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LETTER TO THE EDITOR

Re: Propofol in Triple Trouble Kearns-Sayre Syndrome, Dyggve-Melchior-Clausen Syndrome, and Chromosome-9 Inversion

Dear Editor,

We read with interest Maddali *et al.*'s article about a 14-year-old female patient with the triple trouble Kearns-Sayre syndrome (KSS), Dyggve-Melchior-Clausen syndrome (DMCS) and chromosome 9 inversion, who underwent anaesthesia with propofol after a bolus with ketamine to perform implantation of a permanent pacemaker because of atrioventricular block-3.[1] Despite anaesthesiologists' concerns about tolerability, propofol was used and well-tolerated, with no major side-effects.[1] It was concluded that propofol can be recommended for monitored anaesthesia care in patients with KSS.[1] The report is impressive, but some points require discussion.

The major limitation of the report is that recommending specific anaesthesia management based on an individual case report is not reliable. Before recommending the administration of propofol in patients with KSS, DMCS, or chromosome 9 inversion, further evidence of its safety is required. As long as studies suggest that propofol use in patients with mitochondrial disorder may be complicated by propofol infusion syndrome, one should be cautious about general recommendations specific to an individual patient.

Another limitation of the report is that the specific variants causing KSS and DMCS were not reported.[1] Readers should know whether KSS was due to a single mtDNA deletion, which is the case in the majority of patients, or was due to an mtDNA point mutation or a variant in POLG1 or SLC25A4.[2] In this respect, we do not agree with the statement in the introduction that KSS is an mtDNA deletion syndrome in each case. It should be also indicated which homozygous variant was detected in *DYM*, the gene associated with DMCS.

A third limitation of the report is that neither the genetic status nor the phenotype of either parent was reported. Did a parent have one of the causative variants for KSS or DMCS? Did either parent have signs of a mitochondrial disorder? Although KSS is transmitted via the maternal line in only 4% of patients, both parents of the index patient should be screened for causative variants. Readers should also know whether the parents were consanguineous or not.

A fourth limitation of the report is that details on chromosome 9 inversion phenotype was not reported. The index patient not only carried variants in mtDNA and *DYM*, but also had a chromosomal structural rearrangement. Readers should know the various phenotypic presentations of chromosome 9 inversion and whether or not it contributed to the overall phenotype. Commonly, patients with pericentric chromosome 9 inversion often present with reproductive failure.[3]

A fifth limitation of the report is that it did not discuss why the patient only received a pacemaker and not a more sophisticated device. Since KSS can be complicated not only by AV-block-3 but also by malignant ventricular arrhythmias (MVAs), implantation of an implantable cardioverter defibrillator (ICD) instead of a pacemaker must definitively be considered.[4] There are no results of long-term ECG recordings to assess whether MVAs were also recorded in addition to the atrio-ventricular block.

Cognitive impairment may not only be a phenotypic feature of DMCS but also of KSS.[5] How did the authors differentiate whether cognitive impairment was due to one syndrome or the other, or was there evidence of a particularly severe cognitive deficit due to an exacerbating effect of both mutations?

In summary, the interesting report has limitations that put the results and their interpretation into perspective. Clarifying these weaknesses would strengthen the conclusions and could improve the report. For patients with a triple genetic trouble, anaesthetic management may depend on all three factors. Although individual patients with a mitochondrial disorder may not develop side-effects from propofol, this does not rule out the possibility that others may experience serious complications.

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Response from the Authors

Dear Readers,

The main point of contention is the interpretation that we recommended administering propofol to patients with Kearns-Sayre syndrome (KSS) for anaesthesia management based on a single case report.[1] We agree that generalisation of single case reports should be done with caution. In patients with mitochondrial diseases, propofol infusion syndrome is typically associated with high infusion rates and long durations. Reports suggest successful administration of propofol in patients with KSS.[2,3] We have taken an individualised approach due to conflicting recommendations for the use of propofol in patients with KSS. This approach involved understanding the unique situation of the patient rather than making generalisations about a larger population. We closely monitored the patient tissue perfusion by checking venous oxygen saturation and serum lactate levels, which indicate cardiac output and aerobic tissue metabolism.

