

# Multidisciplinary Dental Management in a Paediatric Patient with Noonan Syndrome Type 6 and NRAS Mutation - A Case Report

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## ABSTRACT

Noonan Syndrome is a genetically heterogeneous RASopathy marked by characteristic craniofacial features, congenital heart defects, growth delays, and various dental anomalies. This report presents a rare case of Noonan Syndrome Type 6 in a 5-year-old male with an NRAS gene mutation and selective tooth agenesis. The child exhibited multiple missing primary and permanent teeth, delayed eruption, a high-arched palate, and crossbites, alongside systemic features such as pectus excavatum, myopia, and a strong familial history suggestive of autosomal dominant inheritance. Comprehensive dental rehabilitation was completed under general anaesthesia, supported by multidisciplinary care involving paediatric dentistry, genetics, ENT, endocrinology, and anaesthesiology. This case underscores the critical role of paediatric dentists in early syndromic detection through oral manifestations and highlights the importance of coordinated care in managing complex systemic and dental needs.

**KEYWORDS:** Craniofacial Anomalies, Dental Management under General Anesthesia, Genotype/Phenotype Correlation, Multidisciplinary Care, Multiple missing primary and permanent tooth, Multiple unerupted tooth, Noonan Syndrome Type 6, NRAS Mutation, Pediatric Dental Rehabilitation, Selective Tooth Agenesis.

Autosomal Dominant, Congenitally Missing, Dental Care General Anesthesia, Genetic Diseases, NRAS, Pectus Abnormalities, Phenotype, Syndrome, Tooth Agenesis

## INTRODUCTION

Noonan syndrome (NS) is a genetically heterogeneous multisystem disorder belonging to the group of RASopathies, primarily inherited in an autosomal dominant pattern. First characterized in 1963 by Dr. Jacqueline Noonan, NS is marked by a constellation of features including short stature, chest wall deformities, congenital heart defects most frequently pulmonary valve stenosis and, in some cases, hypertrophic cardiomyopathy and distinctive craniofacial dysmorphisms such as hypertelorism, ptosis, down-slanting palpebral fissures, low-set posteriorly rotated ears, micrognathia, a high-arched palate, triangular facies, and a webbed neck with a low posterior hairline<sup>1</sup>.

The pathogenesis of NS is linked to dysregulation in the RAS/MAPK signalling pathway, with mutations identified in at least eleven genes, notably PTPN11 (~50% of cases), SOS1 (10–15%), RAF1, RIT1, KRAS, NRAS, BRAF, MAP2K1, CBL, SHOC2, and RAS<sup>2</sup>. Diagnosis is based on a combination of clinical phenotyping and confirmatory genetic testing. Differential diagnosis includes Turner syndrome and other overlapping RASopathies, necessitating careful evaluation. Given the multisystem involvement, NS requires a coordinated, interdisciplinary care model. Cardiac surveillance, growth hormone therapy for short stature, developmental and educational interventions, dental care, and genetic counselling

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form the cornerstone of management. Dental treatment in NS poses unique challenges, particularly in younger children, due to the interplay of systemic and behavioural complexities. These include congenital cardiac anomalies, coagulation disorders (present in an estimated 30–70% of patients), difficult airway anatomy due to short neck and micrognathia, and limited cooperation during clinical procedures<sup>3</sup>.

Oral and dental manifestations in NS are varied and may include class II skeletal malocclusion, crossbites, anterior open or deep bites, delayed tooth eruption, high-arched palate, dental agenesis, enamel hypoplasia, odontogenic cysts

or tumors, and an increased prevalence of caries—often aggravated by suboptimal oral hygiene practices. Gingivitis and periodontal concerns are also common. In rarer forms of NS, particularly those associated with NRAS mutations (accounting for <2% of cases), cutaneous features such as lentiginos, café-au-lait macules, and translucent skin may be observed<sup>4</sup>.

In such patients, comprehensive dental rehabilitation often necessitates general anesthesia (GA), undertaken only after meticulous preoperative assessment including cardiac and hematological workup. Anesthetic considerations include the use of specialized airway management tools—such as fiber-optic intubation—alongside perioperative antibiotic prophylaxis and gentle, minimally traumatic techniques to mitigate bleeding and other risks. Multidisciplinary coordination involving pediatric dentists, anesthesiologists, cardiologists, and hematologists is vital to ensure procedural safety and successful outcomes<sup>2,5</sup>.

