







CASE REPORT

Decompensation of cardiorespiratory function and emergence of anemia during pregnancy in a case of mitochondrial myopathy, lactic acidosis, and sideroblastic anemia 2 with compound heterozygous YARS2 pathogenic variants

Laura I. Rudaks¹  | Eloise Watson^{1,2} | Carly Oboudiyat¹ |
Kishore R. Kumar^{2,3,4}  | Patricia Sullivan^{5,6}  | Mark J. Cowley^{5,6}  |
Ryan L. Davis^{2,4,7}  | Carolyn M. Sue^{1,2,4,7} 

¹Department of Neurology, Royal North Shore Hospital, St Leonards, New South Wales, Australia

²Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

³Molecular Medicine Laboratory and Department of Neurology, Concord Repatriation General Hospital, Concord, New South Wales, Australia

⁴Translational Genome Informatics Group, Kinghorn Centre for Clinical Genomics, Garvan Institute of Medical Research, Sydney, New South Wales, Australia

⁵Children's Cancer Institute, Lowy Cancer Centre, University of New South Wales, Sydney, New South Wales, Australia

⁶School of Women's and Children's Health, University of New South Wales, Sydney, New South Wales, Australia

⁷Kolling Institute, Royal North Shore Hospital, Northern Sydney Local Health District, St Leonards, New South Wales, Australia

Correspondence

Professor Carolyn Sue, Department of Neurology, Royal North Shore Hospital, Reserve Road, St Leonards, NSW 2065, Australia.
Email: carolyn.sue@sydney.edu.au

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Abstract

Myopathy, lactic acidosis, and sideroblastic anemia 2 (MLASA2) is an autosomal recessive mitochondrial disorder caused by pathogenic variants in YARS2. YARS2 variants confer heterogeneous phenotypes ranging from the full MLASA syndrome to a clinically unaffected state. Symptom onset is most common in the first decade of life but can occur in adulthood and has been reported following intercurrent illness. Early death can result from respiratory muscle weakness and cardiomyopathy. We report a case of MLASA2 with compound heterozygous YARS2 pathogenic variants; a known pathogenic nonsense variant [NM_001040436.3:c.98C>A (p.Ser33Ter)] and a likely pathogenic missense variant not previously associated with disease [NM_001040436.3:c.948G>T (p.Arg316Ser)]. The proband initially presented with a relatively mild phenotype of myopathy and lactic acidosis. During pregnancy, anemia emerged as an additional feature and in the postpartum period she experienced severe decompensation of cardiorespiratory function. This is the first reported case of pregnancy-related complications in a patient with YARS2-related mitochondrial disease. This case highlights the need for caution and careful counseling when considering pregnancy in mitochondrial disease, due to the risk of disease exacerbation and pregnancy complications.

KEYWORDS

mitochondrial myopathy, MLASA2, pregnancy, sideroblastic anemia, YARS2

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1 | INTRODUCTION

Myopathy, lactic acidosis, and sideroblastic anemia 2 (MLASA2) is an autosomal recessive mitochondrial disorder resulting from pathogenic variants in the mitochondrial *tyrosyl-tRNA synthetase 2* (YARS2) gene. Tyrosine-tRNA ligase conjugates tyrosine to the mitochondrial tyrosyl tRNA in the mitochondrial protein translation process (Riley et al., 2018). Patients with YARS2 pathogenic variants demonstrate deficiencies in mitochondrial respiratory chain complexes I, III, and IV (Riley et al., 2010, 2013). YARS2 variants confer heterogeneous phenotypes, ranging from the full MLASA syndrome, to isolated myopathy or sideroblastic anemia, while others have been reported to be clinically unaffected (Riley et al., 2013, 2018). Additional reported features include delayed motor milestones, facial weakness, ptosis, strabismus, ophthalmoparesis, nystagmus, hypertrophic cardiomyopathy, respiratory insufficiency, scoliosis, seizures, gastrointestinal symptoms, hepatomegaly, and proximal renal tubulopathy (Sommerville et al., 2017). Symptom onset is most common in the first decade of life but can occur in adulthood and has been reported following intercurrent illness (Riley et al., 2013). Median age at death has been reported as 25.5 years, with major causes being respiratory muscle weakness and cardiomyopathy (Sommerville et al., 2017).

