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CASE REPORT

ANAESTHETIC MANAGEMENT FOR A RARE CASE OF LOEYS-DIETZ SYNDROME FOR LAPAROTOMY

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ABSTRACT: Loeys-Dietz syndrome (LDS) is an autosomally dominant connective tissue disorder characterised by vascular and skeletal manifestations. It is caused by mutations in the TGFBR1, TGFBR2, TGFB2 or SMAD3 genes. There are four types of which type I is the most common accounting for more than 75% of the cases. Here we report the anaesthetic management of a case of LDS type I who presented with abdominal pain with suspected twisted ovarian cyst for laparotomy.
KEYWORDS: Loeys-Dietz syndrome, connective tissue disorder, arterial aneurysms.

INTRODUCTION: Loeys-Dietz syndrome (LDS) is an autosomally inherited genetic disorder that affects the connective tissues of the body. This disorder was first described by Dr. Bart Loeys and Dr. Hal Dietz at the John Hopkins University school of Medicine in 2005. Four main characteristics that suggest the diagnosis of LDS include Arterial tortuosity, most often occurring in the vessels of the neck and observed on imaging techniques, Hypertelorism, Bifid or broad uvula, Aneurysms most often seen in the aortic root but can be seen in other arteries throughout the body. Mutations in either the TGFBR1 or TGFBR2 genes can cause LDS types I and II. SMAD3 gene mutation cause LDS type III and TGFB2 gene mutation cause LDS type IV. These genes play a role in cell signalling that control cell proliferation and differentiation.[1,2,3] Other features noted are (1) craniofacial abnormalities like craniosynostosis, malar hypoplasia, cleft palate, blue sclera, micrognathia and/or retrognathia. (2) skeletal abnormalities like long fingers, clubfoot or skewfoot deformity, scoliosis, cervical spine instability, joint laxity, pectus excavatum, pectus carinatum, osteoarthritis, soft translucent skin which bruises easily (3) congenital heart defects such as PDA, ASD/VSD and bicuspid aortic valve. Scars may be atrophic and wound healing may be delayed. LDS has been associated with a high prevalence of immunologic features including asthma, food allergy, eczema and allergic rhinitis.[4]

CASE REPORT: A 39 year old female presented with complaints of pain abdomen, suspected twisted ovarian cyst. She was a known case of LDS type I diagnosed in 2012 after her two children were diagnosed with the same disorder. CT angiogram done at that time showed arterial tortuosity in Internal carotid arteries on both sides of the neck and saccular aneurysm of intracranial left Internal carotid artery soon after the carotid canal measuring 1.3cm. Patient was started on T. Losartan 50mg BD then and was continuing the same. Diagnosed case of bronchiectasis for the past 15 years and presented with severe cough with expectoration. Known diabetic for the past 5 years not on any drugs at present. History of cleft palate since birth, operated at the age of 9 years. She had a residual cleft palate of size 2X1 cm in the midline just above the bifid uvula. She had a previous history of two LSCS under spinal anaesthesia at 25 and 30 years of age respectively which was uneventful. History of bilateral cataract operated uneventfully. As pain subsided with analgesics, it was decided to

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investigate her further regarding her cardiovascular status, treat the acute respiratory infection and to plan her for an elective surgery.

ON EXAMINATION: Patient was thin built, Weight 45kgs, Height 157cms, Arm span 167cms. Other features were Frontal bossing, contractures of fingers, joint laxity, hypertelorism, residual cleft palate 2x1cm and bifid uvula. PR: 90/min, BP: 110/70mm Hg. Breath holding time was 16 seconds.

- **CVS:** S1S2 heard. No murmur heard.
- **RS:** Normal vesicular breath sounds heard along with occasional crepitations. (Figures 1-6)
- **INVESTIGATIONS:** Blood investigations were within normal limits.
- ECG showed features of Left Ventricular Hypertrophy (LVH).
- Chest X ray showed features suggestive of Left lower lobe bronchiectasis with features of emphysema.
- CT angiogram of brain showed three saccular aneurysms one on Right Internal carotid artery (ICA), two on Left ICA measuring 1.6 x 1.54cm.
- Transoesophageal echo cardiography showed mild MVP of AML, mild MR, type I diastolic dysfunction, mildly dilated aortic root, trivial AR, apical LVH with normal LV systolic function. She was now started on T. Inderal 40mg BD by the cardiologist.
- Neurosurgical opinion was conservative management.
- Ophthalmic examination done ruled out signs of raised intracranial tension.
- X ray cervical spine: no spinal instability.
- PFT- obstruction and possible restriction.

