGURE 1: Pictures showing the patient's facial dysmorphia: broad forehead, hypertelorism, micrognathia, a broad nasal bridge and bulbous nasal tip (A: aged 1 month; B and C: at birth).

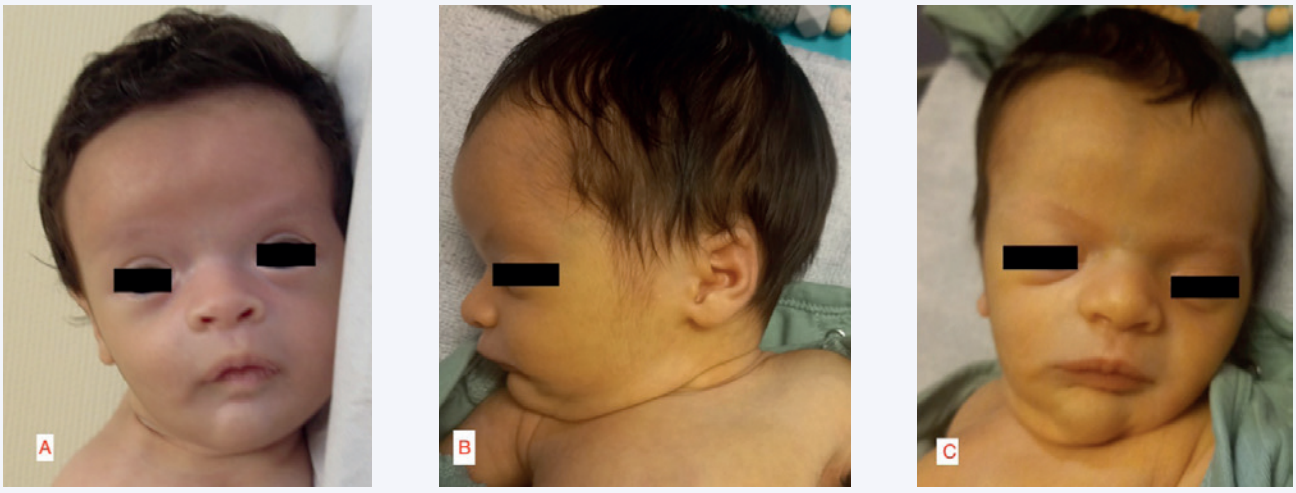
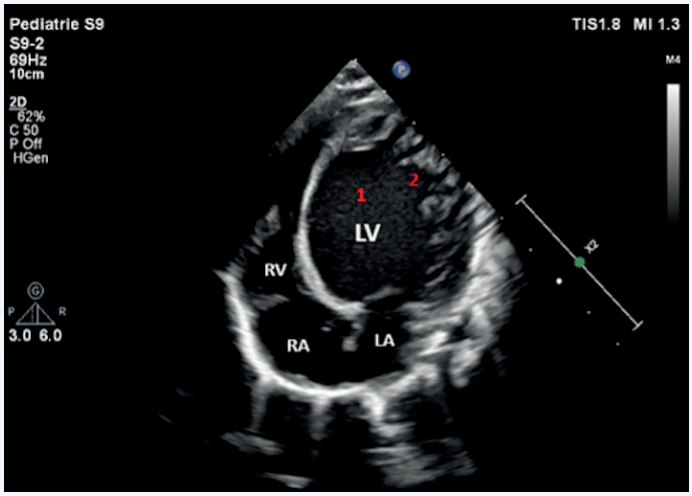


FIGURE 2: Echocardiogram of the patient aged two months and three weeks revealed left ventricular non-compaction (LVNC) with severe left ventricular (LV) dilatation (end-diastolic diameter 37 mm (>2SD)) and LV dysfunction (ejection fraction (EF) <20%) (1). The left ventricular apex appeared trabeculated (2).



Similarities and differences of our case compared to the literature

The literature reports a total of twenty-one distinct variants in the *NONO* gene implicated in the *NONO*-associated syndrome (7). We report a novel likely pathogenic variant (class 4) identified in our patient in *NONO* gene (NM_007363.5, GRCh38):c.441dup p.(Ala148Cysfs*36), in the hemizygous state and occurring de novo. This variant is responsible for a frame shift with a premature STOP codon at exon 5/12 and the absence of the production of a functional protein resulting in a loss-of-function mechanism. This mechanism is known to be responsible for *NONO*-associated disorder.

Our clinical case is consistent with the phenotype previously described in the literature and underscores the importance of a comprehensive malformative assessment in the presence of dysmorphic features and minor anomalies, such as hypotonia, hypospadias and asymmetry of the cardiac ventricles. These findings may serve as an early indicator of a genetic syndrome characterized by macrocephaly and cardiomyopathy. As observed in other reports, our patient presented with generalized hypotonia, progressive macrocephaly, low weight for gestational age, and left ventricular non compaction cardiomyopathy (LVNC). He exhibited well known dysmorphic features, including a prominent forehead and nasal abnormalities (nasal ensellure, broad nasal base, bulbous nasal tip). He also displays characteristics that are rarely described, such as hypertelorism and microretrognathia. Additionally, glandular hypospadias—although not definitively linked to *NONO*-associated syndrome—has been observed in other case reports (Table 1).

What can we learn from our case?

