The Challenges of a Successful Pregnancy in a Patient with Adult Refsum's Disease due to Phytanoyl-CoA Hydroxylase Deficiency

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Abstract We describe the management and outcomes of pregnancy in a 27-year-old woman with infantile-onset Adult Refsum's disease (ARD). She presented in infancy but was diagnosed with ARD at the age of 10 on basis of phytanic acidemia and later confirmed to have the phytanoyl-CoA hydroxylase (*PHYH*) c.164delT, p. L55fsX12) mutation. Despite repeated plasmapheresis sessions and strict dietary surveillance for 20 years, her phytanic acid levels persistently stayed above the ideal target level of 100 $\mu\text{mol/L}$ but remained below 400 $\mu\text{mol/L}$. Initially the pregnancy was uncomplicated but in the third trimester of pregnancy the patient was admitted to the hospital with fluctuating hypertension, sinus tachycardia and breathlessness. The patient was compliant with diet during pregnancy and her phytanic levels were remained

well controlled: 177 and 188 $\mu\text{mol/L}$ in the first and second trimester, respectively. Peri-partum management required a coordinated team approach including a high-calorie and restricted diet to reduce the risk of acute metabolic decompensation. During the induced labour she required 10% dextrose infusions.

Post-partum it took the mother a long time to recover from childbirth – her appetite was poor due to post-natal depression and her body weight decreased rapidly by 11 kg within 3 weeks after childbirth, resulting in a spike in phytanic acid to 366 $\mu\text{mol/L}$. Measures were taken to minimise the risk of acute neurological decompensation. The infant was unaffected and has made normal developmental progress in the subsequent 2 years.

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Refsum's Disease Syndrome

Classical or Adult Refsum's disease (ARD; OMIM 266510) is a rare autosomal recessive condition. About 250 cases have been identified and the frequency of the condition in the population is thought to be 1 in 1,000,000. The ARD syndrome is associated with raised levels of phytanic acid due to defective peroxisomal α -oxidation of this dietary-derived isoprenoid fatty acid. About 90% of cases are caused by mutations in phytanoyl-CoA hydroxylase (*PHYH*; EC 1.14.11.18) with phenocopies caused by mutations in peroxin-7 (van den Brink et al. 2003) and α -methyl- α -acyl CoA racemase (AMACR; EC 5.1.99.4) (Lloyd et al. 2008).

ARD usually presents in adolescence with impaired night vision and retinitis pigmentosa though anosmia and

osteological features are present from birth (Wierzbicki et al. 2002). Most patients develop retinitis pigmentosa, demyelinating polyneuropathy, cerebellar ataxia and elevated CSF protein by the age of 20 (Skjeldal et al. 1987). Other clinical features of ARD include sensorineural hearing loss, cataracts, cardiac arrhythmias and ichthyosis (Burns et al. 2003). The retinal condition is slowly progressive. Neuropathic symptoms may appear intermittently and are associated with acute rises in phytanic levels that occur during intercurrent illness, anorexia, deliberate weight loss or starvation prior to surgery (Burns et al. 2003; Wierzbicki et al. 2003). Dietary restriction lowers plasma phytanic acid levels by 50–100%, leading to significant improvement in neurological function (Baldwin et al. 2010). Acute or long-term plasmapheresis is also used in the management of ARD (Kohlschutter et al. 2012; Zolotov et al. 2012). Although visual loss, anosmia and deafness are irreversible, their progression may slow with dietary therapy (Baldwin et al. 2010). Pregnancy is a stress-inducing state characterised by fat mobilisation. Pregnancy-related anorexia or weight loss potentially could lead to decompensation of phytanic acid levels. This is the first case report of infantile-onset ARD who had successful pregnancy.

