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CASE REPORT

Propofol and Kearns-Sayre Syndrome

An idiographic approach

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ABSTRACT: With the focus on an idiographic approach whereby the observations incorporated the various dimensions of individual functioning 'top-down' to 'bottom-up', this case report describes the successful management of a 14-year-old girl with Kearns-Sayre syndrome and Dyggve-Melchior-Clausen disease requiring a transvenous permanent pacemaker implantation for complete heart block. The patient presented to a tertiary care centre in Muscat, Oman, in 2023 seeking consultation. The current idiographic approach appears to have a heuristic value for 2 interrelated reasons. Firstly, it is unlikely that even tertiary care units can accrue such rare presentations and scrutinise them under nomothetic approach. Secondly, by employing the idiographic approach that is capable of examining each case in-depth, the aspiration for good health and well-being may come to the forefront. To the best of the authors' knowledge this is the first published idiographic report in anaesthesia care.

Keywords: Intravenous Anaesthetics; Artificial Pacemaker; Kearns-Sayre Syndrome; Propofol; Idiographic Approach; Case Report; Oman.

Kearns-Sayre syndrome (KSS) is a mitochondrial DNA deletion syndrome that may affect many organs and tissues.[1] Patients with KSS present concerns for anaesthesiologists as mitochondria are a potential site of action of general and local anaesthetics and both anaesthesia and sedation may carry an increased risk in these patients with a propensity for developing propofol infusion syndrome.[2,3] Monitored anaesthesia care in lieu of general anaesthesia where possible may then be an option. Propofol is often the anaesthetic of choice under such circumstances and the question of how safe is it to administer monitored anaesthesia care with propofol in these patients may be worth exploring.

This article reports a case of an adolescent girl with KSS and Dyggve-Melchior-Clausen disease requiring a transvenous permanent pacemaker implantation for complete heart block. Her chromosomal analysis revealed that she was 46XX with an inverted chromosome 9 and had a homozygous variant of the Dyggve-Melchior-Clausen syndrome gene. She had phenotypic features and clinico-pathologic findings befitting the 2 syndromes including intellectual delay and in addition mitochondrial myopathy and possible susceptibility to malignant hyperthermia. Because of her uncooperativeness, monitored anaesthesia care was requested and her genetic abnormalities posed a significant anaesthetic challenge. The importance of serial lactate level estimation as well as an idiographic approach in manuscript writing is highlighted.

Case Report

A 14-year-old girl (weight: 18 kg, height: 121 cm, body surface area: 0.8 m^2) in complete heart block presented to a tertiary care unit in Muscat, Oman in 2023 and was taken to the electrophysiology laboratory for transvenous permanent pacemaker implantation.

In terms of 'top-down' approach, her cognitive status was significant as she exhibited an intellectual disability. Wechsler Intelligence Scale for Children (WISC-V) evaluation suggested a below-average intelligence quotient in both verbal and performance skills. She had speech impediments and distinctive facial features. She had repeated episodes of loss of consciousness. In terms of 'bottom-up' approach, her electrocardiogram on multiple occasions revealed a 2:1 heart block progressing to a higher degree block and often resulting in complete heart block with premature ventricular contractions [Figure 1]. Transthoracic echocardiography revealed good ventricular function with no structural abnormality. In the electrophysiology laboratory, monitoring included the standard American Society of Anaesthesia recommended monitoring modalities and bispectral index (BIS). Following a bolus of ketamine (1 mg/kg) and glycopyrrolate (10 µg/kg) intravenously, an infusion of propofol was started (propofol 150 µg/kg/min). The BIS values of 50–60 were targeted and propofol infusion was adjusted to achieve these values (100–200µg/kg/min). Oxygen was administered

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Table 1: Venous blood gas analysis

