Anaesthesia in a parturient with Noonan's syndrome

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Purpose: To report the management of labour analgesia and subsequent anaesthesia for postpartum bleeding in a 19-yr-old parturient with Noonan's syndrome.

Clinical features: The patient presented in active labour at 36-wk gestation. She was known to have Noonan's syndrome and had been assessed regularly throughout pregnancy. Features of the syndrome exhibited by the patient included typical facies, chest skeletal abnormalities, pulmonary valve dysplasia, mental retardation and lymphoedema. In addition, she had Factor XI deficiency ($0.46 \text{ mg}\cdot\text{L}^{-1}$) and thrombocytopenia ($92 \times 10^9\cdot\text{L}^{-1}$), previously unreported in a parturient with this syndrome. Although epidural analgesia may have been considered the labour analgesic technique of choice, the risk of epidural haematoma caused by her bleeding diathesis made this unacceptable. This risk was balanced against the possibility of a potentially difficult intubation due to facial abnormalities, should emergency operative delivery become necessary. Labour analgesia was provided with intravenous patient controlled opioid analgesia (fentanyl $25 \mu\text{g}$ bolus, five minute lockout) despite her mental retardation. Dilatation and curettage required general anaesthesia after intubation with awake direct laryngoscopy using cautious sedation.

Conclusion: Noonan's syndrome is characterised by multi-system involvement, requiring thorough pre-operative assessment of cardiovascular, skeletal, haematological and central nervous systems. Clotting and platelet defects considerably restrict the possible analgesic and anaesthetic options for labouring patients with this syndrome.

Objectif : Présenter une ligne de conduite appropriée pour l'analgésie durant le travail et l'anesthésie pour saignement post partum chez une parturiente de 19 ans porteuse du syndrome de Noonan.

Éléments cliniques : La patiente s'est présentée en travail actif à 36 semaines de gestation. Elle était connue porteuse du syndrome de Noonan et avait été suivie régulièrement durant sa grossesse. Les composantes du syndrome présentées par la patiente étaient: facies typique, déformation thoracique, dysplasie valvulaire pulmonaire, retard mental et lymphoedème. De plus, elle présentait deux éléments non rapportés chez une parturiente atteinte de ce syndrome, soit un défaut en facteur XI ($0,46 \text{ mg}\cdot\text{L}^{-1}$) et une thrombocytopénie ($92 \times 10^9\cdot\text{L}^{-1}$). L'analgésie épidurale aurait pu être considérée comme la technique de choix chez cette patiente mais le risque d'un hématome épidural causé par la diathèse hémorragique rendait cette option inacceptable. Ce risque a été évalué par rapport à la possibilité d'une intubation difficile secondaire aux anomalies faciales si une urgence obstétricale nécessitait une approche chirurgicale. Malgré son retard mental, l'analgésie durant le travail a donc été réalisée avec une ACP avec fentanyl en bolus de $25 \mu\text{g}$ avec intervalle minimal de 5 minutes. Pour la dilatation et le curetage, on a utilisé une anesthésie générale avec intubation, cette dernière ayant été réalisée avec laryngoscopie directe sous sédation prudente.

Conclusion : Le syndrome de Noonan se caractérise par une atteinte multisystémique nécessitant une évaluation complète des systèmes cardiovasculaire, squelettique, hématologique et nerveux central. Des défauts affectant la coagulation ou les plaquettes limitent considérablement les options anesthésiques et analgésiques pour les patientes en travail porteuses de ce syndrome.

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NOONAN'S syndrome is characterised by abnormalities of the face, and cardiovascular and skeletal systems.¹ Few cases of anaesthesia in Noonan's syndrome have been described and only two in parturients.^{2,3} We describe labour analgesia and subsequent anaesthesia for postpartum bleeding in a parturient with Noonan's syndrome. Previous cases have identified potential anaesthetic concerns of difficult tracheal intubation and haemodynamic instability associated with the syndrome. However, in addition to these concerns, our parturient had a factor XI deficiency and thrombocytopenia.

