

# orphan<sup>a</sup>inesthesia

Anaesthesia recommendations for patients suffering from

## Noonan syndrome

**Disease name:** Noonan syndrome

**ICD 10:** Q87.1

**Synonyms:** -

O. Koblinsky first described this syndrome in 1883. The term "Noonan syndrome" was first used in 1963 when Jacqueline Noonan and Dorothy Ehmke described nine children with a combination of congenital heart defect, short stature and characteristic appearance. Originally these patients were thought to resemble patients with Turner syndrome, despite having a normal karyotype. Patients with Noonan syndrome (NS) typically have characteristic facial, cardiovascular, and skeletal/growth abnormalities. The disease is transmitted as an autosomal dominant trait but the majority of the cases are sporadic due to de novo mutations.

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Medicine in progress



Perhaps new knowledge

Every patient is unique

Perhaps the diagnostic is wrong

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Find more information on the disease, its centres of reference and patient organisations on Orphanet: [www.orpha.net](http://www.orpha.net)

## Disease summary

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Incidence has been estimated to be between 1:1000 and 1:2500 without gender preponderance. Mutations in various components of the RAS-MAPK signaling pathway are known to cause Noonan syndrome [1]. Around 50% of patients with Noonan syndrome have mutations of the PTPN11 gene which encodes for a protein called SHP-2. Noonan syndrome-associated mutations cause the SHP-2 protein to be continuously active, rather than switching on and off in response to other cellular proteins. This constant activation results in aberrant activation and up-regulation of RAS signaling, and disrupts the regulation of systems that control cell functions such as growth and division and result in the abnormal features common to Noonan syndrome by mechanisms that are incompletely understood. The diagnosis of Noonan syndrome is primarily clinical. Diagnostic criteria have been suggested by van der Burgt [1]. Nowadays molecular testing offers the opportunity to confirm the diagnosis in the majority of patients. The craniofacial features of Noonan syndrome include hypertelorism, down-slanting palpebral fissures with high arched eyebrows, epicanthic folds, a depressed nasal root with a wide nasal base, a full upper lip, dental malocclusion, a high arched palate, micrognathia, and a broad or webbed neck. Cardiac anomalies like pulmonary valve stenosis (commonest-50-60%), hypertrophic cardiomyopathy (20%), atrial septal defects (8%), ventricular septal defects (5%) and patent ductus arteriosus (3%) are commonly present. About half of patients with Noonan syndrome have an unusual electrocardiographic pattern characterized by left-axis deviation, an abnormal R/S ratio over the left precordial leads, and an abnormal Q wave. Cardiac rhythm disturbance may occur particularly in patients with hypertrophic cardiomyopathy. Growth delay usually is of postnatal onset and short stature is of mild to moderate degree and proportionate. Relative macrocephaly is frequent. Other commonly associated anomalies may include feeding difficulties during infancy and childhood, gastroesophageal reflux and cryptorchidism in males. Pectus carinatum or excavatum, cubitus valgus and spina bifida and other vertebral and rib anomalies are common skeletal changes in Noonan syndrome. However, there is no evidence that true spinal malformations (hemivertebrae and spina bifida) are really associated with RASopathies.

Abnormal bleeding is a frequent accompaniment. Coagulation screens may show variable abnormalities such as a prolonged prothrombin time (PTT), activated partial thromboplastin time, platelet count, or bleeding time. Approximately 25% of individuals with Noonan syndrome have been reported to have partial factor XI deficiency, but various other coagulation deficits have been observed, for which an accurate estimate of the prevalence is not available (e.g. low factor XII and factor VIII activity, von Willebrand disease, rarely factor IX and factor II deficiencies). Further variable features include deficits in psychomotor and cognitive development, ocular abnormalities, dermatologic symptoms (hyperkeratosis, eczema), lymphedema, and renal anomalies. Occasionally Noonan syndrome may be associated with malignancy (particularly leukemia), a transient myeloproliferative disorder of infancy, jaw tumors (multiple giant cell lesions), hydrocephalus, Arnold-Chiari I malformation, and atlanto-axial dislocation. The multi-system involvement makes anaesthetic management of these patients demanding.

## Typical surgery

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Cardiac surgeries for correction of pulmonary stenosis (pulmonary valve balloon angioplasty), hypertrophic obstructive cardiomyopathy, septal defects or other heart defects, surgical correction of cryptorchidism in males, ocular ptosis, or pterygium colli; adenotomy and oral surgery. Abdominal procedures include surgery for malrotation of gut and

Caesarean section. Although, malrotation of gut is not a typical problem of Noonan patients. Both of these abdominal procedures are probably not more frequent than in the general population. Although a few cases of malrotation have been documented, none of them have been reported in the era of molecular confirmation.

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### **Type of anaesthesia**

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Use of both general anaesthesia and regional anaesthesia has been documented in this population of patients depending on the systemic involvement. Skeletal defects like kyphoscoliosis and lumbar lordosis can complicate regional anaesthetic techniques in these patients.

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### **Necessary additional diagnostic procedures (preoperative)**

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Haemoglobin, platelet count, coagulation studies (especially prothrombin time and factor XI levels, activated partial thromboplastin time, platelet count, and bleeding time). If scoliosis and/or significant pectus excavatum is present, chest X-ray, ABG, and pulmonary function tests should be performed. Echocardiography helps in confirming preoperative findings, detecting new anomalies, intraoperative monitoring and to assess the adequacy of surgical repair.