Parameter	Baseline values (3 L/min oxygen flow)	90 mins post propofol infusion values (room air)	Values next day, prior to discharge (room air)	Range
pH	7.38	7.29	7.41	7.35–7.45
pCO_2 in mmHg	44	51	42	35–48
pO_2 in mmHg	40	28	38	83–108
Base excess in mmol/L	2.0	–2.1	2.0	
Oxygen saturation in %	72	42	72	95–99
Chloride in mmol/L	97	103	108	98–106
Lactate in mmol/L	1.6	3.2	1.6	0.5–1.6
Glucose in mmol/L	4.50	4.70	4.2	3.89–5.83

through a face mask and end-tidal carbon dioxide levels were monitored continuously to detect the pattern of her breathing [Figures 2A and C]. Paracetamol (15 mg/kg) was administered during the procedure which lasted about 100 mins. 5% dextrose in 0.9% normal saline (2 mL/kg/hr) was used for fluid maintenance. A single lead transvenous ventricular pacemaker (Sphera SureScan™ MRI device, Medtronic, Minneapolis, USA) was implanted through the left subclavian vein and the device was placed in a pocket that was created below the left clavicle [Figure 2D]. Normothermia and normoglycaemia were maintained.

Once the pacemaker implantation was completed, the propofol infusion was stopped. The patient started responding to orders by 18 mins with BIS values of above 80 [Figure 2B]. Venous blood gas analysis was done before, 90 mins after cessation of propofol infusion and on the next day [Table 1]. There was an increase in lactate levels with a drop in venous oxygen saturation after the procedure. This was managed by the administration of supplemental oxygen and volume resuscitation. The child was discharged home the next day with the venous blood gas levels normalised to her baseline values.

Institutional ethical committee approval (SRC#CR13/2023) was obtained to publish this report. Written informed consent for publication of the participants' details and/or clinical images was obtained from all the caregivers of the participant. The relative of the patient included as part of the ideographical study provided written consent that personal/clinical details along with any identifying images be published.

Discussion

For rare genetic disorders such as those in the current case report, it may not be possible to run randomised controlled trials. In such circumstances, less rigorous methodologies such as case series and case reports may be in accordance with the European Commission's recommendation.[4] With an idiographic emphasis, a case report may be presented with the aim of understanding in-depth a human phenomenon and also with the objective of a better understanding the impact of a medical condition on an individual or individuals. An idiographic method is a form of research that focuses on an individual or on the unique aspects of a particular phenomenon.[5] It is a method of investigation that aims to understand the specific and unique experiences, characteristics and behaviors of individuals. An idiographic approach tilts towards more in-depth, individualised interventions and treatments which in turn, fulfill the mission of sustainable development goals to strive for good health and well-being.[6] Countries with a high prevalence of consanguinity, as is the case from where this current report originates, are rife with rare cases that would warrant the utilisation of an idiographic rather than a nomothetic approach for reporting such cases.

To date, idiographic research has received scant attention in clinical medicine with a few exceptions.[7] The primary objective of idiographic research is to gain a comprehensive and in-depth understanding of a particular individual rather than generalising about a larger population. As against an idiographic approach, a nomothetic approach may try to make generalisations. Like for instance in the current report, a nomothetic approach would probably investigate the use of propofol in patients with mitochondrial diseases of which KSS is an example. It would be a generalisation and would not be an individualised approach.

In the present case, an idiographic approach was necessary due to the uniqueness of the case that described the successful anaesthesia management of a 14-year-old girl with KSS and Dyggve-Melchior-Clausen disease who required transvenous permanent pacemaker implantation for a complete heart block. In addition to physiological observations and interventions (sometimes known as 'bottom up' approach), the present case report was concurrently documented using a 'top-down' approach that included an assessment of intellectual capacity and

Table 2: Anaesthetic implications in patients with Kearns Mayer Syndrome[2–5,12,13]