Case

The mother was born at full term with no obvious abnormalities to consanguineous parents. At week six post-partum the neonate presented with horizontal nystagmus. As a child she had poor eyesight and limited night vision. Her vision gradually deteriorated over time from 6/36 to 6/24 at the age of 10 years and she was registered as partially sighted. Fundoscopy showed a waxy pallid disk and very early macular atrophic scarring in keeping with ‘salt and pepper’ retinitis pigmentosa of ARD. Sensorineural hearing loss was diagnosed at age 9. She had slight developmental delay at school and coped using short sentences but managed to start a course in fashion design. She suffered from chronic constipation from the neonatal period. She had multiple admissions with abdominal pain and heartburn. At the age of 11 years she was diagnosed with ‘psoriasis’ (probably ichthyosis) affecting her scalp and eyelids. She had eczema on her hands, feet and legs that responded well to topical therapy. On examination at the age of 10 she was noted to have short fingers and toes and incurved fifth fingers. Hand and foot X-rays confirmed symmetrical shortening of fourth and fifth metacarpals and short fourth and fifth toes due to short fourth metatarsals. The proximal phalangeal epiphyses of each hallux were cone-shaped.

At 11 years of age, the local ophthalmologist noted visual impairment, horizontal nystagmus and osteological

abnormalities, and referred her to the regional genetics department. A diagnosis of ARD was made. Her initial phytanic acid level was 670 $\mu\text{mol/L}$ ($<15 \mu\text{mol/L}$). Her very-long chain fatty acids (VLCFA) were within normal reference ranges: C22 = 72 (15–112), C24 = 51.9 (14–80), C26 = 0.99 (0.5–4.0), C24:C22 = 0.72 (0.35–1.10), C26:C22 = 0.008 (0.005–0.030). Pristanate was suppressed. Skin fibroblast culture showed a reduced rate of phytanic acid α -oxidation (25–31; normal range 57–90 pmol/h/mg). Peroxisomal enzyme activities for β -oxidation and dihydroxyacetone phosphate acyltransferase (DHAP-AT; EC 2.3.1.42) activity (6.76; normal 3.5–7.5 $\mu\text{mol/h/g}$ protein) were normal. Genetic sequencing later confirmed homozygosity for phytanoyl-CoA hydroxylase (*PHYH*) c.164delT, p.L55fsX12 mutation (Jansen et al. 2000). Her younger brother was also affected. He commenced a strict dietary regime and did not acquire visual and hearing impairments.

She was managed with a low phytanic acid diet and multivitamins (Brown et al. 1993; Baldwin et al. 2010, 2016). Her phytanic acid could be brought down temporarily with plasmapheresis sessions but varied between 300 and 600 $\mu\text{mol/L}$ between sessions (Fig. 1). She adhered well to her diet reasonably but on one occasion her phytanic acid spiked to 860 $\mu\text{mol/L}$ as a result of acute weight loss. Standardised portion meals were introduced to help her maintain body weight and prevent rapid weight loss.

Pregnancy

At the age of 27 she presented to the regional Adult Inherited Metabolic Disorders Clinic in the 6th week of pregnancy. She was reviewed monthly in person by a Metabolic Clinician or by telephone by a Metabolic Dietician. She also had regular appointments with the local Obstetrics Team. In the first trimester she was admitted locally with epigastric pain and lower abdominal pain. Foetal ultrasound scans showed a normal foetal development. She was advised to avoid any dairy spreads, cheese, fat olive, vegetable oil, tomatoes, walnuts and peanuts (Baldwin et al. 2010). Omega-3 fatty acids, iron and vitamin supplements were introduced throughout the pregnancy (Baldwin et al. 2016). The aim was to maintain adherence to the restrictive diet and a phytanic acid below 100 $\mu\text{mol/L}$ (our local guidelines) and optimise her calorie intake to minimise weight gain during pregnancy. Her phytanic acid levels remained stable during pregnancy (Fig. 1).

