THE LETTER TO EDITOR

doi: 10.5455/medarh.2018.72.234-236
MED ARCH. 2018 APR; 72(3): 234-236
RECEIVED: MAR 20, 2018 | ACCEPTED: MAY 15, 2018

Broad Phenotypic Heterogeneity and Multisystem Involvement in Single mtDNA Deletion-associated Pearson Syndrome

Josef Finsterer[1], Fulvio A. Scorza[2], Carla A. Scorza[2]

[1]Krankenanstalt Rudolfstiftung, Vienna, Austria
[2]Disciplina de Neurociência. Escola Paulista de Medicina/Universidade Federal de São Paulo/ (EPM/UNIFESP). São Paulo, Brasil

Corresponding author: Josef Finsterer, MD, PhD. Postfach 20. 1180 Vienna, Austria, Europe. Tel. +43-1-71165-92085. Fax. +43-1-4781711. E-mail: fipaps@yahoo.de

We read with interest the article by Khasawneh et al. about a 4 months-old male with Pearson syndrome due to a novel mtDNA deletion (1). We have the following comments and concerns.

The authors mention that Pearson syndrome may be due to mtDNA point mutations (1). We do not agree with this notion. If at all, this is a completely rare event. In the vast majority of the cases, Pearson syndrome is due to mtDNA deletions, which usually occur spontaneously, without germline transmission. Only in about 4% of the cases, single mtDNA deletions are inherited from the mother's side (2). Duplications are also a rare event, but may occur more frequently than point mutations (3, 4).

With regard to the phenotype of Pearson syndrome, it has to be stressed that it is not confined to the bone marrow and the pancreas as originally reported, but is in fact a multisystem disease (Table 1) (5). Affected organs other than the bone marrow and the pancreas include the kidneys (Fanconi syndrome (glucosuria, hyperphosphatemia, proteinuria, aminoaciduria), renal insufficiency, global sclerosis of glomerula, 3-methyl glutaconic aciduria (6), tubulopathy and tubular atrophy) (5), the liver (steatosis (6), liver dysfunction (6), hepatomegaly (6), or vacuolated hepatocytes) (6, 7, 8), the central nervous system (seizures, ataxia, retarded speech development, muscle hypotonia, hypointensities of the brain stem, or subcortical white matter lesions with white or grey matter lesions (9), or as movement disorders, particularly tremor) (9), the eyes (retinal or corneal compromise (9), corneal endothelial dysfunction) (8), the endocrine organs (growth retardation with short stature, diabetes, hypoparathyroidism (9), or adrenal insufficiency) (10), the heart (myocardial thickening, repolarisation abnormalities, QT-prolongation, bicuspid right ventricle (9), or as complex–IV deficiency) (6), the blood (anemia, leucopenia, thrombocytopenia, acute myeloid leukemia) (9), the skin (focal hyperpigmentation, café aux lait spots (9), or as cutaneous zygomatosis (11)), the gastro-intenstinal tract (duodenal ulcer, diarrhea (12, 13), reflux, or malabsorption (Table 1), the skeletal muscle (ptosis, muscle weakness, or myopathy (6)), or other abnormalities (e.g. splenomegaly (9)).

Since most organs can be clinically or subclinically affected in Pearson syndrome (Table 1), it is essential to investigate patients with Pearson syndrome prospectively for central nervous system involvement, endocrine abnormalities, kidney disease, cardiac compromise, renal disease, skin abnormalities, gastrointestinal compromise, myopathy, and for ophthalmologic disease. Were prospective investigations for subclinical disease in any organ/tissue in the described patient carried out, and were any phenotypic manifestations in addition to bone marrow dysfunction and pancreas insufficiency detected as listed in Table 1?

The patient is reported to have had developed hepatomegaly (1), which has been only rarely previously reported (Table 1). Was hepatomegaly due to primary hepatic compromise or secondary due to heart failure? Heart failure cannot be excluded since the presented patient had been admitted for dyspnea and cyanosis (1). Which were the ECG and echocardiographic findings?