Syndrome	Anaesthetic concerns	Investigations	Anaesthetic considerations
Kearns Mayer Syndrome	Cardiovascular system:[5,12,13] Cardiac conduction abnormalities: 1. Atrioventricular node and infranodal conduction abnormalities 2. Supraventricular and ventricular arrhythmias 4. Preoperative electrocardiogram and echocardiograms in patients with cardiac failure symptoms	Preoperative electrocardiogram and echocardiograms in patients with cardiac failure symptoms	In the presence of conduction defects: Consider keeping available: 1. Isoproterenol infusion 2. External cardioverter/defibrillator unit with a pacing property connected by external defibrillator pads 3. A magnet 4. Antiarrhythmics, vasopressor 5. Inotropic medications on standby 6. Use of bipolar electrocautery whenever possible
	Respiratory system: Impaired ventilatory drive (respiratory control abnormality rather than impaired respiratory mechanics)[12]	Preoperative Spirometry	1. Neuromuscular blockers: In view of possible myopathy, may be prudent to avoid 2. Consider local anaesthesia and peripheral nerve blocks where applicable.
	Musculoskeletal system:[5,12] 1. Growth retardation and short stature 2. Hypotonia		1. Neuromuscular blockers: In view of possible myopathy, may be prudent to avoid
	Nervous system: 1. Peripheral neuropathy 2. Reduced tendon reflexes 3. Hemiplegia/hemiparesis 4. Cerebellar ataxia 5. Myoclonus epilepsy with ragged red fibers 6. Progressive intervertebral space narrowing	Neuromuscular function monitoring	1. Short- or intermediate-acting neuromuscular blocking agents alongside close monitoring of train-of-four ratio. 2. Neuromuscular blockers may be avoided if not mandatory
	Endocrine system:[4] 1. Endocrinopathies 2. Diabetes 3. Hypothyroidism	Preoperative valuation	
	Mitochondrial disorder: 1. Potential site of action of general and local anaesthetics and both anaesthesia and sedation may carry an increased risk.[2] 2. Undue sensitivity to anaesthetic induction agents.[12] 3. Drug-induced myocardial depression, sensitivity to sedating medications and neuromuscular blocking medications[3] 4. Possible malignant hyperthermia susceptibility[12]		1. Propofol infusion syndrome 2. Regional blocks and Neuraxial analgesia 3. Normothermia and normoglycaemia 4. Avoid prolonged periods of fasting 5. Prone to lactic acidosis during times of stress. 6. Consider intravenous induction to avoid the use of a high-dose volatile agent for induction and its effects on cardiac conduction 7. Glucose-containing solutions to prevent anaerobic metabolism and lactic acid production while taking nothing by mouth. 8. Schedule the case as the first case, if possible.
	• Short stature with associated spine deformity • Restrictive lung disease	• Pulmonary function tests • Blood gas analysis • Echocardiography (cor pulmonale)	Difficult tracheal intubation (even without atlantoaxial instability): short neck, prominent, big jaws, macroglossia, limited mouth opening. Tracheal intubation: performed either fibreoptically with inline stabilisation of the cervical spine. Restrictive lung disease: ventilation and oxygenation challenging preclude the use of neuraxial regional anaesthesia Difficulty in patient positioning: atlantoaxial instability, dislocations (hip, shoulder), deformities and muscle contractures

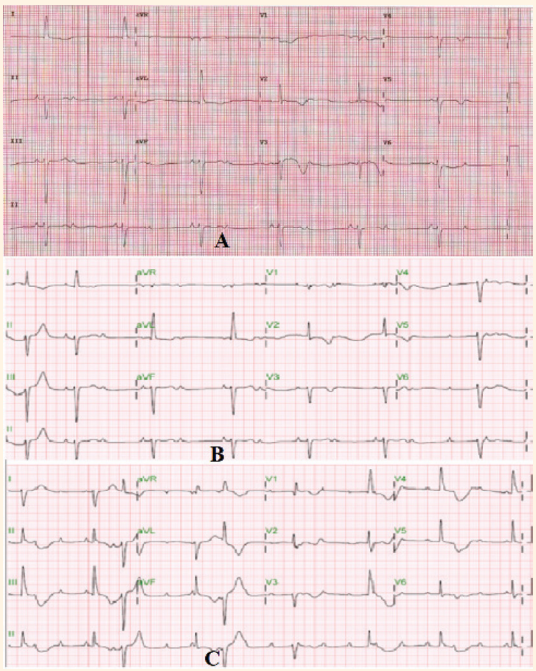

Figure 1: Electrocardiogram panel showing (**A**) 2:1 block, (**B**) progression of a 2:1 block to higher degree of heart block and (**C**) complete heart block with premature ventricular contractions.

other indices of functionality such as the presence of speech impediment.