Patient was assessed under ASA III and was planned for elective laparotomy with hysterectomy and bilateral salphingo-oophorectomy. Patient was cannulated intravenously, bladder catheterised and ECG, pulse oximetry and non-invasive blood pressure monitors were connected.

Under strict aseptic precautions, sub arachnoid block performed using 26G Quincke's spinal needle with 2.8ml of 0.5% hyperbaric Bupivacaine heavy +10 µg of fentanyl. Patient was haemodynamically stable throughout the procedure with BP maintaining around 100/60 mm Hg. The total duration of the surgery was 1hr and 45 minutes. Intraoperative blood loss was about 300ml. Totally 1200ml of crystalloids and 500ml of colloid was transfused during the procedure. Urine output was 350ml. No vasopressors were used.

Postoperative period was uneventful.

ANAESTHETIC IMPLICATIONS IN THIS PATIENT:

1. Intracranial aneurysm
2. COPD
3. Dilated aortic root, mild MR, LVH, type I diastolic dysfunction.
4. Cleft palate.

DISCUSSION: LDS is an autosomal dominant genetic disorder involving the connective tissues throughout the body. LDS features can occur in the heart, blood vessels, bones, joints, skin and internal organs such as the intestines, spleen and uterus. The defects of the heart and blood vessels need imaging tests for diagnosis.

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Disorders that share the features with LDS include Marfan's syndrome, vascular Ehler-Danlos syndrome and Sphrintzen-Goldberg syndrome. There is considerable variability in the symptoms associated with LDS. Some people can be severely affected, while others only show mild symptoms. Knowing the signs is the key to early and accurate diagnosis and life-saving treatment. LDS affects both males and females, people of all ethnicities. Mutations in either TGFBR1 or TGFBR2 predispose patients to aggressive and widespread vascular disease. The severity of the clinical presentation is predictive of the outcome.[5]

KEY FEATURES IN LDS[6]:

1. Arteries that twist and wind (arterial tortuosity).
2. Widely spaced eyes (hypertelorism).
3. Wide and split uvula and/or cleft palate.
4. Widening or dilation of arteries (aneurysms) most often occur in the aortic root but can be seen in other arteries throughout the body as well.

OTHER FEATURES INCLUDE[6]:

1. Craniofacial abnormalities like craniosynostosis, malar hypoplasia, cleft palate, blue sclera, micrognathia and/or retrognathia.
2. Skeletal abnormalities like long fingers and toes, contractures of the fingers, clubfoot or skewfoot deformity, scoliosis, cervical spine instability, joint laxity, pectus excavatum, pectus carinatum, osteoarthritis, poor mineralisation of the bones.
3. Soft translucent skin which bruises easily.
4. Congenital heart defects like PDA, ASD/VSD and bicuspid aortic valve.
5. Gastrointestinal problems such as chronic diarrhoea, abdominal pain etc.,
6. Food and environmental allergies.
7. Rupture of the spleen or bowel.
8. Rupture of the uterus during pregnancy.

TYPES OF LDS: There are four types of which type I is the most common accounting for more than 75% of the cases.

Type I – Mutation of TGFBR1 gene.

Type II – Mutation of TGFBR2 gene.

Type III – Mutation of SMAD3 gene – Aneurysms, osteoarthritis syndrome.

Type IV – Mutation of TGFB2 gene – Aneurysm aortic and cerebral, with arterial tortuosity & skeletal manifestations.[1,2,3,4]

GUIDELINES FOR CARDIOVASCULAR CARE AND SURGERY FOR LOEYS–DIETZ SYNDROME CARDIOVASCULAR CARE[4]:

1. Yearly echocardiography; more frequently depending on severity of aortic disease.
2. Blood pressure–lowering medication, such as angiotensin receptor blocker, β-blocker or angiotensin-converting enzyme inhibitor and avoid abrupt cessations of the same.
3. Strict control of hypertension.

