Molecular Genetics and Metabolism xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

The challenges of managing coexistent disorders with phenylketonuria: 30 cases

A. MacDonald [a,*], K. Ahring [b], M.F. Almeida [c,d], A. Belanger-Quintana [e], N. Blau [f], A. Burlina [g], M. Cleary [h], T. Coskum [i], K. Dokoupil [j], S. Evans [a], F. Feillet [k], M. Giżewska [l], H. Gokmen Ozel [m], A.S. Lotz-Havla [n], E. Kamieńska [o], F. Maillot [p], A.M. Lammardo [q], A.C. Muntau [r], A. Puchwein-Schwepcke [n], M. Robert [s], J.C. Rocha [c,t,u], S. Santra [a], R. Skeath [h], K. Strączek [l], F.K. Trefz [v], E. van Dam [w], M. van Rijn [w], F. van Spronsen [w], S. Vijay [a]

[a] The Children's Hospital, Birmingham, UK
[b] Center for PKU, The Kennedy Centre, University Hospital, Glostrup, Copenhagen, Denmark
[c] Centro de Genética Médica Doutor Jacinto de Magalhães, CHP EPE, Porto, Portugal
[d] Unit for Multidisciplinary Research in Biomedicine, Abel Salazar Institute of Biomedical Sciences, University of Porto-UMIB/ICBAS/UP, Porto, Portugal
[e] Hospital Ramon y Cajal Madrid, Spain
[f] Dietmar-Hopp Metabolic Center, University Children's Hospital, Heidelberg, Germany
[g] Division of Inherited Metabolic Diseases, University Hospital, Padua, Italy
[h] Hospital for Sick Children, Great Ormond Street, London, UK
[i] Department of Inherited Metabolic Disorders, Hacettepe University, Ankara, Turkey
[j] Department of Metabolism and Nutrition, Dr. von Hauner Children's Hospital, University of Munich, Munich, Germany
[k] Hôpital d'enfants Brabois, Vandoeuvre les Nancy, France
[l] Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology, Pomeranian Medical University, Szczecin, Poland
[m] Department of Nutrition and Dietetics, Hacettepe University, Ankara, Turkey
[n] Dr. von Hauner Children's Hospital, University of Munich, Munich, Germany
[o] Department of Paediatrics and Haematology, Pomeranian Medical University, Szczecin, Poland
[p] CHRU de Tours, service de medicine interne, Université François Rabelais, Tours, France
[q] Depart Ped, San Paolo Hosp Univ Milan, Milan, Italy
[r] University Children's Hospital, University Medical Center Hamburg Eppendorf, Hamburg, Germany
[s] Hôpital Universitaire des Enfants Reine Fabiola, Brussels, Belgium
[t] Faculdade de Ciências da Saúde, Universidade Fernando Pessoa, Porto, Portugal
[u] Center for Health Technology and Services Research (CINTESIS), Portugal
[v] Division of Inborn Metabolic Diseases, University Children's Hospital, Heidelberg, Germany
[w] Section of Metabolic Diseases, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

ARTICLE INFO

Article history:
Received 17 August 2015
Received in revised form 6 October 2015
Accepted 7 October 2015
Available online xxxx

Keywords:
Phenylketonuria
Phenylalanine
Diet
Co-existent
Sapropterin

ABSTRACT

Introduction: The few published case reports of co-existent disease with phenylketonuria (PKU) are mainly genetic and familial conditions from consanguineous marriages. The clinical and demographic features of 30 subjects with PKU and co-existent conditions were described in this multi-centre, retrospective cohort study.
Methods: Diagnostic age of PKU and co-existent condition, treatment regimen, and impact of co-existent condition on blood phenylalanine (Phe) control and PKU management were reported.
Results: 30 patients (11 males and 19 females), with PKU and a co-existent condition, current median age of 14 years (range 0.4 to 40 years) from 13 treatment centres from Europe and Turkey were described. There were 21 co-existent conditions with PKU; 9 were autoimmune; 6 gastrointestinal, 3 chromosomal abnormalities, and 3 inherited conditions. There were only 5 cases of parental consanguinity. Some patients required conflicting diet therapy (n = 5), nutritional support (n = 7) and 5 children had feeding problems. There was delayed diagnosis of co-existent conditions (n = 3); delayed treatment of PKU (n = 1) and amenorrhea associated with Grave's disease that masked a PKU pregnancy for 12 weeks. Co-existent conditions adversely affected blood Phe control in 47% (n = 14) of patients. Some co-existent conditions increased the complexity of disease management and increased management burden for patients and caregivers.