At 5 months, she had gained 7 kg and weighed 82.6 kg. During pregnancy she developed some common complications including carpal tunnel syndrome in 6th month. In the third trimester she presented with sinus tachycardia of mean

Fig. 1 Fluctuations in phytanic acid over 20 years

120/min on 24-hour ECG and shortness of breath. Investigations for pulmonary embolism and echocardiogram were normal. No cause for her sinus tachycardia was found but she was advised to start labetalol. She had breathlessness, fluctuating hypertension, dry skin and pruritus until the end of her pregnancy which improved post-partum. The dryness of the skin and pruritus were thought to be exacerbated by high phytanic acid levels (DiGiovanna and Robinson-Bostom 2003). She treated her dry skin with hydroxyzine and emollient as a supplement of soap. At 36 weeks her blood pressure was 156/93 mmHg and fluctuating. Her height of 155 cm and weight 92.2 kg gave a body mass index of 38.38 kg/m^2 . Her clinical examination was normal. The patient was compliant with diet during pregnancy. Her phytanic acid levels were $177 \mu\text{mol/L}$ and $188 \mu\text{mol/L}$ in the first and second trimester, respectively. They increased to $443 \mu\text{mol/L}$ at 36 weeks.

During the induced labour, 100 g/day Polycal[®] (384 kcal) and 30mls tds Calogen[®] (420 kcal) were provided to reduce the risk of acute metabolic decompensation. After the delivery of a healthy girl at term (whose phytanic acid at the age of 6 weeks was not raised), it took the mother a long time to recover from her childbirth – her appetite was poor due to post-natal depression (1,417 kcal daily intake, including 40 g protein). She was advised to continue isotonic drinks and eating small portions when she could. She decided not to breastfeed. Artificial formula feeding was used by the infant from birth.

She was advised not to lose more than 0.5 kg per week post-partum but her weight decreased rapidly by 11 kg

within 3 weeks resulting in a spike of phytanic acid to $366 \mu\text{mol/L}$. The patient was prescribed Fresubin[®] (3 cartons daily; 90 kcal) as a source of additional calories and was advised to monitor her body weight on a daily basis. She continued experiencing episodes of fatigue and general weakness. She had problems with her episiotomy for many months causing dyspareunia that required a refashioning of episiotomy and treatment with antibiotics (gentamycin). Physical examination and ultrasound scan of her pelvis did not show any abnormal findings. Post-natally her blood pressure was raised and she was treated with diuretics. Echocardiography was normal. She developed headaches and dizziness and tried a calcium channel blocker, diuretics, amitriptyline and tricyclic anti-depressants but could not tolerate any. She had persistent episodes of nausea, vomiting and epigastric abdominal pain radiating to her back associated with raised amylase (429; reference range $<110 \text{ IU/L}$). Cholecystitis and pancreatitis were considered but never confirmed. A gastroscopy showed a 3 cm hernia. She underwent detailed specialist investigations and her symptoms were eventually attributed to irritable bowel syndrome.

She has mild learning difficulties and receives support from her husband and family. She is engaging effectively with healthcare services and tries to be compliant with diet. Twelve months post-delivery, her BMI is stable at 33.6 kg/m^2 . She has remained on strict diet with 1,500 kcal intake including 78 g protein but is still struggling on a daily basis with fatigue, shortness of breath and variable bowel movements. The child is healthy and developing well.

Discussion

We present a case of infantile-onset ARD syndrome in a female patient, who despite significantly raised levels of phytanic acid, has had a successful pregnancy. One other case description of infantile-onset ARD syndrome exists but describes a more severe clinical but similar biochemical phenotype in a male child (Herbert and Clayton 1994). Her delayed diagnosis is not unusual in cases of ARD where the delay in diagnosis is typically 11 years (Claridge et al. 1992; Ruther 2005). This is the first case report describing the birth of a healthy baby despite very high phytanic acid levels in the mother. In our patient the only significant defect was in alpha-oxidation of phytanic acid. Pristanate was suppressed as is typical in ARD rather than elevated as in severe peroxisomal biogenesis disorders (Poulos et al. 1988). Despite a phytanic acid-restricted diet for many years and repeated plasmapheresis, she continued to have an elevated plasma phytanic acid in the typical range for many treated patients (Baldwin et al. 2010). The effect of elevated maternal phytanic acid on maternal or foetal outcomes in pregnancy has never been described. It has been postulated that phytanic acid does not cross the placenta (Zomer et al. 2000) but clinical data is lacking. In this case it seems that elevated plasma phytanic acid that was not detrimental to the mother or foetus.

