CASE REPORT

Pearson marrow-pancreas syndrome with cardiac conduction abnormality necessitating prophylactic pacemaker implantation

Mats Steffi Jennifer MD | Daniel Cortez MD

Division of Pediatric Cardiology, University of Minnesota Masonic Children's Hospital, Minneapolis, Minnesota

Correspondence

Daniel Cortez, Division of Pediatric Cardiology, University of Minnesota Masonic Children's Hospital, 5th floor, East building, 8951H (Campus Delivery Code), 2450 Riverside Avenue, Minneapolis, MN 55454.
Email: dcortez@umn.edu

Abstract

Pearson marrow-pancreas syndrome (PS), an exceedingly rare mitochondrial disorder, involves multiple systems including hematologic system and pancreas. Other mitochondrial disorders have been associated with progressive infranodal block but this has not yet been described as a major feature of PS. We report a 7-year-old girl with classical features of PS and cardiac conduction defect. Her electrocardiogram revealed QRS prolongation with right bundle and left anterior fascicular blocks. Follow-up Holter revealed bifascicular block, alternating left and right bundle branch blocks, supraventricular tachycardia (with alternating bundles), and suspicion for nonsustained ventricular tachycardia. She underwent successful transvenous single-chamber ventricular pacemaker.

KEYWORDS

bundle branch blocks, fascicular block, pacemaker, Pearson syndrome

1 | INTRODUCTION

Pearson marrow-pancreas syndrome (PS) is an exceedingly rare mitochondrial disorder, involving multiple systems mainly the hematologic system, exocrine and endocrine pancreas, liver, muscle, kidneys, and nervous system (Rötig et al., 1990; Sato et al., 2015). Since Pearson's initial report in 1979, there have been only about 100 cases described till now (Manea et al., 2009). This syndrome is caused by large deletions in mitochondrial DNA, accounting for various tissue dysfunctions. Mitochondrial disorders have an impaired respiratory chain function, and therefore, cells or organs with higher energy requirements such as the brain, skeletal and cardiac muscles, specific conduction systems, sensory organs (eyes, ears), and kidneys are affected the most (Moraes et al., 1989).

The syndrome is characterized by hematologic disturbances that manifest as bone marrow failure syndrome with refractory sideroblastic anemia, and variable degrees of neutropenia, and thrombocytopenia; pancreatic dysfunction involves both the exocrine and endocrine pancreas manifesting as pancreatic insufficiency and presents as failure to thrive due to low or absent production of pancreatic enzymes and insulin-dependent type 1 diabetes mellitus

(Pearson et al., 1979; Stoddard, McCurnin, Shultenover, Wright, & deLemos, 1981); kidney dysfunction ranges from mild proximal tubulopathy to chronic kidney disease that requires dialysis and/or kidney transplantation. PS patients may develop phenotypic transformation to have Kearns-Sayre Syndrome (KSS) later (Grady et al., 2014; Kabunga et al., 2015).

The literature review of previously reported patients with Pearson syndrome includes cardiac functional decline (Krauch, Wilichowski, Schmidt, & Mayatepek, 2002) but there are no cardiac conduction abnormalities that have been described to date. Cardiac abnormalities have not yet been regarded as a major feature of Pearson syndrome. In our report, we aim to describe the cardiac conduction defect that was found in our patient, its treatment plan and outcome.

2 | CASE PRESENTATION

A 7-year-old girl with Pearson marrow-pancreas syndrome characterized by mitochondrial dysfunction, refractory anemia, neutropenia, thrombocytopenia, exocrine pancreatic insufficiency,

FIGURE 1 12 Lead EKG showing bifascicular block

insulin-dependent type 1 diabetes mellitus, proximal renal tubular acidosis/ Fanconi's anemia with stage IV chronic kidney disease, short stature, generalized hypotonia and slapping gait, mild-moderately severe sensorineural hearing loss, exotropia, and corneal clouding with photophobia that required corneal transplant was evaluated in the pediatric cardiology clinic for her cardiac status after she was noted to have a sudden increase in heart rate during the recovery phase of anesthesia. Diagnosis of mitochondrial abnormality was made at 2 years of age and her diagnosis of Pearson marrow-pancreas syndrome was confirmed at age 3 years by the finding of large heteroplasmic deletions of mitochondrial DNA (mtDNA) m.6249_14098del7850 in blood cells by next-generation sequencing (NGS) analysis and Southern blot analysis. During her initial evaluation in the pediatric electrophysiology clinic, she was asymptomatic and denied chest pain, palpitations, activity intolerance, presyncope, or syncope. She had no previous history of cardiovascular disease. She was born at full term to healthy nonconsanguineous parents with an unremarkable in-utero and birth history, and an uneventful newborn period. She has two healthy older siblings.

On physical examination, she was a cheerful 7-year-old in no apparent distress, unremarkable cardiac and respiratory findings, and 2 + palpable peripheral pulses. Her blood pressure and pulse rate were 101/62 mmHg and 114/min, respectively. Her pulse oximetry saturation was 99%.

