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CASE REPORTS/CASE SERIES

Postoperative adrenal crisis in an adolescent with Loeys-Dietz syndrome and undiagnosed adrenoleukodystrophy

Crise surrénale postopératoire chez un adolescent souffrant de syndrome de Loeys-Dietz et de leucodystrophie avec insuffisance surrénale non diagnostiquée

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Abstract

Purpose *We present an unusual case involving an adolescent who experienced cardiovascular collapse postoperatively. He had more than one rare life-threatening genetic disorder, and herein we review the anesthetic management of a patient with Loeys-Dietz syndrome (LDS) and adrenoleukodystrophy.*

Clinical features *A 12-yr-old male (41.5 kg, American Society of Anesthesiologists' physical status III) with LDS, a connective tissue disorder, underwent posterior spinal fusion for spondylolisthesis. This patient demonstrated many signs of LDS: bifid uvula, retrognathia, dilated aortic root, aortic arch aneurysm, inguinal hernias and vertebral subluxations, and multiple areas of tortuous intracranial vessels. A fibreoptic intubation was performed and a balanced anesthetic was administered, consisting of opioids and a low-dose volatile agent. The patient was stable throughout surgery, and at the end of the procedure, his trachea was extubated and he was admitted to the intensive care unit. During the postoperative period, the patient became acutely hemodynamically unstable. Initially, the intensive care team considered the differential diagnoses of postoperative hemorrhage, postoperative sepsis, and cardiac failure secondary to aortic dissection. Supportive care was instituted, and these diagnoses were systematically ruled out. The differential diagnosis was expanded, and the patient was treated with corticosteroids after baseline cortisol levels were drawn. Later he was found to have primary adrenal failure, and it was determined by biochemical and genetic blood analysis that he also had adrenoleukodystrophy.*

Conclusions *Although Occam's razor states that physicians should exercise diagnostic parsimony when treating patients, it is possible for a patient to have two or more life-threatening unrelated genetic disorders. Consequently, diagnosticians must always develop and test new hypotheses when treating patients.*

Résumé

Objectif *Nous présentons le cas inhabituel d'un adolescent ayant manifesté une défaillance cardiovasculaire en période postopératoire. Il souffrait de plus d'un trouble génétique potentiellement fatal, et nous passons ici en revue la prise en charge anesthésique d'un patient atteint d'un syndrome de Loeys-Dietz (SLD) et de leucodystrophie avec insuffisance surrénale.*

Éléments cliniques *Un garçon de 12 ans (41,5 kg, statut physique III de l'American Society of Anesthesiologists) atteint de SLD, un trouble qui affecte les tissus conjonctifs, a subi une spondylodèse pour traiter une spondylolisthésis.*

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Ce patient a manifesté de nombreux signes de SLD: il avait une luette bifide, une rétrognathie, une racine aortique dilatée, un anévrisme de l'anneau aortique, des hernies inguinales et des subluxations vertébrales, ainsi que de nombreux sites de vaisseaux intracrâniens sinueux. Une intubation par fibre optique a été réalisée et une anesthésie balancée consistant en opioïdes et une faible dose d'agents volatils a été administrée. Le patient était stable pendant toute la chirurgie, et à la fin de l'intervention, on a extubé sa trachée avant de l'admettre à l'unité des soins intensifs. Pendant la période postopératoire, le patient est devenu hémodynamiquement instable de façon très prononcée. L'équipe de soins intensifs a d'abord envisagé les diagnostics différentiels d'hémorragie postopératoire, de sepsis postopératoire et d'insuffisance cardiaque secondaire à une dissection aortique. Des soins de soutien ont été mis en place, et ces diagnostics ont été méthodiquement écartés. Le diagnostic différentiel a été élargi, et le patient a été traité à l'aide de corticostéroïdes après que les niveaux de base de cortisol ont été déterminés. On a plus tard découvert qu'il souffrait d'insuffisance surrénale primaire, et une analyse sanguine biochimique et génétique a permis de déterminer qu'il était également atteint de leucodystrophie avec insuffisance surrénale.