We report a patient with compound heterozygous pathogenic variants in YARS2, initially presenting with a relatively mild phenotype of myopathy and lactic acidosis. During pregnancy, anemia emerged as an additional feature and in the postpartum period she experienced severe decompensation of cardiorespiratory function.

2 | CASE

The 40-year-old proband, the second child of two healthy non-consanguineous parents, was born full-term after an uncomplicated pregnancy. From birth she was noted to have bilateral ptosis and left-sided strabismus. The strabismus progressively worsened with age and in young adulthood she developed an additional, milder right-sided strabismus. She underwent bilateral corrective surgery for the strabismus at age 21, and for the ptosis at age 23, with an additional procedure at age 35. Childhood ophthalmologic review identified ocular albinism with bilateral congenital optic nerve hypoplasia, more prominent on the left. However, optical coherence tomography at age 33 demonstrated normal thickness of the optic nerves bilaterally (OD 90 μ m and OS 98 μ m). She experienced exertional fatigue during childhood that became more apparent in her teenage years when she developed increasing dyspnoea on exertion. Transthoracic echocardiogram at age 33 demonstrated mild posterior left ventricular hypertrophy (12 mm) with normal left ventricular systolic function. Pulmonary function tests at age 35 demonstrated low-normal FEV1 (2.28 L, 80% predicted) and FVC (2.90 L, 88% predicted), with a reduction in supine FVC by 12% (to 2.54 L). Maximal inspiratory pressure was -65 cmH₂O (91% predicted).

Muscle biopsy of the right thigh at age 30, demonstrated marked depletion of cytochrome oxidase (COX) staining and increased

subsarcolemmal Gomori trichome staining indicative of mild mitochondrial proliferation. Electron microscopy confirmed a mild excess of subsarcolemmal mitochondria. Respiratory chain analysis of the muscle biopsy showed a marked defect involving complexes I, III, and IV, while complex II activity was spared. Long-range PCR analysis of mitochondrial DNA from muscle demonstrated no large-scale deletions or rearrangements. Whole mitochondrial genome sequencing of muscle DNA did not detect any pathogenic mtDNA variants.

She became pregnant via IVF at age 38. Donor sperm was used due to infertility in her partner. The first two trimesters of her pregnancy proceeded uneventfully. At 30–31 weeks gestation she was admitted to hospital with increasing dyspnoea. Before pregnancy her hemoglobin (Hb) was 122–126 g/L (normal 115–165 g/L). In early pregnancy, Hb was 113 g/L with a normal ferritin level, and she was able to walk up 1.5 flights of stairs, or 15–20 min on flat ground. As pregnancy progressed, she was only able to walk up three to four stairs, or 5 min on flat ground before needing a rest. She was found to be anemic with an Hb of 66 g/L. MCV was mildly elevated at 101.6 fL (normal 80–100 fL) and ferritin was now elevated at 359 μ g/L (normal 15–200 μ g/L). Reticulocyte percentage was mildly elevated at 2.4% (normal 0.2%–2.0%), with a normal absolute reticulocyte count of 44.4×10^9 /L (normal 20 – 80×10^9 /L), and normal haptoglobin level, which was inconsistent with hemolysis. Blood films demonstrated anisopoikilocytosis, teardrop poikilocytes, and very occasional target cells. The suspected diagnosis of sideroblastic anemia was made, but a confirmatory bone marrow biopsy was declined during her pregnancy. She received a total of eight red blood cell transfusions and remained in hospital for monitoring until the delivery of a healthy baby by cesarean section at 37 + 4 weeks gestation. Repeat pulmonary function tests on day seven postpartum demonstrated progression of respiratory muscle weakness. FVC was 1.98 L (60% predicted), with severely reduced maximal inspiratory pressure of -23.4 cmH₂O (36% predicted). She was discharged home on day eight postpartum.

Nine days postpartum, she developed respiratory distress due to acute pulmonary edema. An ECG demonstrated a short PR interval, left axis deviation and changes meeting criteria for left ventricular hypertrophy. A transthoracic echocardiogram showed progression to moderate left ventricular concentric hypertrophy (septum 13 mm and posterior wall 17 mm) and prominent hypertrophic papillary muscle. New impairment in left ventricular systolic function became apparent.