Initial Electrocardiogram (EKG) showed right bundle branch block (RBBB) and right axis deviation. Most recent EKG, 4 years after the initial EKG revealed a heart rate of 119 bpm, PR interval was normal at 146 msec, right bundle branch block and left anterior fascicular block without significant ST-T-wave changes. Echocardiography revealed normal intracardiac connections with normal left and right ventricular chamber size and systolic function, calculated biplane left ventricular ejection fraction of 61%. Initial outpatient cardiac rhythm monitoring showed an average HR of 117 with no ventricular ectopy, 4 ectopic atrial beats without bundle branch block. Follow-up Holter report revealed a HR of 85 to 180 bpm, QT interval of 320 msec (QTc 482 msec), bifascicular

block (Figure 1), alternating left and right bundle branch blocks, supraventricular tachycardia (SVT) (with alternating bundles), and variable QRS morphologies.

Given the progressive nature of her infrahisian block and the progressive nature of her PS, she was planned for prophylactic pacemaker placement, given other similar mitochondrial diseases benefit from pacemaker implantation (Epstein et al., 2008). Benefits versus risks of transvenous pacemaker versus epicardial pacemaker were considered. Transvenous single-chamber ventricular pacemaker was believed to be the best option due to her pancytopenic status, and a possibility of kidney and/or bone marrow transplantation in the near future that would necessitate immunosuppressive medications which increases her risk of infection, given the lower risk for endocarditis. She underwent successful single-chamber ventricular pacemaker implantation. The pacemaker was set to VVI at 60 bpm. The initial values at implant were stable with optimum thresholds, impedances, and sensing. The patient was followed up in the pediatric electrophysiology clinic 12 days as well as 3 months after the pacemaker placement. She was doing well with improved threshold, impedance, and sensing values. At 3-month follow-up, no episodes of nonsustained ventricular arrhythmias were noted by her device.

3 | DISCUSSION

Pearson marrow-pancreas syndrome (PS) is a multisystem mitochondrial disorder, in which an accompanying cardiac disorder is not yet regarded as a specific feature. Krauch et al reported a 5-year-old with worsening cardiac function that mainly involved the left ventricle (Krauch et al., 2002). An autopsy study of a 3-year-old girl found that there was markedly reduced mitochondrial enzyme activity in the heart and other organs like the liver and muscles, although there were no clinical cardiac manifestations in that patient (Sato et al., 2015). Cardiovascular pathologies most commonly determine life expectancy, but little is known about the nature of the underlying cardiac abnormality in patients with PS.

PS patients may develop phenotypic transformation to have Kearns-Sayre syndrome (KSS) later, which is an example of tissue-specific modifications of mitochondrial heteroplasmy (mitotic segregation) (Grady et al., 2014; Kabunga et al., 2015). KSS is another mitochondrial disorder with onset before 20 years of age that classically involves the eyes and heart. Cardiac involvement in KSS manifests as conduction abnormalities of varying degrees in more than 50% and sudden cardiac death is reported in as high as 20% of the patients (Chawla, Coku, Forbes, & Kannan, 2008; Kabunga et al., 2015). Many of the mitochondrial DNA deletion syndromes (PS, KSS, chronic progressive external ophthalmoplegia (CPEO), and others) have reduced enzymatic activities of common mitochondrial respiratory chain complexes (MRCC) (Sato et al., 2015). We hypothesize that the same mechanism that involves the cardiac muscles and conduction system in KSS could possibly be the reason for the cardiac involvement in PS as well, but this needs to be further studied and confirmed through molecular diagnostics.

It is possible that cardiac involvement may be a later feature of PS; more than half of the patients die before the age of 4 years and our patient is a 7-year-old. Deleted mitochondrial DNA (mtDNA) may be distributed unevenly in various tissues of the body. This is probably another critical determinant of the varied phenotypic presentation, determining the varying degrees of involvement of the organ systems.

The unknown and unpredictable clinical course of our patient necessitated a prophylactic indication of pacemaker placement; a permanent pacemaker placement is a class 1 indication in patients with alternating bundle branch blocks per the 2008 American College of Cardiology/American Heart Association recommendations (Gregoratos et al., 1998). To our knowledge, this is the only patient-reported thus far to have this cardiac conduction defect associated with the classical features of PS, and also to undergo prophylactic pacemaker implantation.

4 | CONCLUSION

Our report demonstrates that patients with Pearson marrow-pancreas syndrome may also have cardiac involvement that manifests as conduction abnormalities. Thus, one should evaluate and consider that patients diagnosed with Pearson syndrome have electrocardiographic and echocardiographic studies at disease diagnosis, and also need follow-up periodically thereafter. If they are found to have alternating bundle branch blocks, we recommend consideration of prophylactic pacemaker placement, given the progressive nature of the disease. If they also have documented ventricular tachycardia (VT), it would be reasonable to assess the cause of VT (evaluation for the presence of ventricular scarring or inducible VT) before a decision on the kind of permanent device (pacemaker or intracardiac device (ICD) implantation) is made, and as was the case in this patient, continued serial monitoring and potential treatment of nonsustained ventricular tachycardia must be considered. This case highlights the importance of having cardiologists and electrophysiologists as part of the multidisciplinary team to ensure careful and

timely intervention, and also to prevent sudden cardiac death from an undiagnosed heart block.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests. This research received no grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONSENT INFORMED

Informed consent was obtained from the patient's parents for publication of this case report and any accompanying images.