Vomiting, nausea and anorexia in pregnancy may exacerbate the underlying condition (Langendonk et al. 2012). Decreases in glucose, insulin and alanine and increases in ketone body production occur in a fasting state, and occur faster than in a non-pregnant state (Butte 2000). In ARD starvation induces a rapid rise in phytanic acid levels with long-term sequelae in some patients (Wierzbicki et al. 2003). In our patient nausea and vomiting led to decrease in meal frequency and food intake, but this had only a small effect on plasma phytanic acid levels. Ideally phytanic acid levels need to be monitored monthly in pregnancy. The patient maintained good contact with IMD services and was very compliant with diet. As a result, her phytanic acid levels were better than prior to the pregnancy and repeated monitoring was not thought necessary.

It has been shown that enhanced catabolism and increased phytanic acid levels may exacerbate retinitis pigmentosa and reduce visual fields in the third trimester of pregnancy as described in an unpublished case report of a woman with ARD (Leroy BP, unpublished observations). No deterioration in visual fields was seen in our patient. Pruritus is a feature of pregnancy. The incorporation of phytanic acid into cholesterol esters reduces the amount of free cholesterol in the blood and may lead to a relative deficiency of linoleate in many organs, including skin. This

may contribute to ichthyosis which is also seen in essential fatty acid deficiency (Laurell et al. 1972).

During labour and delivery the requirements for energy increase. In principle it is important that the woman keeps her caloric intake adequately maintained during labour so that she does not go into catabolic stress at the time of delivery. Therefore she should be encouraged to have oral foods and drinks at frequent intervals during the earlier stages of labour when she is able to tolerate this. In our case, labour was induced and not prolonged and the woman was managed on intravenous 10% dextrose (2 mL/kg/h). After she delivered and was able to eat and drink there was no need for the dextrose infusion. Breastfeeding will increase energy demands on a mother (Langendonk et al. 2012) but our patient did not breastfeed so this was not an issue.

There is little data on drug interactions with the alpha-oxidation pathway. Ibuprofen is generally avoided because it is metabolised by AMACR and may interfere with the metabolism of phytanic acid (Lloyd et al. 2008). Most medications are safe as long as they do not contain animal fat but even if these contain phytanic acid then the additional exposure is likely to be small. The only exception is in omega-3 fatty acid preparations. Partially purified preparations derived from fish oils (e.g. MaxEPA) may contain significant quantities of phytanic acid though ultra-pure formulations derived from plant sources (e.g. Omacor) do not (Wierzbicki AS, unpublished data). Gelatine and lactose are safe as are lidocaine, diamorphine, phenylephrine, ondansetron, co-amoxiclav, suxamethonium, paracetamol, codeine and morphine (Stepien KM, unpublished data). All those medications were considered prior to childbirth and confirmed with the pharmacist to likely be safe. There is no evidence that levonorgestrel (the active medication in a mirena coil) will affect phytanic acid levels so this method of contraception was proposed to the patient after pregnancy.

The risk of metabolic decompensation is increased in pregnancy in a patient with ARD. Dietary advice prior to the pregnancy should include detailed assessment to ensure adequate caloric intake and this should be reviewed and adjusted during the pregnancy. In conclusion, a multidisciplinary team approach is required to manage patients with inherited metabolic disorders in pregnancy.

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Synopsis

The challenges in the management of pregnancy in a patient with Adult Refsum's disease.

Compliance with Ethics Guidelines

Contributions

All authors performed the literature search. KS wrote the first draft of the manuscript and reviewed the literature, with AW, BTPT, HRW and CJH involved in revisions. All authors approved the final article.

Guarantor

CJH is the guarantor.

Conflict of Interest

All authors declare no conflict of interest for this publication.

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Informed consent was obtained from the patient.