Overall, this interesting report could benefit from provision of prospective investigations for multi-

Organ/tissue	Abnormality	Frequency	Reference
Central nervous system			
	Epilepsy	+	[12]
	Ataxia	+	[14]
	Movement disorder (tremor)	+	[14]
	Hypotonia	++	[15]
	Failure to thrive	++	[15]
	Diffuse white matter lesions	+	[15]
	Subcortical white matte lesions	+	[9]
	Delayed motor milestones	++	[14,15]
	Attention deficit	+	[12]
	Hypomyelination (PLIC)	+	[15]
	Leigh-like features	+	[9,16]
	Hypointensities of brain stem, cerebellum, pons	+	[9,14]
	Cortical blindness	+	[12]
	Cerebral atrophy	+	[12]
	Basal ganglia calcification	+	[14]
	Lactic acidosis	+++	[15]
Peripheral nervous system			
	Myopathy	+	[6]
	Ptosis	+	[13]
	Absent deep tendon reflexes	+	[15]
Eyes			
	Corneal opacities	++	[8,9,17]
	Retinal compromise	+	[9]
Endocrine organs			
	Diabetes	+++	[5]
	Growth retardation (short stature)	+++	[9,13,15]
	Adrenal insufficiency	++	[10,17]
	Hypoparathyroidism	+	[9]
Heart			
	Complete heart block	+	[18]
	Right (left) myocardial thickening	+	[9,13,15]
	Repolarisation abnormalities	+	[9]
	QT-prolongation	+	[9]
	Bicuspid right ventricle	+	[9]
Gastrointestinal			
	Exocrine pancreas insufficiency	+++	[15]
	Steatosis	+++	[16]
	Hepatomegaly	++	[15]
	Malabsorption	++	[15]
	Liver dysfunction	+++	[6,8]
	Vacuolated hepatocytes	+	[6]
	Reflux	++	[15]
	Duodenal ulcer	+	[12]
	Diarrhoea	++	[12]
Kidneys			
	Renal cysts	+	[19]
	Tubulopathy	+++	[5]
	Fanconi syndrome	++	[6]
	Renal insufficiency	+	[6]
	Global sclerosis of glomerula	+	[6]
Blood			
	Anemia	+++	[9,13]
	Leucopenia	+++	[9]
	Thrombocytopenia	+++	[9]
Skin			
	Hyperpigmentation	+	[9]
	Café au lait spots	+	[9]
Other			
	Hypospadia	+	[20]
	Cleft lip/palate	+	[20]
	Serum lactate ↑	+++	[15]
	Urine organic acids ↑	++	[15]
	3-methly-glutaconic aciduria	++	[6]
	Splenomegaly	+	[9]
	Acute myeloid leukemia	+	[9]

Table 1. Phenotypic manifestations of patients with Pearson syndrome

organ involvement, and a comprehensive discussion of previously reported data, including the broad phenotypic heterogeneity between patients.

- **Conflict of interest:** There are no conflicts of interest
- **Author's contribution:** All authors contributed equally in design, literature search, discussion, first draft.
- **Competing interest:** No funding was received..
- Declaration of patient consent: Authors certify that they have obtained patient consent form.

REFERENCES

1 Khasawneh R, Alsokhni H, Alzghoul B, Momani A, Abualsheikh N, Kamal N, Qatawneh M. A Novel Mitochondrial DNA Deletion in Patient with Pearson Syndrome. Med Arch. 2018; 72(2): 148-150.

2 Poulton J, Finsterer J, Yu-Wai-Man P. Genetic Counselling for Maternally Inherited Mitochondrial Disorders. Mol Diagn Ther. 2017; 21(4): 419-429.

3 Muraki K, Sakura N, Ueda H, Kihara H, Goto Y. Clinical implications of duplicated mtDNA in Pearson syndrome. Am J Med Genet. 2001; 98(3): 205-209.

4 Jacobs LJ, Jongbloed RJ, Wijburg FA, de Klerk JB, Geraedts JP, Nijland JG, Scholte HR, de Coo IF, Smeets HJ. Pearson syndrome and the role of deletion dimers and duplications in the mtDNA. J Inherit Metab Dis. 2004; 27(1): 47-55.

5 Superti-Furga A, Schoenle E, Tuchschmid P, Caduff R, Sabato V, DeMattia D, Gitzelmann R, Steinmann B. Pearson bone marrow-pancreas syndrome with insulin-dependent diabetes, progressive renal tubulopathy, organic aciduria and elevated fetal haemoglobin caused by deletion and duplication of mitochondrial DNA. Eur J Pediatr. 1993; 152(1): 44-50.