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4. Exercise restrictions, including avoidance of contact or competitive sports, isometric exercises (sit-ups, push-ups, pull-ups, or weight lifting), exercising to the point of exhaustion, and activities with routine blows to the chest or head.
5. Avoid prescribed medications that may negatively impact cardiovascular systems, including stimulant medications (such as decongestants, certain attention-deficit hyperactivity disorder medications) and vasoconstrictors (triptans) for headache or migraine management.
6. Subacute bacterial endocarditis prophylaxis in those with artificial valves undergoing dental or other procedures expected to contaminate the blood stream (American Heart Association guidelines do not specifically address connective tissue disorders, thus individualized decision making should be employed based on echocardiogram findings and/or other risk factors).
7. Atrial fibrillation or other arrhythmias managed per typical protocol
8. Consultation with cardiothoracic surgeon when approaching surgical thresholds for aortic root dimensions.

GUIDELINES FOR VASCULAR CARE IN LOEYS–DIETZ SYNDROME[4]:

1. Baseline head to pelvis magnetic resonance angiography or computerized tomography angiography imaging with three-dimensional reconstruction performed at diagnosis. Repeat imaging after 1 year. Thereafter, progression rate, location, and size of aneurysm should guide frequency of head through pelvis imaging. Recommended to have visualization of each part of the vascular tree at least every 2 years. Attention should be paid to cumulative radiation from computed tomography imaging. Imaging in severely affected individuals should begin in infancy; for infants lacking severe craniofacial or skeletal features, consider initial imaging at 2–3 years of age.
2. Consultation with vascular/neurovascular specialists for surveillance and/or surgical plan with presence of aneurysms.
3. Monitor type B dissections aggressively for rapid growth of aortic dimension. Standard follow-up imaging at 7–14 days, then 1, 3, 6, and 12 months post dissection, and yearly thereafter is required.
4. Consider duplex arterial screening in presence of abnormal physical exam to identify arterial aneurysm or dissection.

GUIDELINES FOR ORTHOPEDIC CARE IN LOEYS–DIETZ SYNDROME[4]:

1. Cervical spine X-rays in the flexion and extension position performed at diagnosis to assess for instability and when found managed as per protocol. In children, if normal at baseline, consider repeat imaging at 3–5 year intervals through growth.
2. Clubfoot and contracture interventions done as per protocol.
3. Scoliosis intervention needed as required (bracing most effective for small curves <25°).
4. Symptomatic treatment of osteoarthritis.
5. Avoidance of activities that cause joint injury or pain.
6. Hard shoe inserts or shoes with good arch support may help decrease lower extremity pain caused by significantly flat feet. Consider orthotics or other therapeutic bracing as indicated.
7. Routine occupational or physical therapy given for joint hypermobility or hypotonia.
8. In presence of fractures without adequate trauma, consider dual-energy X-ray absorptiometry scan. Medical therapy is unclear.

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PHYSIOLOGICAL CONSIDERATIONS OF INTRACRANIAL ANEURYSMS: An aneurysm represents a structural defect of the artery wall characterized by a reduction in the middle muscular layer of unknown etiology, but which probably results from a combination of genetic and hemodynamic factors, as well as alcohol and nicotine abuse. Other risk factors include location, age, gender, and smoking. Aneurysms represent the main cause of spontaneous subarachnoid hemorrhage – approximately 75% of the cases.[7,8]

Aneurysms increase in frequency with age beyond the third decade, are 1.6 times more common in women and are associated with a number of genetic conditions.[9]

The cerebral artery and its aneurysm occupy the subarachnoid space, overlying the brain tissue. Mean arterial pressure (MAP) is transmitted to the cerebral artery as the cerebral arterial pressure (CAP). CAP is defined here as the pressure applied to the walls of the aneurysm from within, and is counteracted (but not necessarily balanced) by the intracranial pressure (ICP) which is transmitted through the cerebrospinal fluid.

ANAESTHETIC GOALS: Transmural aneurysmal pressure (TAP) is defined as the difference between the internal pressure of the aneurysm (ie) mean arterial pressure (MAP) and external pressure (ie) intracranial pressure(ICP), i.e., TAP = MAP – ICP. Thus, an increase in MAP and/or reduction in ICP elevate transmural pressure, leading to aneurysmal rupture.

INTRACRANIAL ANEURYSMAL RUPTURE (IAR): Detection of IAR can be challenging. However, during stable anaesthetic conditions, a gradual unexplained increase in blood pressure along with a sudden decrease in heart rate is a common manifestation of IAR. Sudden raised ICP and subsequent herniation can be manifested as a blown pupil, severe hemodynamic perturbations including arrhythmias, and ischemic signs on neurophysiologic monitoring (NPM).