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References

- Baldwin EJ, Gibberd FB, Harley C, Sidey MC, Feher MD, Wierzbicki AS (2010) The effectiveness of long-term dietary therapy in the treatment of adult Refsum disease. *J Neurol Neurosurg Psychiatry* 81:954–957
- Baldwin EJ, Harrington DJ, Sampson B, Feher MD, Wierzbicki AS (2016) Safety of long-term restrictive diets for peroxisomal disorders: vitamin and trace element status of patients treated for Adult Refsum Disease. *Int J Clin Pract* 70:229–235
- Brown PJ, Mei G, Gibberd FB et al (1993) Diet and Refsum's disease. The determination of phytanic acid and phytol in certain foods and application of this knowledge to the choice of suitable convenience foods for patients with Refsum's disease. *J Hum Nutr Diet* 6:295–305
- Burns TM, Ryan MM, Darras B, Jones HR Jr (2003) Current therapeutic strategies for patients with polyneuropathies secondary to inherited metabolic disorders. *Mayo Clin Proc* 78:858–868
- Butte NF (2000) Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. *Am J Clin Nutr* 71:1256S–1261S
- Claridge KG, Gibberd FB, Sidey MC (1992) Refsum disease: the presentation and ophthalmic aspects of Refsum disease in a series of 23 patients. *Eye (Lond)* 6(Pt 4):371–375
- DiGiovanna JJ, Robinson-Bostom L (2003) Ichthyosis: etiology, diagnosis, and management. *Am J Clin Dermatol* 4:81–95
- Herbert MA, Clayton PT (1994) Phytanic acid alpha-oxidase deficiency (Refsum disease) presenting in infancy. *J Inher Metab Dis* 17:211–214
- Jansen GA, Hogenhout EM, Ferdinandusse S et al (2000) Human phytanoyl-CoA hydroxylase: resolution of the gene structure and the molecular basis of Refsum's disease. *Hum Mol Genet* 9:1195–1200
- Kohlschütter A, Santer R, Lukacs Z, Altenburg C, Kemper MJ, Ruther K (2012) A child with night blindness: preventing serious symptoms of Refsum disease. *J Child Neurol* 27:654–656
- Langendonk JG, Roos JC, Angus L et al (2012) A series of pregnancies in women with inherited metabolic disease. *J Inher Metab Dis* 35:419–424
- Laurell S, Nilsen R, Norden A (1972) Incorporation of phytanic and linoleic acid into plasma lipids in Refsum's disease. *Clin Chim Acta* 36:169–174
- Lloyd MD, Darley DJ, Wierzbicki AS, Threadgill MD (2008) Alpha-Methylacyl-CoA racemase – an 'obscure' metabolic enzyme takes centre stage. *FEBS J* 275:1089–1102
- Poulos A, Sharp P, Fellenberg AJ, Johnson DW (1988) Accumulation of pristanic acid (2, 6, 10, 14 tetramethylpentadecanoic acid) in the plasma of patients with generalised peroxisomal dysfunction. *Eur J Pediatr* 147:143–147
- Ruther K (2005) Adult Refsum disease. A tapetoretinal degeneration accessible for therapy. *Ophthalmologe* 102:772–777
- Skjeldal OH, Stokke O, Refsum S, Norseth J, Petit H (1987) Clinical and biochemical heterogeneity in conditions with phytanic acid accumulations. *J Neurol Sci* 77:87–96
- van den Brink DM, Brites P, Haasjes J et al (2003) Identification of PEX7 as the second gene involved in Refsum disease. *Am J Hum Genet* 72:471–477
- Wierzbicki AS, Lloyd MD, Schofield CJ, Feher MD, Gibberd FB (2002) Refsum's disease: a peroxisomal disorder affecting phytanic acid alpha-oxidation. *J Neurochem* 80:727–735
- Wierzbicki AS, Mayne PD, Lloyd MD et al (2003) Metabolism of phytanic acid and 3-methyl-adipic acid excretion in patients with adult Refsum disease. *J Lipid Res* 44:1481–1488
- Zolotov D, Wagner S, Kalb K, Bunia J, Heibges A, Klingel R (2012) Long-term strategies for the treatment of Refsum's disease using therapeutic apheresis. *J Clin Apher* 27:99–105
- Zomer AW, Jansen GA, van Der BB et al (2000) Phytanoyl-CoA hydroxylase activity is induced by phytanic acid. *Eur J Biochem* 267:4063–4067