* Corresponding author at: Consultant Dietitian in Inherited Metabolic Disorders, Birmingham Children's Hospital, Steelhouse Lane, Birmingham B4 6NH, UK.

http://dx.doi.org/10.1016/j.ymgme.2015.10.001
1096-7192/© 2015 Published by Elsevier Inc.

Please cite this article as: A. MacDonald, et al., The challenges of managing coexistent disorders with phenylketonuria: 30 cases, Mol. Genet. Metab. (2015), http://dx.doi.org/10.1016/j.ymgme.2015.10.001

Conclusions: Occurrence of co-existent disease is not uncommon in patients with PKU and so investigation for co-existent disorders when the clinical history is not completely consistent with PKU is essential. Integrating care of a second condition with PKU management is challenging.

© 2015 Published by Elsevier Inc.

1. Introduction

Since the introduction of dietary treatment for phenylketonuria (PKU) 60 years ago, there are less than 30 case reports of co-existent conditions that have occurred co-incidentally. The identification and reporting of co-existent conditions are essential to quantify any interrelationship and effect [1] on PKU. Neuropsychological symptoms of an undiagnosed co-existent condition may be mistakenly attributed to PKU; the presence of a co-existent condition may also alter morbidity and mortality [2], enhance the complexity of treatment regimens [3] and increase management burden for patients and caregivers. It is also probable that the co-existence of conditions is likely to amplify with increasing age [2], and so worsen health outcomes and increase health care costs. The difficulties and complications associated with co-existent conditions are rarely quantified in PKU.

Co-existent conditions with PKU that have been reported include Fabry disease [4], Down syndrome [5], Goldenhar syndrome [6], acute myeloblastic leukaemia [7], familial hyperglycinuria [8], Type 1 diabetes mellitus (T1DM) [9], hereditary fructose intolerance [10], Vitamin D dependent rickets Type 1 [11], cystic fibrosis [3,12], acute lymphoblastic leukaemia [13], and precocious puberty [14,15]. There has also been association with Duchenne muscular dystrophy [16], cystinuria [17], homozygous hypobetalipoproteinemia [18], and bilateral iris coloboma [19]. There have been case reports of family members with other inherited conditions such as galactosaemia and glycogen storage disease type 3 [20]. Genetic and familial conditions are some of the most common reported co-existent conditions.

Although rarely examined, it is possible that many PKU centres have one or more patients with PKU who have a co-existing second condition. The purpose of this paper is to describe cases from 13 PKU treatment centres of co-existent conditions together with PKU, outlining any impact of PKU on delay of diagnosis of co-existent disease and effect of co-existent disorders on PKU management. We have used the following definition for 'co-existent' condition: '*an additional medical condition(s) that co-exists simultaneously but independently from PKU.*' Any condition that may be as a consequence of PKU (e.g. disorder complication) is excluded.

2. Methods

In this multi-centre, retrospective cohort study, the clinical and demographic features of patients with PKU and co-existent conditions were documented. Patients were recruited predominantly from PKU centres who had health professionals representing the European Nutrition Expert Panel on Nutrition (ENEP) or the Sapropterin Advisory Board. The following parameters were recorded as relevant for each patient: type of co-existent condition, age of diagnosis of PKU/co-existent condition, gender, treatment regimen and clinical symptoms, blood phenylalanine (Phe) control, and psychosocial impact on caregivers and patients. Written informed consent was obtained from the patients or parents/appointed caregivers of the patient for publication of case reports. Children gave consent when they had age appropriate understanding.

