Author’s response to reviews

Title: Fitting the pieces of the Dunnigan-type of familial partial lipodystrophy puzzle in the adolescent girl - a case report

Authors:

Paulina Krawiec (paulina.krawiec@wp.pl)
Beata Melges (beamed1@wp.pl)
Elzbieta Pac-Kozuchowska (epac@mp.pl)
Agnieszka Mroczkowska-Juchkiewicz (aga_juchkiewicz@poczta.onet.pl)
Kamila Czerska (kamila.czerska@medgen.pl)

Version: 3
Date: 24 November 2015

Author’s response to reviews: see over
Reply to Reviewers’ comments
We would like to thank all Reviewers for their careful and thorough reading of this manuscript and their constructive remarks that helped us to improve the quality of this manuscript. We would like to express our sincere appreciation of the positive feedback from all Reviewers.

Our detailed response is as follows:

Reviewer #1: Vinaya Simha
This is a well-written, comprehensive case report highlighting the characteristic presentations of FPLD. The authors should, however, point out what is unique in this particular case which is worth publishing.

Thank you for that comment. We wrote as follows

“We present a unique case of an adolescent girl who remained under the comprehensive supervision of dermatologist due to acanthosis nigricans and gynaecologist due to suspicion of polycystic ovary syndrome, and at the age of 14 years old was admitted to the Department of Paediatrics with chronic hypertransaminasemia. The liver biopsy showed features of steatohepatitis. However, it was not the final diagnosis but just another piece of puzzle. Medical history, clinical phenotype and the results of additional tests strongly suggested FPLD2, which was confirmed by molecular testing. Although our patient remained under the comprehensive supervision of paediatrician, dermatologist and gynaecologist, the final diagnosis was stated at the age of 14 years. It should be stressed that despite young age of our patient, delay in FPLD2 diagnosis led to severe metabolic derangements and decreased quality of life. We present that case to highlight the importance of clinical acumen and holistic approach to a patient based on thorough medical history and careful physical examination. We would like to emphasise that the recognition of steatohepatitis should alert one to the possible diagnosis of rare metabolic disorder including FPLD2. We believe that present case report will improve awareness of FPLD2 among paediatricians and result in earlier diagnosis of that disorder.”

We have also changed the title of the manuscript to “Fitting the pieces of the Dunnigan-type of familial partial lipodystrophy puzzle in the adolescent girl - a case report” to highlight that the recognition of FPLD2 may be confusing and require ingenuity.

They should provide a reference for the quoted prevalence of 1 in 15 million.

The reference has been provided. Moreover, as other Reviewer suggested we have added the information about the prevalence reported by other researchers, as follow “The estimated incidence of FPLD 2 is 1 case per 15 million persons [1]. However, the real prevalence may be 1 out of 200, 000 [5].”

Needs some language corrections before being published.

Language corrections have been made.

Reviewer #2: Davide Carvalho
Please refer to “Dunnigan-type familial partial lipodystrophy [FPLD2], to emphasise the existence of different types of lipodystrophy, namely in the Background – page 3
We have added that information to the manuscript.

**It is necessary to correct the prevalence - Estimated prevalence is of 1 in 200,000 people (Al-Shali KZ, Hegele RA. Laminopathies and atherosclerosis. Arterioscler Thromb Vasc Biol 2004; 249):1591-5.)**

The incidence of FPLD 1 in 15 million is reported by Vantyghem et al. [Ann Endocrinol (Paris). 2012; 73:170-89]. However, as suggested by the Reviewer we have added the information about the prevalence reported by other researchers, as follow “The estimated incidence of FPLD 2 is 1 case per 15 million persons [1]. However, the real prevalence may be 1 out of 200, 000 [5].”

**Clarify the medical history of the mother and grandmother. The authors said, “because her mother and grandmother presented similar features”. Are there any metabolic abnormalities in the family members?**

Both mother and grandmother presented similar physical features like our patient. However, they deny any medical conditions and they did not consent on any further diagnostic evaluation, including molecular testing.