Postoperatively-delayed awakening, sudden deterioration of consciousness, changes in hemodynamic parameters, seizures, and focal neurological deficits may be signs of aneurysm rerupture.

Regardless of the anaesthetic technique chosen, maintaining a stable transmural pressure in the aneurysm to prevent rupture is the main objective.[7,8,10] (Figure No.7).

GENERAL ANAESTHESIA: Intraoperative rupture can be precipitated by sudden fluctuations in TAP gradient, either due to significant increase in MAP or significant decrease in ICP. The degree of hypertension at which aneurysm rupture is likely to occur is not presently known. Rarely, induction of anaesthesia can also precipitate aneurysm rupture (1-2% incidence).[7,8] Rupture on induction portends very poor outcome, with a mortality rate up to 75%.At present, data is inconclusive regarding the incidence of aneurysm rupture during conditions of stable induction of anaesthesia and intubation. General anaesthesia should not be discarded, but the anaesthesiologist must remember those particularities and should try to reduce the response to laryngoscopy and, therefore, decrease the risk of aneurysmal rupture during anaesthetic induction. At the conclusion of surgery, extubation can again impose increased risk for aneurysm rupture or rebleed.

Assuming that evaluation of the airway indicated that intubation would not be difficult, one would begin with preoxygenation. Thiopental 3 to 5 mg per kg or Propofol 1.5 to 2.5 mg per kg have similar effects on CBF and cerebral metabolic rate and can be used for induction[10]. Ketamine for induction is avoided because of its associated increase in CBF and ICP.

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After loss of consciousness and apnea, care must be taken to maintain a normal PaCO2 and avoid extreme hyperventilation. Vigorous hyperventilation will lower PaCO2, decreasing CBF. This may lower ICP to such a degree that if MAP is maintained or increased, transmural pressure may be increased, leading to rupture of the aneurysm.

A nondepolarizing muscle relaxant, which has no effect on ICP or CBF, should be added to facilitate intubation. The neuromuscular junction should be monitored to ensure that paralysis is adequate to avoid coughing with intubation. Fentanyl 3 to 5 μg per kg, Sufentanil 0.5 to 1 μg per kg, or Remifentanil 0.25 to 1 μg per kg can be added 3 to 5 minutes before laryngoscopy to blunt the hemodynamic response. Isoflurane, Desflurane, or Sevoflurane is added to deepen the anaesthesia. Finally, approximately 90 seconds before laryngoscopy, Lidocaine 1.5 to 2 mg per kg or Esmolol 0.5 mg per kg can be added to further blunt the hemodynamic response to intubation. Lidocaine decreases both CBF and cerebral metabolic rate for oxygen, and at high concentrations, it can cause seizures. Esmolol and labetalol have no effect on CBF and ICP, even in brain areas where autoregulation may not be intact. Extreme reductions in MAP (greater than 35%) may compromise cerebral perfusion pressure in patients with increased ICP.

If rapid-sequence induction is indicated, one may consider using Vecuronium 0.15 to 0.20 mg per kg or Rocuronium 0.9 mg per kg rather than Succinylcholine. Succinylcholine may cause an increase in ICP, although this increase can be attenuated or eliminated by deep anaesthesia or prior defasciculation. Succinylcholine, more importantly, may lead to hyperkalemia and possibly ventricular fibrillation in those patients presenting with motor deficits following subarachnoid haemorrhage. In the case of a full stomach or an anticipated difficult airway, careful awake fiber-optic intubation, with use of appropriate sedation and topical application of local anaesthesia, is an appropriate alternative. Under such circumstances, it is useful to have an assistant so that while one person is securing the airway, the other is solely focused on controlling the hemodynamics with titration of appropriate medication.

REGIONAL ANAESTHESIA: Regional techniques are not devoid of risks. Aneurysmal rupture after lumbar puncture have been reported in patients with un-ruptured aneurysms in the literature. Puncture of the dura mater can reduce intracranial pressure and trigger the rupture of an aneurysm. However, other causes of rupture, such as postoperative hypertension or spontaneous rupture, cannot be ruled out. In most cases it is not possible to confirm whether puncture of the dura mater is the cause or just a coincidence. Considering the high prevalence of underdiagnosed unruptured aneurysms (approximately 2% of the general population) and the large number of neuroaxial blocks performed every year, one would expect a high incidence of post-spinal block subarachnoid hemorrhage. However, a review of the literature revealed only 11 reports of post-spinal block subarachnoid hemorrhage.[7] Thus, it is thought that subarachnoid hemorrhage after spinal block is, most likely, a rare situation and, therefore, this technique would be relatively safe in this case, especially when one considers the technical resources currently available (small gauge needles with low risk of acute cerebral spinal fluid hypotension), the lack of elevation of MAP in subarachnoid block, and inherent risks of general anaesthesia in this patient.