ORCID

Mats Steffi Jennifer <https://orcid.org/0000-0002-5547-6386>

REFERENCES

- Chawla, S., Coku, J., Forbes, T., & Kannan, S. (2008). Kearns-Sayre syndrome presenting as complete heart block. *Pediatric Cardiology*, 29(3), 659–662. <https://doi.org/10.1007/s00246-007-9040-z>
- Epstein, A. E., DiMarco, J. P., Ellenbogen, K. A., Estes, N. A. M., Freedman, R. A., Gettes, L. S., ... Yancy, C. W. (2008). ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, 5(6), e1–e62. <https://doi.org/10.1016/j.hrthm.2008.04.014>
- Grady, J. P., Campbell, G., Ratnaike, T., Blakely, E. L., Falkous, G., Nesbitt, V., ... McFarland, R. (2014). Disease progression in patients with single, large-scale mitochondrial DNA deletions. *Brain*, 137(Pt 2), 323–334. <https://doi.org/10.1093/brain/awt321>
- Gregoratos, G., Cheitlin, M. D., Conill, A., Epstein, A. E., Fellows, C., Ferguson, T. B., ... Silka, M. J. (1998). ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices: Executive Summary—a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). *Circulation*, 97(13), 1325–1335. <https://doi.org/10.1161/01.CIR.97.13.1325>
- Kabunga, P., Lau, A. K., Phan, K., Puranik, R., Liang, C., Davis, R. L., ... Sy, R. W. (2015). Systematic review of cardiac electrical disease in Kearns-Sayre syndrome and mitochondrial cytopathy. *International Journal of Cardiology*, 181, 303–310. <https://doi.org/10.1016/j.ijcard.2014.12.038>
- Krauch, G., Wilichowski, E., Schmidt, K. G., & Mayatepek, E. (2002). Pearson marrow-pancreas syndrome with worsening cardiac function caused by pleiotropic rearrangement of mitochondrial DNA. *American Journal of Medical Genetics*, 110(1), 57–61. <https://doi.org/10.1002/ajmg.10410>
- Manea, E. M., Leverger, G., Bellmann, F., Stanescu, P. A., Mircea, A., Lèbre, A.-S., ... Munnich, A. (2009). Pearson syndrome in the neonatal period: Two case reports and review of the literature. *Journal of Pediatric Hematology/Oncology*, 31(12), 947–951. <https://doi.org/10.1097/MPH.0b013e3181bbc4ef>
- Moraes, C. T., DiMauro, S., Zeviani, M., Lombes, A., Shanske, S., Miranda, A. F., ... Rowland, L. P. (1989). Mitochondrial DNA deletions in progressive external ophthalmoplegia and Kearns-Sayre syndrome. *The New England Journal of Medicine*, 320(20), 1293–1299. <https://doi.org/10.1056/NEJM198905183202001>

- Pearson, H. A., Lobel, J. S., Kocoshis, S. A., Naiman, J. L., Windmiller, J., Lammi, A. T., ... Marsh, J. C. (1979). A new syndrome of refractory sideroblastic anemia with vacuolization of marrow precursors and exocrine pancreatic dysfunction. *The Journal of Pediatrics*, 95(6), 976–984. [https://doi.org/10.1016/S0022-3476\(79\)80286-3](https://doi.org/10.1016/S0022-3476(79)80286-3)
- Rötig, A., Cormier, V., Blanche, S., Bonnefont, J. P., Ledeist, F., Romero, N., ... Saudubray, J. M. (1990). Pearson's marrow-pancreas syndrome. A multisystem mitochondrial disorder in infancy. *The Journal of Clinical Investigation*, 86(5), 1601–1608. <https://doi.org/10.1172/JCI114881>
- Sato, T., Muroya, K., Hanakawa, J., Iwano, R., Asakura, Y., Tanaka, Y., ... Adachi, M. (2015). Clinical manifestations and enzymatic activities of mitochondrial respiratory chain complexes in Pearson marrow-pancreas syndrome with 3-methylglutaconic aciduria: A case report and literature review. *European Journal of Pediatrics*, 174(12), 1593–1602. <https://doi.org/10.1007/s00431-015-2576-7>
- Stoddard, R. A., McCurnin, D. C., Shultenover, S. J., Wright, J. E., & deLemos, R. A. (1981). Syndrome of refractory sideroblastic anemia with vacuolization of marrow precursors and exocrine pancreatic dysfunction presenting in the neonate. *The Journal of Pediatrics*, 99(2), 259–261. [https://doi.org/10.1016/S0022-3476\(81\)80470-2](https://doi.org/10.1016/S0022-3476(81)80470-2)

How to cite this article: Jennifer MS, Cortez D. Pearson marrow-pancreas syndrome with cardiac conduction abnormality necessitating prophylactic pacemaker implantation. *Ann Noninvasive Electrocardiol*. 2020;25:e12681. <https://doi.org/10.1111/anec.12681>