**Regarding laboratory results if it is available introduce androstenedione values.**

We performed many laboratory test to evaluate hormone balance, however androstendione was not performed.

**Regarding table 1 5.1 - Correct Triglycerides instead of triglicerides 5.2 – Standardize the Units – The authors write “Bilirubin [mg/dl]” and “Lipids profile [mg/dL]”. Change all to mg/dL.**

Corrections have been made.

**Reviewer#3: Véronique Béréziat**

If the case report is well built with a precise description of the clinical data, my main criticism remains that the authors do not put enough evidence in the uniqueness of this case. As mentioned by the authors in the discussion section, three cases of FPLD2 have already been described in Poland, including a girl of 17 years-old (Ref 1). Moreover, some 85% of FPLD2 patients present an heterozygous missense substitutions at LMNA codon 482 (Ref 2). However, authors should have one or two paragraphs indicating why this case is unique, as required in the CARE Checklist.

Thank you for that comment. We have added the paragraph highlighting the unique features of that case as follows:

“We present a unique case of an adolescent girl who remained under the comprehensive supervision of dermatologist due to acanthosis nigricans and gynaecologist due to suspicion of polycystic ovary syndrome, and at the age of 14 years old was admitted to the Department of Paediatrics with chronic hypertransaminasemia. The liver biopsy showed features of steatohepatitis. However, it was not the final diagnosis but just another piece of puzzle. Medical history, clinical phenotype and the results of additional tests strongly suggested FPLD2, which was confirmed by molecular testing. Although our patient remained under the comprehensive supervision of paediatrician, dermatologist and gynaecologist, the final diagnosis was stated at the age of 14 years. It should be stressed that despite young age of our
patient, delay in FPLD2 diagnosis led to severe metabolic derangements and decreased quality of life. We present that case to highlight the importance of clinical acumen and holistic approach to a patient based on thorough medical history and careful physical examination. We would like to emphasise that the recognition of steatohepatitis should alert one to the possible diagnosis of rare metabolic disorder including FPLD2. We believe that present case report will improve awareness of FPLD2 among paediatricians and result in earlier diagnosis of that disorder.”

We have also changed the title of the manuscript to “Fitting the pieces of the Dunnigan-type of familial partial lipodystrophy puzzle in the adolescent girl - a case report” to highlight that the recognition of FPLD2 may be confusing and require ingenuity.

**Familial partial lipodystrophy of the Dunnigan type must be refer as FPLD2.**

Corrections have been made.

*Page 3 line 9 the authors indicated that the LMNA gene encodes lamins instead of A-type lamins (lamin A and C). The authors should correct the sentence.*

Corrections have been made.

*Page 3 lines 14-16 “holistic approach to a patient” is written twice, the authors should correct this.*

Corrections have been made.

*Page 3 line 23 fist should be replaced by first.*

Corrections have been made.

*When describing the genetic test performed page 5 the authors should add a figure with the DNA sequencing revealing the heterozygous substitution.*

We have added the figure with the DNA sequencing.

*In the discussion, the authors indicated that FPLD2 incidence was 1 case per 15 millions. In fact, the incidence of the disease is rather than 1 in 200, 000 (Ref 3).*

Vantyghem et al. report the incidence of FPLD 1 in 15 million [Ann Endocrinol (Paris). 2012; 73:170-89]. However, as suggested by the Reviewers we have added the information about the prevalence reported by other researchers, as follow “The estimated incidence of FPLD 2 is 1 case per 15 million persons [1]. However, the real prevalence may be 1 out of 200, 000 [5].”

*Some references are missing. • Page 3, lines 8-10, the authors should include a review which address the structural and functional role of lamin A/C instead of a clinical review. • They also should cite the two original papers about the LMNA p.R482 heterozygous substitutions (Ref 4-5).*

We have improve the references with suggested papers.