This case highlights the challenges in diagnosing malformative syndromes associated with neonatal hypotonia. A structured diagnostic pathway is essential for the early identification and management of genetic conditions in infants presenting with facial dysmorphism and hypotonia (14). Facial dysmorphic features, when combined with other clinical signs, facilitate the formulation of differential diagnoses for syndromes such as Down syndrome, Prader-Willi syndrome, and Cornelia de Lange syndrome. In our patient, midline abnormalities—including hypertelorism and hypospadias—prompted consideration of Opitz G/BBB syndrome (15). However, genetic testing plays a pivotal role in this context. A retrospective study involving 324 hypotonic infants reported diagnostic yields of 19% for chromosomal microarray analysis (CMA) and 31% for exome sequencing (ES) (16). Notably, combining CMA and ES provided the highest diagnostic yield, underscoring the complementary nature of these methods in identifying genetic causes of hypotonia. Due to the rarity of some syndromes, broad phenotypic variability, and clinical overlap, ES is the test of choice, as targeted testing for individual causes often leads to unnecessary delays and costs. Early genetic diagnosis confirms clinical suspicions and allows for targeted interventions, thereby improving patient outcomes. It also guides further investigations, management, and genetic counselling for affected families.

Although the patient does not exhibit entirely novel features, this case report provides a detailed description of both rare and common manifestations of the disease. These findings corroborate previous observations and highlight the phenotypic variability of the disease. Documenting these rare characteristics can help clinicians recognize atypical presentations, leading to improved diagnosis and patient management. Furthermore, collecting additional data on these traits may encourage further research into the underlying mechanisms. Even without newly identified features, our report contributes to a more comprehensive and nuanced understanding of the disease.

For paediatricians, the key message is that male infants presenting with macrocephaly, cardiac anomalies, and developmental delay—including hypotonia—should raise suspicion for a broad range of rare genetic conditions. Although each of these findings can occur in many disorders, their coexistence warrants early and comprehensive investigation. In this context, agnostic whole exome sequencing is the test of choice, as it allows for the identification of numerous rare syndromes, including *NONO*-associated syndrome. Recognizing this pattern early enables appropriate genetic evaluation and the timely implementation of targeted cardiac and neurodevelopmental interventions, ultimately improving patient care and outcomes.

How did this diagnosis influence the patient's follow-up?

This case presents an opportunity to understand the implications for patient management. The molecular diagnosis of a de novo, likely pathogenic variant in the *NONO* gene (OMIM: 300967) in our 2.5-month-old patient confirmed the cause of his severe LVNC. Although sustained cardiac monitoring was initiated based on his baseline cardiac dysfunction (ejection fraction <20%), the genetic diagnosis was instrumental in establishing a personalized care plan. It enabled us to define clear protocols for emergency intervention, resuscitation, and intensive care in case of decompensation.

Additionally, this diagnosis emphasized the need for early developmental support, as hypotonia observed at birth may predict future delays. Early intervention programs could help mitigate these outcomes (12).

The identification of a de novo *NONO* variant also had important implications for genetic counselling. Despite the de novo nature of the variant, the recurrence risk was estimated at approximately 1%, which led to a prenatal diagnosis during the couple's subsequent pregnancy. This highlights the critical role of molecular diagnostics in both clinical decision-making and reproductive planning. Regular follow-up is recommended for affected children, including monitoring of growth, development, vision, and hearing, with supportive therapies as appropriate (6,7).

TABLE 1: Clinical characteristics and proportions of all reported cases (4-9,11,13,17-19)

Human phenotype ontology (HPO)	Postnatal phenotypes	Prenatal phenotypes
Abnormality of the nervous system		
Cerebral anomalies (corpus callosum (17/22) and/or cerebellum anomaly, ventriculomegaly or polymicrogyria)	20/23	5/24
Seizures	5/25	
Neurodevelopmental delay	27/27	
Intellectual disability	23/23	
Behavioural disorders	11/20	
Cardiopathies	22/26	7/7
NCC (non-compaction cardiomyopathy, including LVNC)	18/22	5/7
VSD	9/22	4/7
ASD	7/22	1/7
Abnormality of the musculoskeletal system		
Muscular hypotonia	19/25	
Skeletal malformation	11/26	
Craniofacial Features		
Macrocephaly	24/27	
Prominent forehead	13/25	
Abnormality of the nasal tip	10/26	
Abnormality of the outer ear	12/24	
Hearing impairment	6/19	
Strabismus	10/24	
Visual impairment	9/22	
Deep set eyes	8/26	
Hypertelorism	2	
Micro/retrognathia	4	
Other abnormalities		
Failure to thrive	13/25	
Urinary tract malformation	2	
Cryptorchidism	9/24	
Thrombocytopenia	4	

Conclusion

The *NONO*-associated phenotype represents a complex neurodevelopmental and cardiac disorder, often accompanied by multisystem malformations.

This case reinforces the known clinical spectrum of the syndrome, particularly its association with hypotonia, macrocephaly, non-compaction cardiomyopathy (NCC), low birth weight, and craniofacial dysmorphism. Although the phenotype is consistent with previous reports, the *NONO* variant identified in this patient is novel and adds to the growing genotypic data available for this condition.

Careful phenotypic observation, including the recognition of facial dysmorphism, remains essential for guiding clinical suspicion. A structured diagnostic approach incorporating Whole Exome Sequencing is critical for confirming the diagnosis when a syndromic association is suspected.

In this case, the molecular diagnosis of a de novo *NONO* variant confirmed the aetiology of the cardiac pathology and helped guide a personalized management plan, including protocols for intensive care if decompensation occurred. It also had a direct impact on genetic counselling, allowing the family to benefit from prenatal testing in a subsequent pregnancy.

As the first case reported in Belgium and the 28th globally, this case emphasizes the importance of early recognition and comprehensive follow-up. It highlights the need for vigilant cardiac and developmental monitoring, as well as well as regular genetic follow-up and counselling.

Continued case reporting and research are essential to further refine the phenotype, improve genotype–phenotype correlations, and optimize long-term outcomes for patients with *NONO*-associated syndrome.

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