KSS is a neuromuscular disorder due to abnormalities in the mitochondrial DNA and has a reported incidence of 1–3 in 100,000 individuals.[8] The syndrome is defined by the triad of features: onset of symptoms before age 20 years; pigmentary retinopathy and external ophthalmoplegia. In addition, affected individuals may have: cardiac conduction abnormalities, short stature, peripheral neuropathy, impaired ventilatory drive, etc. [Supplementary Table].[9] Dyggve-Melchior-Clausen is a very rare autosomal recessive inherited disorder characterised by mental disability, dwarfism and skeletal abnormalities (atlanto-axial instability).[10,11] Both these conditions may pose several anaesthetic challenges [Table 2].

This report addresses the risk of the use of propofol in patients with KSS. It was reported that patients with preexisting mitochondrial disorders or beta-oxidation defects are predisposed to develop propofol infusion syndrome associated with a resultant high mortality rate.[3] Propofol infusion syndrome is defined as the development of lactic acidosis with a base deficit >10 mmol/L at least on 1 occasion.[3]

The mechanism for this phenomenon appears to be due to the disruption of specific sites (complex I, complex II, and complex III) of the respiratory chain by propofol. Propofol may also disrupt the mitochondrial permeability transition pore resulting

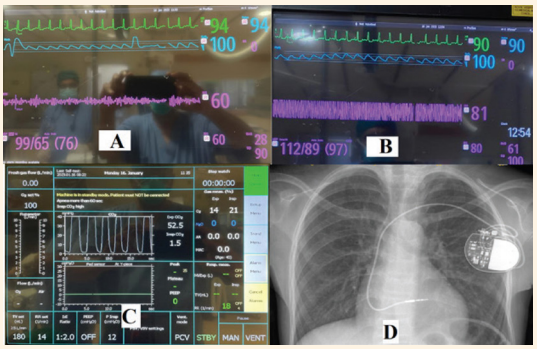

Figure 2: A: Photographs of the monitor showing haemodynamic parameters, bispectral index (BIS) values (**A**) during propofol infusion, (**B**) after cessation of propofol infusion and (**C**) showing the end tidal carbon dioxide trace. Post procedure chest X-ray showing (**D**) the permanent pacemaker.

in decreased mitochondrial membrane potential and apoptosis.[3] Inhibition of the uptake of free fatty acids into mitochondria may also be a causative factor for propofol infusion syndrome. Hence it was suggested that propofol may be toxic to mitochondria and patients with mitochondrial disorders should not receive propofol in high dosages over a prolonged period.[3] Savard *et al.* proposed that propofol infusion syndrome is usually seen with infusion rates >5 mg/kg/h for >48 hours, but even lower dosages may cause the syndrome.[12]

Simultaneously, there are reports of successful propofol administration in patients with KSS.[9,13,14] The current report highlights the measurement of serum lactate levels to assess the extent of mitochondrial dysfunction that ensued with propofol infusion. There was a significant elevation in serum lactate levels in the patient following propofol infusion (300 mg/90 mins, 11mg/kg/hr) that normalised over time. However, the patient did not exhibit any other features of propofol infusion syndrome such as arrhythmias, heart failure, renal insufficiency, hepatomegaly and rhabdomyolysis.

Conclusion

KSS is a rare genetic disorder that tends to impact multiple systems in the body. To date, there is no cure for KSS and treatment is focused on managing the symptoms and complications. It is proposed that propofol may be considered for monitored anaesthesia care in patients with KSS, with the rider that serum lactates should be monitored continuously. The dosage of propofol infusion may be titrated based on targeted BIS values of 40–60 to achieve the desired results during monitored anaesthesia care where general anaesthesia administration may not be the only option.

These protocols could be monitored using idiographic research to shed more light on the natural history of KSS.

AUTHORS' CONTRIBUTION

MMM contributed to the conception and design, acquisition and interpretation of data and drafted the article. TDM contributed to the acquisition and interpretation of data. IAA was involved in the design, analysis and interpretation of data. IAAA was involved in the conception and acquisition of data, analysis and interpretation of data. SAA drafted the article. All authors approved the final version of the manuscript.

DATA AVAILABILITY

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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