She required admission to the intensive care unit and improved following treatment with positive pressure ventilation, diuretics, and medical therapy for cardiac failure. A transthoracic echocardiogram 2 months following her admission demonstrated improvement in left ventricular systolic function and she continues on bisoprolol alone. Repeat blood testing completed several months after delivery demonstrated a return of Hb to normal at 126 g/L.

3 | GENETIC ANALYSIS

Whole genome sequencing was performed at age 36, using our previously published method (Kim et al., 2019; Kumar et al., 2019). Briefly,

blood DNA was sequenced using the Illumina HiSeq X Ten platform (Kinghorn Centre for Clinical Genomics, Garvan Institute for Medical Research). Sequencing data were aligned to GRCh37 using BWA MEM and variants identified using the GATK best practices pipeline (Van der Auwera & O'Connor, 2020). Nuclear variants in a panel of known mitochondrial disease genes were assessed for pathogenicity using Seave and Varsome (Gayevskiy et al., 2019; Kopanos et al., 2019). Variants were considered if they were “pathogenic” or “likely pathogenic” on ACMG criteria (Richards et al., 2015).

Variant analysis identified compound heterozygous single nucleotide variants in *YARS2*; [NM_001040436.3:c.98C>A (p.Ser33Ter)] and [NM_001040436.3:c.948G>T (p.Arg316Ser)]. Sanger sequencing confirmed the variants in the patient and showed that her father was heterozygous for the c.98C>A variant and her mother was heterozygous for the c.948G>T variant.

The *YARS2* c.98C>A (p.Ser33Ter) is a nonsense variant resulting in a null allele, and has been reported as pathogenic in two prior cases (Riley et al., 2018). The variant was classified as “pathogenic” according to ACMG criteria (PVS1 [very strong], PM2 [moderate], PP4 [moderate]) (Richards et al., 2015). To our knowledge, the c.948G>T variant, which causes a missense nucleotide change at position 1 of exon 3 resulting in the amino acid change p.Arg316Ser, has not been previously reported in association with disease and is classified as “likely pathogenic” according to ACMG criteria (PM2 [moderate], PM3 [moderate], PP3 [supporting], PP4 [moderate]) (Kopanos et al., 2019; Richards et al., 2015).

In silico prediction analysis for amino acid changes (PolyPhen2 and PROVEAN) predict that the Serine substitution for Arginine at position 316 is benign, despite being a highly evolutionarily conserved basic residue (Desmet et al., 2009; VarSEAK Online Database, 2021). *In silico* splicing prediction analysis using *Introne* (P. Sullivan, in preparation), indicated that the c.948G>T variant could potentially disrupt splicing. Specifically, a variant of the first base of the exon is predicted to disrupt the native exon 3 splice acceptor site and damage an exonic splicing enhancer. The consequence of this damage is predicted to result in the use of a splice acceptor site 35 bp downstream that would result in a frameshift. In support of this being pathogenic, an alternative *YARS2* transcript utilizing this alternate acceptor splice site has been reported in association with nonsense mediated mRNA decay. Transcript analysis or Western blot from a suitable tissue would be required to confirm aberrant splicing or a lack of protein expression.

4 | DISCUSSION

In the proband described here, the consistent clinical phenotype, presence in *trans* with a known pathogenic variant, and segregation with disease within the family, support pathogenicity of the c.948G>T variant. We therefore describe a case of MLASA2 due to compound heterozygous *YARS2* pathogenic variants, including the first report of disease in association with the c.948G>T variant. Despite the patient initially only displaying features of mitochondrial myopathy and lactic acidosis, anemia emerged during pregnancy and although not

confirmed with bone marrow biopsy, was possibly due to sideroblastic anemia, fulfilling the complete MLASA syndrome.

Sideroblastic anemia is a common feature in *YARS2*-related mitochondrial disease, reported in 13 of 17 (76%) patients in one series (Sommerville et al., 2017). Interestingly, two demonstrated complete spontaneous resolution of the sideroblastic anemia over time. Other manifestations of the syndrome, including myopathy and cardiomyopathy, often demonstrate progression in severity (Sommerville et al., 2017). The case described here had not previously manifested anemia, instead emerging during pregnancy.