3. Results

(See Tables 1 and 2 for summary of individual cases).

3.1. Subjects

A cohort of 30 patients (11 males and 19 females) with PKU from 13 treatment centres caring for 4410 PKU patients are reported. These cases are not inclusive of all patients with a co-existent condition from each clinic; others were not reported due to consent issues, previous documentation or missing data.

All of these 30 cases were diagnosed by newborn screening, with a current median age of 14 years (range 0.4 to 40 years). The treated centres in Europe and Turkey were: Ankara, Turkey; Birmingham, UK; Brussels, Belgium; Copenhagen, Denmark; Groningen, Netherlands; London, UK; Nancy, France; Madrid, Spain; Munich, Germany; Padua, Italy; Porto, Portugal; Szczecin, Poland and Tours, France. Parental consanguinity occurred in only 5 cases; 6 had siblings with PKU, a further three subjects had a family member with the same co-existent condition, and two had siblings who died in early infancy (one from a heart defect; one from an unknown cause). Six patients did not originate in the country of residence. Nine patients had mild PKU requiring minimal or no PKU treatment and 4 patients were treated with sapropterin (tetrahydrobiopterin; BH4) with or without low Phe diet. Fifteen patients were taking ≤1000 mg/day of dietary Phe, supplemented with Phe-free L-amino acid supplement.

3.2. Co-existent conditions

Of the 21 co-existent conditions 9 were autoimmune disorders [ulcerative colitis (n = 2), Type 1 diabetes mellitus (T1DM) (n = 4), autoimmune hepatitis Type 2 (n = 1), alopecia universalis (n = 1), and Grave's disease (n = 1)], 6 involved the gastrointestinal tract [cystic fibrosis, Crohn's disease, ulcerative colitis (n = 2), oesophageal stenosis and eosinophilic colitis], 9 were endocrine disorders [T1DM 1 (n = 4), congenital hypothyroidism (n = 2), Grave's disease(n = 1), and adrenal insufficiency (n = 2)], 3 had malignancies [breast cancer (n = 2), acute lymphoblastic leukaemia (n = 1)], 3 were chromosomal abnormalities [Down syndrome, chromosome 19 p13.3 μ-deletion], 3 inherited conditions [cystic fibrosis, Huntington's disease and Stickler syndrome] and 2 neurological conditions [psychotic behaviour/white matter disease and Chiari 1 malformation]. Two children had dysmorphic syndrome but with unknown diagnosis (BH4 deficiency excluded) and one child with mild PKU had autism (BH4 deficiency excluded). Only 6 (20%) patients had no complicating treatment issues as a consequence of the co-existent condition.

3.2.1. Impact on blood Phe control

Some of the co-existent conditions (n = 14; 47%) affected blood Phe control. This was mainly associated with infections, surgery, trauma, chemotherapy, steroid therapy, inability to eat, and additional nutritional support. In 3 of 6 patients with gastrointestinal disorders, the blood Phe concentrations lowered with uncontrolled malabsorption. In two teenage boys with 'undiagnosed' inflammatory bowel disease, blood Phe levels below lower target range were seen for some weeks before 'obvious' onset of symptoms; additional Phe intake did not cause blood Phe to increase until appropriate treatment medication was commenced. In one newly diagnosed infant with PKU and weight loss, blood phe did not reach target treatment levels until treatment commenced for adrenal insufficiency.

Corticosteroid therapy (intermittent) was associated with increased blood Phe in 3 of 6 cases. Methotrexate was used to treat 2 patients (for ALL; alopecia universalis); the patient with Alopecia

Please cite this article as: A. MacDonald, et al., The challenges of managing coexistent disorders with phenylketonuria: 30 cases, Mol. Genet. Metab. (2015), http://dx.doi.org/10.1016/j.ymgme.2015.10.001

Table 1
Demographic details and mutation analysis of subjects with PKU and co-existent condition(s).