6 Sato T, Muroya K, Hanakawa J, Iwano R, Asakura Y, Tanaka Y, Murayama K, Ohtake A, Hasegawa T, Adachi M. 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. Eur J Pediatr. 2015; 174(12): 1593-602.

7 Crippa BL, Leon E, Calhoun A, Lowichik A, Pasquali M, Longo N. Biochemical abnormalities in Pearson syndrome. Am J Med Genet A. 2015; 167A(3): 621-628.

8 Kasbekar SA, Gonzalez-Martin JA, Shafiq AE, Chandna A, Willoughby CE. Corneal endothelial dysfunction in Pearson

syndrome. Ophthalmic Genet. 2013; 34(1-2): 55-57.
9 Farruggia P, Di Cataldo A, Pinto RM, Palmisani E, Macaluso A, Valvo LL, Cantarini ME, Tornesello A, Corti P, Fioredda F, Varotto S, Martire B, Moroni I, Puccio G, Russo G, Dufour C, Pillon M. Pearson Syndrome: A Retrospective Cohort Study from the Marrow Failure Study Group of A.I.E.O.P. (Associazione Italiana Emato-Oncologia Pediatrica). JIMD Rep. 2016; 26: 37-43.
10 Williams TB, Daniels M, Puthenveetil G, Chang R, Wang RY, Abdenur JE. Pearson syndrome: unique endocrine manifestations including neonatal diabetes and adrenal insufficiency. Mol Genet Metab. 2012; 106(1): 104-107.
11 Kefala-Agoropoulou K, Farmaki E, Tsiouris J, Roilides E, Velegraki A. Cutaneous zygomycosis in an infant with Pearson syndrome. Pediatr Blood Cancer. 2008; 50(4): 939-940.
12 Arzanian MT, Eghbali A, Karimzade P, Ahmadi M, Houshmand M, Rezaei N. mtDNA Deletion in an Iranian Infant with Pearson Marrow Syndrome. Iran J Pediatr. 2010; 20(1): 107-112.
13 Broomfield A, Sweeney MG, Woodward CE, Fratter C, Morris AM, Leonard JV, Abulhoul L, Grunewald S, Clayton PT, Hanna MG, Poulton J, Rahman S. Paediatric single mitochondrial DNA deletion disorders: an overlapping spectrum of disease. J Inherit Metab Dis. 2015; 38(3): 445-457.
14 Lee HF, Lee HJ, Chi CS, Tsai CR, Chang TK, Wang CJ. The neurological evolution of Pearson syndrome: case report and literature review. Eur J Paediatr Neurol. 2007; 11(4): 208-214.
15 Morel AS, Joris N, Meuli R, Jacquemont S, Ballhausen D, Bonafé L, Fattet S, Tolsa JF. Early neurological impairment and severe anemia in a newborn with Pearson syndrome. Eur J Pediatr. 2009; 168: 311-315.
16 Yamadori I, Kurose A, Kobayashi S, Ohmori M, Imai T. Brain lesions of the Leigh-type distribution associated with a mitochondriopathy of Pearson's syndrome: light and electron microscopic study. Acta Neuropathol. 1992; 84(3): 337-341.
17 Ribes A, Riudor E, Valcárel R, Salvá A, Castelló F, Murillo S, Dominguez C, Rötig A, Jakobs C. Pearson syndrome: altered tricarboxylic acid and urea-cycle metabolites, adrenal insufficiency and corneal opacities. J Inherit Metab Dis. 1993; 16(3): 537-540.
18 Rahman S, Leonard JV. Early onset of complete heart block in Pearson syndrome. J Inherit Metab Dis. 2000; 23(7): 753-754.
19 Gürgey A, Ozalp I, Rötig A, Coşkun T, Tekinalp G, Erdem G, Akeören Z, Caglar M, Bakkaloglu A. A case of Pearson syndrome associated with multiple renal cysts. Pediatr Nephrol. 1996; 10(5): 637-638.
20 Lohi O, Kuusela AL, Arola M. A novel deletion in a Pearson syndrome infant with hypospadias and cleft lip and palate. J Inherit Metab Dis. 2005; 28(6): 1165-1166.