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### **Particular preparation for airway management**

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Potential for airway difficulties in Noonan syndrome exists due to aberrations in the airway like high palatal arch (55-100%), dental malocclusion (50-67%), micrognathia (33-43%) in children [2,3]. However adults have normal chin. Adequate airway preparation entails mandatory availability of age appropriate airway adjuncts like laryngoscopes, laryngeal mask airways and flexible fiberoptic bronchoscopes. Devices like video laryngoscopes and glidescopes can also be helpful. Ideally maintenance of spontaneous breathing until the airway is secured should be the preferred technique but since awake intubation technique is not ideal in paediatric patients, inhalational induction or slow intravenous induction are acceptable methods to maintain spontaneous ventilation.

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### **Particular preparation for transfusion or administration of blood products**

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In Noonan syndrome abnormal bleeding (epistaxis, easy bruising, menorrhagia), prolonged PTT and bleeding time are often encountered, due to a variable combination of deranged coagulation system and platelet defects. Specific testing may identify deficiency of various factors like factor XI (commonest and may require single factor replacement) [4], factor XII, factor VIII, factor IX and factor II and von Willebrand disease. Platelet defects occur due to decrease in megakaryocytes and splenomegaly. Severe postsurgical hemorrhage has been described following surgery despite normal in vitro clotting assays and platelet count [3]. Bleeding has been found to occur in surgical procedures in tissues with high content of plasminogen activators like dental extraction, tonsillectomy and nasal surgery [5]. The association of Noonan syndrome with von Willebrand disease has been reported for which preoperative desmopressin was administered to increase platelet function and von Willebrand factor levels.[6]

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### **Particular preparation for anticoagulation**

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In one of the reported cases Noonan syndrome was associated with bilateral moyamoya disease associated with activated protein C resistance and there was heterozygosity for the factor V Leiden mutation [7]. Anticoagulation (conservative treatment) helped to abolish the transient ischaemic attacks. However, this is a single case description of an association that is clearly by chance. There is no evidence of a general susceptibility to thromboembolism in Noonan syndrome.

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### **Particular precautions for positioning, transport or mobilisation**

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Not reported.

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### **Probable interaction between anaesthetic agents and patient's long term medication**

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The preexisting cardiac conditions of the patients may necessitate the administration of diuretics (amiloride, furosemide) or beta blockers (propranolol, sotalol). Negative inotropic effect of beta blockers may be exaggerated under anaesthesia.

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### **Anaesthesiologic procedure**

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If an uncorrected septal defect is present, air should be carefully removed from intravenous tubings and syringes [6].

Infective endocarditis prophylaxis is also recommended in presence of the structural defects of the heart. Recommendations are similar to those in cardiac anomalies of other etiologies

Association of cardiac anomalies (specifically pulmonary stenosis and HCM) demands slow and titrable administration of cardio stable anaesthetics (minimum sympathetic stimulation and minimum variations in heart rate, contractility and filling pressures) along with meticulous fluid administration. The main anesthetic goals can be summarized as:

- 1) to minimize sympathetic activation,
- 2) to avoid direct or reflex increases in contractility or HR,
- 3) to expand the intravascular volume in order to avoid hypovolemia and
- 4) to minimize the decreases in the LV afterload.

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### **Particular or additional monitoring**

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Pulse oximetry, direct arterial pressure monitoring and central venous pressure (CVP) monitoring is necessary especially if pulmonary stenosis is present. Echocardiography is invaluable in confirming the preoperative findings, detection of new onset anomalies, intraoperative monitoring and assessing the adequacy of repair in the postoperative period

[8]. Bispectral index can also be used to measure the depth of anaesthesia during induction and maintenance.

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### **Possible complications**

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Right ventricular failure can be precipitated by an increase in pulmonary vascular resistance or excessive administration of intravenous fluids.

Evidence supporting the triggering of malignant hyperthermia with volatile anaesthetics in patients of Noonan syndrome is weak. Only one purported case for which details are unknown is available [9]. Of note, Noonan syndrome can be mistaken for King-Denborough syndrome which has high propensity to develop malignant hyperthermia.

The multitude of coagulation and platelet defects can cause unexpected blood losses intraoperatively. Surgeries should be done in a centre where adequate blood products (including FFP) are available for immediate use to counter the haemorrhagic emergencies.

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### **Postoperative care**

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Post-operative management is not much different from any other post-surgical paediatric patient. However, specific attention has to be paid to cardio-pulmonary rehabilitation and extreme vigilance should be exercised during the first 24 hours with regards to vital parameters. Factors precipitating pain, hypotension, hypovolemia, hypothermia and sympathetic stimulation should be avoided as it can be highly detrimental to cardio-pulmonary system.

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### **Information about emergency-like situations / Differential diagnostics**

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caused by the illness to give a tool to distinguish between a side effect of the anaesthetic procedure and a manifestation of the diseases, e.g.:

Not reported.

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### **Ambulatory anaesthesia**

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Should be avoided. It should be only attempted (if at all) in low risk patients and surgeries

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### **Obstetrical anaesthesia**

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Anaesthesia for obstetric population involves the complex interplay of impaired cardiopulmonary function, difficulty in airway management and technical complexities in regional anaesthesia.

Sympathetic stimulation due to labour pain exacerbated by episodic prolonged Valsalva maneuver, increases in blood volume during uterine contractions or reduction with bleeding can cause significant haemodynamic instability[10,11, 12].

The complexity of airway management in pregnancy is compounded in presence of the preexisting difficult airway with an added risk of aspiration.

In presence of pulmonary stenosis, fluid administration acts like a double edged sword. Excessive fluid administration can precipitate right ventricular failure. However inadequate hydration prior to spinal or epidural block may cause and inordinate decrease in right ventricular output [13]

However despite these defects many females with Noonan Syndrome have delivered children without any complications.

## Literature and internet links

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*Please note that this guideline has not been peer-reviewed by an anaesthesiologist but by two disease experts.*

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