Subject number	Co-existent condition	Age of diagnosis of co-existent condition	Age at time of reporting	Gender	Caregiver consanguinity	Relevant family history	Country of origin
1	Crohn's disease	12 years	14 years	M	Non-consanguineous	Family history bowel cancer	UK
2	Ulcerative colitis	13.8 years	14.3 years	M	Non-consanguineous	Paternal uncle with inflammatory bowel disease 2 siblings with PKU	UK
3	Ulcerative colitis	14 years	22 years	F	Non-consanguineous	None	Spain
4	Eosinophilic colitis	4 years	14 years	F	Non-consanguineous	None	UK
5	Cystic fibrosis	6.9 months	2.75 years	F	Consanguineous	Older sibling born at 32 weeks and died at 15 days but cause unknown.	Turkey
6	Oesophageal stenosis	21 years	25 years	M	Non-consanguineous	None	France
7	Acute lymphoblastic leukaemia	4.1 years	6.5 years	M	Non-consanguineous	2 older siblings with PKU. 3rd sibling (without PKU) died in first few days of life with complex heart defect.	Poland
8	Breast cancer	38 years	40 years	F	Non-consanguineous	None	France
9	Breast cancer	29 years	33 years	F	Non-consanguineous	None	France
10	Huntington's disease	8 years	24 years	M	Consanguineous	Father same co-existent condition	Ireland/ UK immigrant
11	Type I diabetes mellitus	3 years	25 years	F	Non-consanguineous	Sibling with PKU	Denmark
12	Type I diabetes mellitus	13.8 years	14.3 years	F	Non-consanguineous	None	France
13	Type I diabetes mellitus	15 years	29 years	M	Non-consanguineous	N/A	Germany
14	Type I diabetes mellitus	17 years	23 years	F	Non-consanguineous	One brother and one sister with PKU	France
15	Grave's disease	22 years	22 years	F	Non-consanguineous	None	France
16	Autoimmune hepatitis Type 2 (LKM +)	13 months of age	4.1 years	F	Non-consanguineous	N/A	Moroccan/ Italian immigrant
17	Alopecia universalis	8 years	13 years	M	Consanguineous	Younger sibling with PKU	Moroccan/ Netherlands immigrant.
18	Congenital hypothyroidism	9 days (newborn screening)	5.7 years	F	Non-consanguineous	Maternal aunt with PKU	Poland/Belgium immigrant.
19	Congenital hypothyroidism	3 days of age (newborn screening)	5 years	F	Non-consanguineous	None	Germany
20	Adrenocortical deficiency	4 weeks	5 months	F	Consanguineous	None	Turkish
21	Partial adrenal insufficiency Probably primary.	1 year	8 years	F	Non-consanguineous	Maternal obesity	France
22	Down syndrome (trisomy 21)	Birth	3.4 years	F	Non-consanguineous	Sibling with PKU	Denmark
23	Autistic spectrum disorder. Rearrangement of chromosome material between chromosomes 9 and 12.	3.5 years	6 years	F	Non-consanguineous	Non-PKU sibling diagnosed with same co-existent condition	UK
24	Chromosome 19 p13.3 μ-deletion on chromosome 12	0.8 months	1.8 years	M	Non-consanguineous	None	Slovakia/UK immigrant
25	Stickler syndrome	7 years	26 years	M	Non-consanguineous	Father with ophthalmologic manifestations	Portugal
26	Chiari 1 malformation (Ch1)	7 years	10 years	M	Non-consanguineous	None	Italian
27	Dysmorphic syndrome Non-specified cause	Antenatal diagnosis of hydronephrosis	15 years	F	Consanguineous	None	Lebanese/UK immigrant
28	Dysmorphic syndrome Non-specified cause	Neonatal period	6.5 years	M	Non-consanguineous	None	UK
29	Autistic syndrome	Not documented	14 years	F	Non-consanguineous	N/A	Italian
30	Psychotic behaviour White matter disease Mild Hyperphe	20 years	24 years	F	Non-consanguineous	None	France

Footnote: PKU diagnosed by newborn screening.

universalis was also prescribed sapropterin and blood Phe was maintained within target range. L-thyroxin was associated with lower blood Phe concentrations and an increase in Phe tolerance in one of 2 subjects. Low energy intake and catabolism associated with food refusal, vomiting, stomatitis and mouth ulcers and refusal of gastrostomy feeds were all associated with higher blood Phe concentrations. In one condition (Huntington's disease) associated with a poor prognosis attaining blood Phe control within target range was a low treatment priority.