Her progressive dyspnoea was attributed primarily to the combination of anemia and weakness in muscles of respiration. She also demonstrated gradual deterioration of her respiratory function. In the healthy pregnant population, FVC remains stable or may increase after 14–16 weeks gestation (Grindheim et al., 2012). However, in neuromuscular disorders, impaired diaphragm and expiratory muscle function may be unable to compensate for the heightened load placed on respiratory muscles. Furthermore, splinting of the diaphragm can occur due to the gravid uterus, and pregnancy results in heightened oxygen consumption (Norwood & Rudnik-Schöneborn, 2012). These factors may contribute to exacerbation of respiratory failure in pregnancy. Avoidance of pregnancy has been recommended in patients with a vital capacity less than 1 L, with caution for any decompensation in those with lesser degrees of impairment (Norwood & Rudnik-Schöneborn, 2012). It is recommended to monitor patients with neuromuscular disorders during pregnancy in each trimester with pulmonary function tests including FVC and inspiratory pressures, gas exchange, assessment for respiratory symptoms, and cough function (Norwood & Rudnik-Schöneborn, 2012).

An additional physiologic stressor of pregnancy is the increase in cardiac output by approximately 20% at 8 weeks gestation, and by 40%–50% at 20–28 weeks gestation. Labor can increase cardiac output by a further 50% due to heightened sympathetic tone and auto-transfusion of blood from the uterus to the systemic circulation during uterine contractions (Burt & Burbridge, 2009). These physiologic changes result in increased cardiac demand and can exacerbate pre-existing cardiac impairment. Decompensation of cardiac disease has been seen to occur at various stages during pregnancy and postpartum (Burt & Burbridge, 2009). The patient described here experienced severe decompensation in cardiac status in the postpartum period requiring admission to ICU with consideration of cardiac transplant. Fortunately, with the removal of the physiologic stress of pregnancy and initiation of medications for cardiac failure, the cardiac function improved postpartum.

This is the first reported case of *YARS2*-related mitochondrial disease that was precipitated during pregnancy in an oligosymptomatic patient. Death after cesarean section has been reported in a family member of a *YARS2* patient with presumed transfusion-dependent sideroblastic anemia (Riley et al., 2010). Symptom onset in MLASA2, including lactic acidosis, cardiomyopathy, and sideroblastic anemia, has previously been reported in the setting of suspected intercurrent infective illness (Riley et al., 2013). Our patient initially demonstrated relatively minor clinical features of mitochondrial myopathy and lactic

acidosis, and in retrospect, the potential risks for clinical deterioration during pregnancy were perhaps underrated. This case highlights the need for caution and careful counseling when considering pregnancy, due to risk for pregnancy induced complications and mitochondrial disease exacerbation precipitated by enhanced physiologic and bioenergetic demand. Pregnant patients with YARS2 pathogenic variants should be closely monitored, especially for deterioration in cardiorespiratory and hematologic state, and monitoring should encompass the early postpartum period.

5 | CONCLUSION

We describe a case of MLASA2 with compound heterozygous YARS2 pathogenic variants and a clinical phenotype evolving during the physiological stress of pregnancy. This case highlights the broader clinical spectrum and temporal evolution of YARS2-related mitochondrial disease, as well as complications during pregnancy. It further emphasizes the need for caution and close monitoring during pregnancy and the early postpartum period in those affected, even when clinical manifestations are mild.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

AUTHOR CONTRIBUTIONS

Laura I. Rudaks was the primary author of the article and performed collation of the clinical data. Kishore R. Kumar, Patricia Sullivan, Mark J. Cowley, and Ryan L. Davis performed and analyzed genetic/molecular testing, in addition to contributing to the writing of the article. Eloise Watson and Carly Oboudiyat contributed to the writing of the article and edits. Carolyn M. Sue was the senior author, contributing to the conception, study design, collation of clinical data, supervision, project administration, funding acquisition, writing of the article, and final approval.

ORCID

Laura I. Rudaks  <https://orcid.org/0000-0002-1100-319X>
 Kishore R. Kumar  <https://orcid.org/0000-0003-3482-6962>
 Patricia Sullivan  <https://orcid.org/0000-0002-4886-8883>
 Mark J. Cowley  <https://orcid.org/0000-0002-9519-5714>
 Ryan L. Davis  <https://orcid.org/0000-0003-0512-8989>
 Carolyn M. Sue  <https://orcid.org/0000-0003-1255-3617>

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