Another point of contention is that KSS is a condition often linked to the deletion of significant portions of mitochondrial DNA. We agree with the critique that KSS may not always exhibit the usual large deletion of mitochondrial DNA. In certain cases, it can be caused by point mutations found in mitochondrial DNA.[2] In the indexed child, the cause of KSS was due to a point mutation. Specifically, a variant of LRP5 variant c.2029G>C p.(Ala677Pro) was responsible for a change in amino acids from Ala to Pro at position 677. The child had associated Dyggve-Melchior-Clausen disease and whole exome sequencing revealed that the specific variant to be c.1157T>C p.(Val386Ala), causing a change of amino acids from Val to Ala at position 386. This is clinically characterised by progressive dwarfism, microcephaly and varying degrees of mental retardation. The phenotype of this indexed child was short stature and severe growth retardation with delayed bone age (9 years versus current 14 years).

Insufficient information on parental genetic status, phenotype and consanguinity was mentioned as a limitation. In our initial submission, we did not include some information that was considered irrelevant to patient management due to word limitations. The parents were related to each other. The chromosomal analysis of the father showed the presence of a pericentric inversion of chromosome 9, 46, XX, inv(9) (p12q13). The mother of the indexed patient had a normal female karyotype (46, XX), while neither parent showed phenotypic characteristics as the daughter. The patient's younger brother, who was 9 years old, had a short stature and was undergoing growth hormone therapy. The pericentric inversion of the heterochromatin region of chromosome 9, also known as inv9, is a common genetic variation found in approximately 1–3.57% of the general population.[4] This variation can occur in inv9(p11q13) or inv9(p12q13) forms. Both the indexed child and her father had inv9(p12q13) form. Previously, chromosome 9 inversion was considered a normal variant with no observable clinical effects in individuals. Recent studies using classical cytogenetics have suggested that inv9 may be associated with infertility, recurrent miscarriages, and idiopathic reproductive failure.[4] The father did not present a phenotype, while delayed puberty was observed in the child.

In response to the question 'why a permanent pacemaker was implanted' instead of an implantable cardioverter defibrillator, this was for the following reasons: (1) individuals with KSS have a 20% risk of death from heart block. However, early pacemaker implantation can improve life expectancy; (2) Tte American College of Cardiology, the American Heart Association and the Heart Rhythm Society suggest implantation of pacemakers in patients with KSS with neuromuscular diseases for conduction disorders (third-degree and advanced second-degree atrioventricular block at any anatomical level; class: I, evidence level: B);[5] (3) for patients with KSS and conduction disorders, additional defibrillator capability along with permanent pacemaker implantation may

be required only if appropriate. This is supported by class IIa evidence with a level of evidence grade: C;[6] (4) considering the small stature of the child, it was considered appropriate to allow her to grow after pacemaker implantation, at which point an automated implantable cardiac defibrillator may be implanted; and (5) after the permanent pacemaker implantation, telemetry monitoring was carried out for several days. There were no signs of arrhythmias or premature ventricular contractions during the monitoring period.

The authors were asked about cognitive impairment and whether it could be differentiated due to one syndrome or the other. Cognitive impairment was assessed using the Wechsler Intelligence Scale for Children, which showed below-average intelligence quotient scores in both verbal and performance skills. However, it was unclear which syndrome caused cognitive impairment and to what extent.

It is important to note that our case report does not suggest that propofol can be safely used in every patient with KSS. Propofol may be an option as long as doses known to cause propofol infusion syndrome are avoided and anaerobic metabolism markers are closely monitored. The decision to use propofol in patients with mitochondrial diseases should be determined by the treating team.

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