Conclusion *Bien que le principe de parcimonie dicte que les médecins fassent appel à un seul diagnostic lorsqu'ils traitent des patients, il est possible qu'un patient soit atteint de deux troubles génétiques potentiellement fatals et non associés, ou plus. C'est pourquoi les diagnosticiens doivent toujours mettre au point et tester de nouvelles hypothèses lorsqu'ils traitent des patients.*

Patients with Loeys-Dietz syndrome (LDS), a connective tissue disorder similar to Marfan syndrome, present challenges to anesthesiologists because the many systemic manifestations of the disease necessitate that the children undergo general and cardiac surgery at a young age. These general anesthetics are complicated because the patients can have abnormal airways or unstable necks due to cervical subluxations, and they are also at risk for aortic rupture and other cardiovascular complications during surgery. After review by our Institutional Review Board and obtaining parental consent, we report a case of a patient who had previously undergone multiple uneventful general anesthetics, who presented with an adrenal crisis postoperatively.

Case description

This 12-yr-old, 41.5 kg, male underwent posterior spinal instrumentation and fusion for spondylolisthesis and excision of an iliac osteochondroma under general anesthesia. His medical history was significant for LDS, seasonal asthma, migraine headaches, and severe dyslexia. His manifestations of LDS included craniofacial dysmorphisms, a congenital aneurysmal aortic root dilatation, a bicuspid aortic valve, tortuous and ectactic head and neck blood vessels, bifid uvula, pectus excavatum, spondylolisthesis, retrognathia, inguinal hernias, and cervical subluxations of C2 and C3. Multiple brain magnetic resonance imaging (MRI) examinations revealed dural ectasia, mild tortuosity of the blood vessels, and subcortical white matter abnormalities. Previous cardiac surgeries included a complete aortic valve and aortic root replacement at the age of 22 months and aortic arch replacement at age ten. All of his past surgeries, including inguinal herniorrhaphies and club foot repair, had been uneventful.

His maintenance medications included coumadin, losartan, and atenolol with no history of steroid use. Anesthetic induction medications included propofol, fentanyl, and vecuronium, and the patient received routine prophylactic antibiotics. Multiple intravenous lines and an arterial line were placed; tracheal intubation was accomplished fibreoptically after general anesthesia was induced with in-line neck stabilization to avoid unnecessary neck manipulation, and the patient was positioned in the prone position for the surgery. Initially, after induction and before tracheal intubation, the patient had one manual blood pressure (BP) reading of 60/30 mmHg, which normalized after intubation and in response to intravascular fluids. All other BPs during the procedure were acceptable, with mean arterial BPs in the 55 to 60 mmHg range, although the patient received a single dose of phenylephrine once for a mean arterial pressure of 50 mmHg. Maintenance anesthesia included 0.4 to 0.6% isoflurane, 50% nitrous oxide, and intermittent doses of fentanyl. Neuromonitoring (motor and somatosensory evoked potentials) was used throughout the case with normal signals. The case lasted five hours with an estimated blood loss of 300 mL. Crystalloid fluid 2 L and 5% albumin 250 mL were administered during the procedure. The patient received a cumulative dose of fentanyl 475 μg, and his trachea was extubated at the end of the procedure. At this point, the patient was responsive to verbal stimuli by opening his eyes to command, but he was still quite sedated.

Postoperatively, he arrived in the surgical critical care unit with a pulse of 141 beats·min^{-1} and a BP of 86/41 mmHg. His vital signs stabilized in response to a bolus of intravenous fluids. He remained stable until two hours postoperatively, when his BP decreased suddenly to 54/28 mmHg. At this point, active resuscitation was initiated, and he received additional fluid boluses of normal saline and albumin as well as two doses of epinephrine. He continued to be poorly perfused, and his trachea was

re-intubated after administration of etomidate and rocuronium. Following a second dose of epinephrine, the patient developed supraventricular tachycardia, which resolved with two doses of adenosine. He required dopamine and norepinephrine infusions for cardiovascular support. Head and abdominal computerized tomography scans following his resuscitation were unrevealing. An echocardiogram done at this time was normal. Seeing that the patient was febrile, blood cultures were drawn and broad-spectrum antibiotics were started. Given his catecholamine refractory state, a cortisol level was drawn and hydrocortisone stress dosing was initiated empirically with immediate improvement in hemodynamics. Over the next eight hours, his dopamine and norepinephrine infusions were weaned, and the patient's trachea was successfully extubated. His cortisol level was subsequently found to be $< 0.3\ \mu\cdot dL^{-1}$, consistent with adrenal shock.