Herein, we present a rare case of Noonan syndrome type 6

in a 5-year-old male child harboring an NRAS gene mutation, with clinical presentation including selective tooth agenesis. The patient underwent successful dental rehabilitation under general anesthesia, following a tailored, multidisciplinary protocol consistent with best practice guidelines for managing medically complex pediatric patients. The case underscores the importance of early diagnosis and integrative care in improving oral and systemic health outcomes in children with rare genetic syndromes.

**CASE PRESENTATION**

A 5-year-old male presented to the Department of Paediatric and Preventive Dentistry with complaints of pain in the upper right and left posterior teeth for the past two weeks. Medical history revealed a strong familial pattern of systemic and dental anomalies. The father exhibited congenitally missing permanent teeth, myopia, allergic rhinitis, diabetes, and hypothyroidism; the mother had hypothyroidism and a history



Fig. 1 A EXTRAORAL



FIG 1 B, PECTUS EXCAVATUM



Fig 2 A intraoral pre op maxillary arch

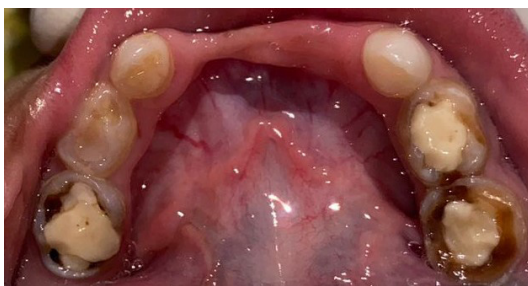


Fig 2 B intraoral pre op mandibular arch



Fig 2 C Intraoral pre op front view



Fig 3 Pre op OPG



Fig 4 A post op intraoral maxillary arch



Fig 4 B intraoral post op mandibular arch



Fig 4 C intraoral post op front view



of poliomyelitis; and the paternal grandmother had congenital absence of lower anterior teeth and hypothyroidism. There was no history of consanguinity, and the child had no siblings.

The prenatal period was complicated by maternal pregnancy-induced hypertension. The child was delivered at full term by caesarean section due to failed labor induction. Birth weight was 2.9 kg. Notably, five natal teeth were present at birth, with three extracted on day three and the remaining two extracted at three months. At four months, a vascular lesion in the anterior mandible was excised and diagnosed histopathologically as a haemangioma. The child also exhibited borderline growth delay and recurrent upper respiratory tract infections since infancy. Additional concerns included myopia since age three, allergic rhinitis with adenoid hypertrophy (managed with intranasal corticosteroids), and delayed speech development, for which therapy was initiated.

### Clinical Findings

Extraoral examination revealed prominent craniofacial features including hypertelorism, low-set and large ears, a depressed nasal bridge with a bulbous nasal tip, and a prominent philtrum groove (Fig 1A). Chest inspection revealed pectus excavatum (Fig 1B). The child was moderately built and nourished (height: 95 cm; weight: 18 kg; head circumference: 49 cm). No syndactyly or joint hypermobility was observed.

Intraoral examination noted multiple missing primary teeth (54, 52, 61, 62, 64) (Fig 2A), with grossly carious teeth (65, 72); (Fig 2B) and deep dentinal caries in 53 and 63 (Fig 2A). A dentoalveolar abscess was observed in 51 (Fig 2C). Crossbite was noted in both anterior and posterior regions (Fig 2C), along with a high-arched, narrow palate (Fig 2A). The patient's dental caries risk was high, reflected by a dmft score of 9.

Orthopantomography (OPG) confirmed the absence of several permanent tooth buds including 17, 14, 24, 27, 35, 33, 31, 41, 42, 43, 45, and 47, as well as several missing primary teeth. Previously restored teeth included 55, 51, 74, 75, and 85. The prognosis for teeth 55, 65, 51, and 72 was deemed poor (Fig 3).

### Investigations

Electrocardiography revealed sinus tachycardia, while echocardiography findings were within normal limits. Laboratory investigations including CBC, ESR, RBC indices, platelet count, coagulation profile, serum calcium, phosphorus, alkaline phosphatase, thyroid panel (TSH, T3, free T3), bleeding time, and clotting time were all within reference ranges. Serum Vitamin D was borderline. A peripheral blood smear showed a normocytic, normochromic pattern.

Chromosomal microarray and genetic analysis identified a heterozygous variant of uncertain significance in the **LRP6** gene, associated with autosomal dominant selective tooth agenesis. Additionally, a variant in **NRAS** (Exon 4) consistent with **Noonan Syndrome Type 6** was identified.