Epidural block is, indeed, an extremely safe technique in the absence of accidental puncture of the dura mater, which could be catastrophic due to the possibility of sudden and severe fall in ICP.[7] Experimental or clinical data indicating or contra- indicating general anaesthesia or regional blocks in this context are lacking. Preoperative preparation includes maintaining beta blockade and

angiotensin receptor blockade. Anaesthetics with cerebral and spinal cord protection strategies should be utilized along with appropriate access and monitoring[11]. Therefore, the decision on which technique should be used is individual based, weighing the risks and benefits of each procedure and the experience of the anaesthesiologist.

CONCLUSION: Maintaining a stable transmural pressure in the aneurysm to prevent rupture was the main objective. In this patient choosing a general anaesthetic was deferred since it was a lower abdominal surgery and since the patient had bronchiectasis, probable difficult airway (small mouth with a cleft palate) and diabetes. Intubation and extubation can be catastrophic imposing an increased risk for aneurysm rupture.Sub arachnoid block was considered relatively safe in this patient since the anticipated duration of surgery was < 2hrs, with the technical resources like smaller gauge needles available, lack of elevation of MAP in sub arachnoid block, experience of the anaesthetist and inherent risks of general anaesthesia.

Epidural block was not chosen since the anticipated duration of surgery was <2hrs and it can be catastrophic if an accidental dural puncture occurs with a large bore needle causing a sudden and severe fall in ICP.

The decision on which technique should be chosen is based on the patient's general condition, the surgery planned, the familiarity of the technique chosen and the experience of the anaesthetist weighing the risks and benefits of each technique.

Patients with LDS should be advised of and evaluated for the life- threatening manifestations of the disease that are treatable, including cervical- spine instability, spontaneous or traumatic organ rupture, and catastrophic complications of pregnancy.[5]

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Figure No.1

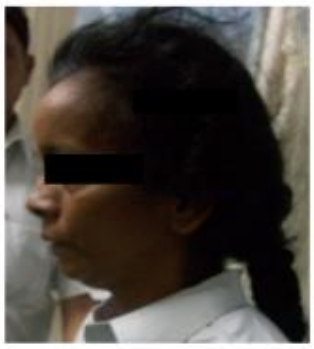


Figure No.2

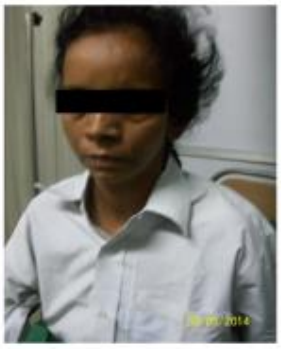


Figure No.3

Figure No.4

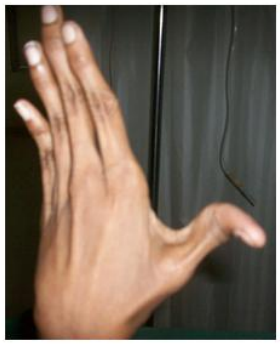
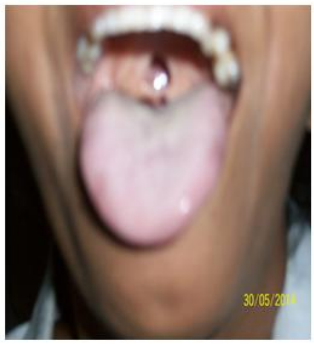


Figure No. 5

Figure No. 6



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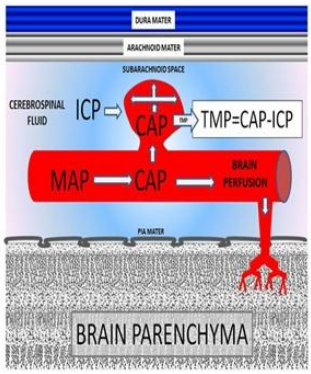

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