Case report

A 19-yr-old primigravida (height 154 cm, weight 67.5 kg) was referred to the obstetric anaesthetic department in active labour at 36-wk gestation. There were additional considerations surrounding the pregnancy, which may have been a result of rape. She was known to have Noonan's syndrome and had been assessed throughout pregnancy. Characteristics of Noonan's syndrome present were as follows: typical facies (widely spaced eyes, downward slanting palpebral fissures, "hooded" eyelids, short-webbed neck, low set ears and micrognathia), skeletal abnormalities (pectus excavatum, "shield shaped" chest), cardiac disease (pulmonary valve dysplasia), mental retardation, lymphoedema and factor XI deficiency. Her mental retardation was such that she required supervision of "activities of daily living" and she had been assessed as having a mental age of eight years.

Although she was breathless on climbing one flight of stairs, her exercise tolerance had remained unchanged during pregnancy. Prenatal tachydysrhythmias required treatment with a small dose of propranolol, which was continued during pregnancy. Her electrocardiogram revealed a sinus tachycardia with right atrial and ventricular hypertrophy. Transthoracic echocardiography showed a dilated pulmonary artery, dysplastic valve without associated pulmonary stenosis/regurgitation and mitral valve prolapse with mild/moderate regurgitation.

The patient had a potentially difficult intubation posed by a high arched palate, short webbed neck and Mallampati grade III view but her mouth opening and neck extension were excellent. She had no history of easy bruising or excessive bleeding with minor trauma, albeit she had not had surgery. There was no family member with characteristics of Noonan's syndrome and the only relevant history was maternal von Willebrand's disease.

Her pregnancy had been complicated by left lower lobe pneumonia at 34-wk gestation, which was successfully treated with antibiotics and physiotherapy.

Due to the potential obstetric/anaesthetic risks and her geographically isolated abode, it was decided to induce labour at 36-wk gestation. During labour, her blood pressure was 140/90 mmHg (previously 115/70 at 34-wk gestation) and she had increasing peripheral oedema but no proteinuria. Her plasma electrolytes, liver enzymes, uric acid were normal, although she had developed progressive thrombocytopenia ($94 \times 10^9 \cdot L^{-1}$), probably related to gestational decline. Her coagulation profile was as follows: PT (prothrombin time) 15.0 sec, APPT (activated partial thromboplastin time) 48.5 sec, fibrinogen 1.74 g·L⁻¹ and factor XI level 0.46 mg·dL⁻¹. Her elevated PT was originally believed to be related to vitamin K deficiency, although two doses of intramuscular vitamin K in the peripartum period failed to improve this result. The elevated APPT was thought to be caused by the factor XI deficiency although the reason for the decreased fibrinogen was uncertain.

During labour our main concern was to provide safe and adequate analgesia, whilst being aware of her fear of vaginal examinations, her problems with comprehension due to her mental ability, her abnormal coagulation parameters and also her potentially difficult airway should emergency delivery become necessary. As regional techniques were thought to pose too great a risk of spinal haematoma and as non-invasive methods of analgesia proved insufficient, it was decided that intravenous patient controlled opioid analgesia was the best option (fentanyl bolus 25 µg, lockout interval five minutes). If the patient had been unable to understand the technique, the next step would have been intravenous nurse administered analgesia. Fortunately, after lengthy explanation to the patient, she was able to understand the principles necessary and this first option proved satisfactory. However, we were aware that this analgesic method this did not remove the problems caused by her potentially difficult airway should intubation become necessary. In addition, vaginal examination, although possible, was still difficult. After four hours and fifteen minutes of labour, a 2.24 kg male infant, with features of Noonan's syndrome, was delivered spontaneously. The Apgar scores at one and five minutes were 3 and 8 respectively. A mediolateral episiotomy was necessary due to fetal bradycardia and this was sutured with difficulty using local anaesthesia.