### MANAGEMENT AND FOLLOW UP

Due to the behavioral and systemic complexity of the case, full-mouth dental rehabilitation was performed under general anesthesia. Treatment included:

- **Pulpectomy:** Teeth 53 and 63

- **Extractions:** Teeth 51, 55, and 65
- **Hall Technique:** Teeth 74, 75, and 85
- **Space Maintenance:** Upper and lower Groper's appliances with bands on 75, 85, 53, 63 and acrylic replacements for missing 55, 52, 51, 61, 62, and 65 ( Fig 4 A, 4 B, 4 C)
- **Preventive Care:** Oral hygiene education, topical fluoride application, and dietary counseling

The patient was scheduled for regular reviews at 3-month intervals. Referrals were made to:

- ENT for adenoid management
- Endocrinology for thyroid function evaluation
- Ophthalmology for visual correction
- Medical genetics for further evaluation of the identified variants and syndromic correlation

### DISCUSSION

Noonan syndrome (NS) represents one of the most common non-chromosomal congenital disorders associated with dysregulation of the RAS/MAPK signaling pathway. Among the genetically heterogeneous group of RASopathies, NS type 6 is specifically attributed to mutations in the **NRAS** gene, which account for less than 2% of all NS cases<sup>4</sup>. This case highlights the complex interplay between craniofacial anomalies, dental developmental defects, and systemic features in a child with a genetically confirmed **NRAS** mutation, emphasizing the need for early diagnosis and coordinated, multidisciplinary care.

The phenotypic spectrum of NS is highly variable, with hallmark features including hypertelorism, ptosis, short stature, congenital heart defects, and webbed neck<sup>2</sup>. In the present case, clinical features such as hypertelorism, low-set ears, pectus excavatum, and growth retardation were consistent with previously described presentations of **NRAS**-related NS<sup>6</sup>. While the patient's echocardiogram was unremarkable, ongoing cardiac surveillance remains warranted, as structural cardiac anomalies, though not universal, are a common manifestation in NS patients<sup>2,5</sup>.

Notably, this case exhibited extensive dental involvement, which served as a primary driver for seeking care. Tooth agenesis involving both primary and permanent dentitions, as observed here, is rare and often underreported in NS. The absence of multiple tooth buds, combined with delayed eruption, crossbites, high-arched palate, and susceptibility to caries, strongly supports a syndromic pattern of dental development disruption<sup>2,5</sup>. These findings align with literature suggesting that **NRAS** mutations can contribute to significant odontogenic disturbances, though the precise mechanisms remain incompletely understood.

The identification of a heterozygous **NRAS** variant, along with phenotypic traits in family members, suggests an autosomal dominant pattern of inheritance. Although genetic confirmation in the father and grandmother has not yet been obtained, their clinical features raise the possibility of vertical transmission. This supports the need for broader familial genetic screening, genetic counseling, and surveillance of at-risk relatives, especially given the variable expressivity of



RASopathies<sup>6</sup>.

From a dental perspective, this case illustrates the diagnostic importance of evaluating developmental anomalies in the context of systemic findings. The severity of dental agenesis, poor prognosis of several teeth, and behavioral challenges necessitated comprehensive dental rehabilitation under general anesthesia. Space maintenance and preventive strategies were implemented to minimize long-term functional, esthetic, and psychosocial consequences. Importantly, the early use of prosthetic appliances helped restore masticatory efficiency and facial esthetics, contributing positively to the patient's quality of life and speech development.

Multidisciplinary management was central to this patient's care. Referrals to endocrinology, ENT, ophthalmology, and clinical genetics ensured a holistic evaluation of the child's medical and developmental status. Coordination among pediatric dentists, anesthesiologists, geneticists, and other specialists is essential, not only for the safe provision of dental treatment but also for long-term management of associated systemic conditions. Pediatric dentists often serve as first-line providers who detect syndromic features through oral examination, underscoring their critical role in early diagnosis and referral<sup>7</sup>.

## CONCLUSION

In summary, this case adds to the growing body of literature on NRAS-related Noonan syndrome and highlights the significance of oral findings as part of a syndromic diagnosis. It underscores the need for heightened clinical awareness, early genetic testing, and collaborative care pathways. Dental

anomalies, particularly severe hypodontia, may be early indicators of underlying genetic syndromes and should prompt thorough evaluation when accompanied by systemic signs.

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