During endocrinologic evaluation, the patient demonstrated complete absence of response to an adrenocorticortophic hormone (ACTH) stimulation test, with a peak cortisol level of $0.5\ \mu\cdot dL^{-1}$ after administration of cosyntropin 250 μg indicating adrenal insufficiency. His baseline ACTH was noted to be markedly elevated at 1,510 $pg\cdot mL^{-1}$ (normal 6 to 55 $pg\cdot mL^{-1}$), indicating that he had primary adrenal insufficiency due to impairment of the adrenal gland itself. On further evaluation, the patient was found to have elevated fasting very long-chain fatty acid levels consistent with adrenoleukodystrophy (ALD). Confirmatory genetic testing demonstrated an AG deletion at nucleotide 1801 of the ABCD1 gene, which is found on the X-chromosome. This is a frameshift mutation with a premature stop codon in exon 7, which has previously been reported as a mutation in adrenoleukodystrophy. Prior genetic testing revealed a single sequence variation at the Nt1379 G>T portion of the TGFBR2 gene on chromosome 3p22, which is associated with LDS. The patient's family history was negative for both of these disorders. The patient was maintained on replacement dosing of oral hydrocortisone upon discharge from hospital, and he has been doing quite well.

Discussion

Loeys-Dietz syndrome, an extremely rare connective tissue disease first described by Dietz and Loeys in 2005, has a reported prevalence of less than one case per 1,000,000 people in the United States.[1,2] The disease involves mutations in the genes encoding the transforming growth factor beta receptor 1 and 2 (TGFBR 1 and TGFBR 2) and is inherited in an autosomally dominant fashion with incomplete penetrance. There are four main characteristics of LDS: arterial tortuosity of the vessels (mainly in the head and neck), hypertelorism, bifid or broad uvula, and aneurysms most commonly occurring in the aortic root (see Table). Other clinical manifestations include skull and head abnormalities, such as craniosynostosis, blue sclerae, micrognathia, downward slanting palpebral fissures, malar hypoplasia, and hydrocephalus. Skeletal abnormalities include elongated fingers and toes, clubfoot, scoliosis, cervical spine instability, joint laxity, pectus excavatum, and pectus carinatum. The skin is characterized by easy bruising and abnormal scarring, and often patients develop inguinal and other abdominal wall hernias. Congenital heart disease is sometimes present and most often includes patent ductus arteriosus, atrial and ventricular septal defects, and bicuspid aortic valves.

Patients are phenotypically classified as having LDS type 1 if they exhibit craniofacial abnormalities, such as hypertelorism, cleft palate, or craniosynostosis. Those with LDS type 2 have no craniofacial abnormalities apart from isolated uvula anomalies.[3] This syndrome has many clinical features in common with other connective tissue disorders, including Marfan syndrome, vascular Ehlers-Danlos syndrome, and familial aortic aneurysm syndromes. It is important to distinguish genetically between the different connective tissue disorders because of variable risks of aortic dissection and surgical complications. In general, patients with LDS type 1 have an earlier onset of vascular disease than patients with LDS type 2, with aortic dissection often occurring in childhood. In addition, a review of LDS patients demonstrated that these patients also have a propensity toward aortic rupture or dissection at an earlier age compared with other connective tissue diseases, such as Marfan disease or Ehlers-Danlos disease.[4] There is a case report of a LDS patient showing aortic root dilatation during the fetal period.[5] Although the criteria for repairing ascending aortic aneurysms have not been established empirically, Loeys and Dietz have recommended to consider surgical repair when the aorta exceeds the 99th percentile for age or 4 cm in diameter and the aortic root is > 1.8 cm in diameter.[4] The surgical mortality risk of vascular surgery in LDS patients is reported to be $< 5\%$ compared with 45% in patients with vascular Ehlers-Danlos syndrome.[4,6] Medical management of patients with LDS includes beta blockade, exercise restrictions, and frequent cardiovascular imaging to assess the size of the ascending aorta and the aortic annulus.