Over the following four hours she continued to bleed per vagina, despite the use of oxytocin. Although the uterus was well contracted, the placenta intact on delivery and no obvious lacerations, the continued postpartum haemorrhage (1200 ml over four hours) made it necessary for a more thorough examination to find the

cause of the blood loss. A second 16 g cannula was inserted for the rapid administration of fluids and the patient received antacid prophylaxis. With the concern over intubation, it was decided the trachea should be intubated with the patient awake using direct visualisation with the aid of local anaesthesia and sedation. Intravenous glycopyrrolate (200 µg) was used as an antisialagogue and antibiotics were given for endocarditis prophylaxis. The patient was monitored using non invasive blood pressure, ECG, oximetry and, after intubation, end tidal carbon dioxide concentrations. Intravenous midazolam (total 2 mg), fentanyl (total 100 µg) and propofol (total 20 mg) were administered incrementally to provide sedation. Topical anaesthesia was established with lidocaine 4% administered via a nebuliser, as well as using a "spray as you go" technique. After tracheal intubation using a 7 mm endotracheal tube, general anaesthesia was induced using 100 mg propofol and the patient's lungs were ventilated with nitrous oxide and oxygen (ratio 2:1). The patient remained cardiovascularly stable throughout the procedure and anaesthesia was maintained with incremental propofol.

There were no lacerations and curettage of the uterus only revealed a few clots and decidual fragments although the uterus appeared less contracted. The final diagnosis for postpartum bleeding was a combination of uterine atony and coagulopathy. The patient was therefore treated with further *iv* oxytocin in addition to 15 µg 1-deamino-8-D arginine vasopressin (DDAVP). This was given as a non specific adjunct to improve coagulation as it increases von Willebrand's and VIII factors in addition to increasing the adhesion and spreading of platelets at the injury site. On completion of the surgery, tracheal extubation was achieved once the patient was fully alert. Postoperatively, the patient continued to ooze per vagina although with diminishing blood loss. During the next week, the platelets, PT, APPT and fibrinogen normalised and the patient made an uneventful recovery.

Discussion

Noonan's syndrome, a disorder first described in 1963,⁴ is characterised by facial, cardiovascular and skeletal abnormalities. The exact incidence is unknown due to variability of phenotypic expression.¹ Most cases occur due to spontaneous mutation, however if inheritance occurs it follows an autosomal dominant pattern. The anaesthetic problems of these patients are listed (Table I). The facial, neck and chest appearance are similar to Turner's syndrome with characteristic features (ptosis, downward slanting eyes, broad flat nose, high arched palate, low set abnormal ear), shield shaped

chest deformity and webbing of the neck). However, unlike Turner's, the patients have a normal karyotype, may have mental retardation and usually a right, rather than left, sided cardiac lesion.

Three cases of anaesthetic management are reported in the literature, one in a child⁵ and the other two in parturients.^{2,3} The major focus of these reports related to intubation and haemodynamic instability (Table II). Our patient exhibited the characteristic facial appearance, skeletal abnormalities, mild cardiomyopathy, mental retardation and lymphoedema. However, in contrast to these cases, our patient also had a coagulopathy. Although bleeding tendency with Noonan's syndrome is known,⁶ it has not been a feature of the previous anaesthetic reports. This problem has great implications for the provision of both labour analgesia and operative anaesthesia, especially in a patient in whom intubation is likely to be difficult.

Thrombocytopenia has been associated with this syndrome⁷ and abnormal bruising after surgery has been reported in patients with normal platelet counts, suggesting platelet dysfunction.⁸ Factor deficiencies occurred in 50% of the patients reported by Sharland,¹⁰ the commonest being a reduction in factor XI activity. In the surgical literature, Sugar described a 22-yr-old man undergoing maxillofacial surgery with a normal platelet count but with decreased plasma fibrinogen level (1.25 g·L⁻¹), factor XI (49% normal) and factor XII (37% normal). Laboratory tests revealed a prolonged PT 62 sec (normal 43 sec) and kaolin cephalin clotting time (KCCT) of 17 sec (normal 14 sec). Despite preoperative prophylactic fresh frozen plasma the patient bled

TABLE I Anaesthetic problems in Noonan's Syndrome

<i>Problem</i>	<i>Aetiology</i>
Difficult airway/intubation	High arched palate, short webbed neck, micrognathia
Limited cardiovascular reserve	Associated cardiovascular disease especially pulmonary stenosis/atrial septal defect (mostly right sided lesions)
Difficulties performing awake procedures or obtaining consent	Mental retardation
Technical difficulties with regional procedures	Kyphoscoliosis/short stature
Increased risk of spinal haematoma with regional procedures	Bleeding diathesis (decreased factor XI, XII, Von Willebrand's factor or platelet dysfunction)
Difficulties with intravenous access	Lymphoedema/redundant skin
Electrolyte disturbances	Congenital renal abnormalities

TABLE II Anaesthetic cases with Noonan's syndrome

Reference	Age (yr)	Features	Operation	Anaesthetic
Dadabhoy ²	20	Noonan's facies Kyphoscoliosis	Elective CS	Failed epidural (technical), Spinal
Schwartz ⁵	7	Noonan's facies Cardiomyopathy (idiopathic hypertrophic subaortic stenosis, VSD) Moderate mental retardation	Cholecystectomy	GA (inhalation induction, difficult intubation)
McLure ³	25	Noonan's facies Shield shaped chest Severe cardiomyopathy (previous pulmonary, aortic, mitral valvotomies)	Intrauterine death at 30 wk Failed attempted induction of labour Followed by CS	Epidural for induction of labour GA (CS) requested by patient, awake fibreoptic intubation

CS = Caesarean Section

GA = General Anaesthesia

profusely intraoperatively and also postoperatively.⁹ With factor deficiencies, it is important to remember that the patient may not only bleed at the time of surgery but also in the postoperative period.

It should be noted that pregnancy itself can cause alterations in the levels of some of the coagulation factors which can be decreased in Noonan's syndrome. Factor XI levels normally decrease during pregnancy,¹¹ whereas factor XII and von Willebrand's factor levels actually increase.¹² In the healthy parturient, these changes do not usually have any clinical significance, although the pregnant patient is often hypercoagulable. However, in the case of a patient with Noonan's syndrome who may already have coagulation abnormalities, pregnancy may result in a clinically significant coagulopathy. These patients can be at increased risk for postpartum haemorrhage or increased blood loss, if Caesarean section becomes necessary. Additional risks are spinal haematoma with a regional technique and airway bleeding that may result from trying to secure a potentially difficult airway. Because of the complex nature of this problem it is advisable to involve a haematologist early in the care of these patients for guidance regarding the potential use of plasma products and/or medications to improve the patient's coagulation profile.

Our anaesthetic dilemma was further complicated by the possibility of a difficult intubation secondary to the typical Noonan's facies exhibited by our patient. Pregnancy increases this risk due to the upper airway mucosal vascular engorgement, oedema, increased facial fatty tissue disposition and breast enlargement. Awake, oral fibreoptic intubation may be the safest option in the event of general anaesthesia. Nasal fibreoptic intubation should be avoided because of technical

difficulties incurred from flattening of the mid face and the increased probability of haemorrhage secondary to vascular engorgement and coagulopathy. If time is limited, due to fetal distress or patient compromise, rapid topicalisation of the upper airway followed by intubation using direct visualisation of the larynx or using an intubation aid (e.g., lighted stylet) may be a better solution. However, the anaesthetist should have a plan of action, as well as the necessary equipment, in the event that intubation is not possible.

To summarise, patients with Noonan's syndrome may present with a wide variety of organ and system abnormalities including coagulation, cardiovascular and skeletal disorders, which present a dilemma for the anaesthetist. These abnormalities may be further compromised in the pregnant state. Emphasis should be aimed at recognising the disease process early in pregnancy, with referral to the appropriate specialists in order to define a suitable anaesthetic and obstetric plan.

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