Table Main characteristics of Loeys-Dietz syndrome

1. Bifid (split) or broad uvula
2. Hypertelorism
3. Aneurysms most often observed in the aortic root or aorta
4. Arterial tortuosity most often occurring in the vessels of the neck

Congenital adrenal hyperplasia is the most common cause of primary adrenal insufficiency in children. It is due to a group of steroidogenic enzyme defects of which 21-hydroxylase deficiency is the most common, occurring in approximately one in 14,000 births. Classic salt-wasting 21-hydroxylase deficiency presents in the first few weeks of life with virilization of the external genitalia and hyponatremic-hyperkalemic dehydration. In a large cohort of children with primary adrenal insufficiency, congenital adrenal hyperplasia accounted for approximately 70% of cases, autoimmune adrenal insufficiency accounted for 13% of cases, and X-linked adrenoleukodystrophy (X-ALD) accounted for 4% of cases.[7] In a separate cohort that excluded congenital adrenal hyperplasia, as it typically presents in infancy, one-third of patients had autoimmune adrenal disease, one-third had X-ALD, and one-third had adrenal hypoplasia congenita due to mutations in the DAX1 transcription factor.[8]

X-linked adrenoleukodystrophy occurs in approximately 1/18,000 male births. It is caused by a mutation in the ABCD1 gene, which codes for the adrenoleukodystrophy protein (ALDP), a peroxisomal membrane channel protein. Defects in ALDP lead to accumulation of very long-chain fatty acids (VLCFA), which ultimately cause demyelination of white matter and adrenal insufficiency. The exact pathogenesis is not well understood. Cerebral manifestations of ALD in the childhood form of the disease occur most commonly in children four to eight years of age. The initial manifestation is usually childhood hyperactivity, but there is rapid progression to cognitive difficulties, behavioural changes, motor dysfunction, and vision and hearing problems, in addition to adrenal dysfunction. Adrenomyeloneuropathy (AMN) is a milder form of the disease, which manifests itself most commonly in the late twenties with spastic paraperesis in the lower extremities, sphincter and sexual dysfunction, and adrenal dysfunction.[9,10] Finally, there is a form of the disease that manifests itself by only adrenal cortical dysfunction. Women who are heterozygotes of the disease can also develop AMN in adulthood. Treatment of the disease consists of a diet low in VLCFA and administration of glyceryl trioleate and glyceryl trierucate (Lorenzo's oil). In cases diagnosed before significant cerebral involvement on MRI, treatment entails bone marrow transplant.

Our patient has the extreme misfortune of having two very rare diseases. Rare diseases are defined as having an incidence of $< 1/10{,}000$ births, which means the likelihood of having two unrelated rare genetic diseases is $< 10^{-8}$. This is a highly unusual case reporting the co-occurrence of LDS and X-linked ALD. Initially, the intensive care team considered the differential diagnoses of postoperative hemorrhage, postoperative sepsis, and cardiac failure secondary to aortic dissection. Supportive care was instituted and these diagnoses were systematically ruled out. The initial differential diagnosis was expanded, and the patient was treated with corticosteroids after baseline cortisol levels were drawn. Occam's razor, *Pluralitas non est ponenda sine necessitate*, translates "plurality should not be posited without necessity". Applied to medicine, this generally means that clinicians should strive for diagnostic parsimony. However, this case illustrates that clinicians should also be open to diagnostic generosity and must always develop and test new hypotheses when treating patients.

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Competing interests None declared.

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