3.2.2. Delayed diagnosis

There was delayed diagnosis of co-existent conditions in 3 cases: eosinophilic colitis, Huntington disease and a chromosomal disorder. In the latter 2 cases, developmental issues/unsteady gait and poor co-ordination was initially associated with previous poor control of blood Phe levels. The infant with cystic fibrosis presented with hyperphenylalaninemia on newborn screening with a Phe level of 265 μmol/l. It was only when pancreatic enzyme supplementation was commenced for cystic fibrosis that blood Phe increased leading to the diagnosis of

Please cite this article as: A. MacDonald, et al., The challenges of managing coexistent disorders with phenylketonuria: 30 cases, Mol. Genet. Metab. (2015), http://dx.doi.org/10.1016/j.ymgme.2015.10.001

ARTICLE IN PRESS

Table 2
Clinical details, treatments, Phe tolerance and blood Phe control of subjects with PKU and co-existent condition(s).

Subject number/co-existent condition (s)	Symptoms/outcome of co-existent condition	Treatment	Growth	Phe-tolerance mg/day	Annual blood Phe (μmol/L) control pre and post diagnosis of co-existence condition (s)	Issues of management
Case 1 • Crohn's disease • Asthma • Persistent bacterial bronchitis • Moderate PKU	6 month history of intermittent blood in stools, diarrhoea and weight loss. Crohn's disease been stable for 12 months. Colonoscopy findings: features of Crohn's colitis in form of aphthous ulceration, deep ulceration, easy bleeding. Appearances worse in rectum, sigmoid and transverse colon.	Infliximab infusions Azathioprine Intermittent prednisolone Omeprazole Symbicort Montelukast Salbutamol PKU: diet only 1.1 g/kg/day PE from Phe-free L-amino acids	Weight z score: 1.86 Height z score: 1.9 BMI: z score: 1.43	Pre-diagnosis: 375 mg/day 8 mg/kg/day At diagnosis: 850 mg/day (18 mg/kg/day)	Pre-diagnostic year: 99 μmol/L; Post diagnostic year: 383 μmol/l; 2y post diagnostic year: 332 μmol/L	Variable blood Phe control and Phe tolerance that appeared to be affected by presence of untreated symptoms (symptoms associated with low blood, Phe = higher Phe tolerance) and treatment regimen (steroid treatment: high blood Phe = lower Phe tolerance). Higher blood Phe with persistent bacterial bronchitis. Multiple hospital appointments; under 3 speciality teams (IMD, gastroenterology, respiratory).
Case 2 • Ulcerative colitis • Severe PKU	6 month history of abdominal pain, blood in stools, diarrhoea, weight loss. Colonoscopy: left sided colitis. Initial diagnosis of ulcerative colitis but subject also developed mouth ulcers. 12 months post diagnosis: symptoms not controlled.	Mesalazine Intermittent prednisolone PKU: diet only 1.7 g/kg/day PE from Phe-free L-amino acids	Weight z score: 0.001 Height z score: −0.586 BMI: z score: 1.927	300 mg/day (6 mg/kg/day) Post diagnosis: highest Phe intake = 850 mg/day (17 mg/kg/day)	1y pre-diagnostic year: 416 μmol/L; Pre-diagnostic year: 354 μmol/L; Post diagnostic year: 210 μmol/L (patient still symptomatic)	Variable blood Phe control that appeared to be affected by presence of untreated symptoms (low blood Phe) and treatment regimen (steroid treatment = high blood Phe). Difficulty taking L-amino acid supplements with mouth ulcers. Multiple hospital appointments; under 3 speciality teams (IMD, gastroenterology, dental).
Case 3 • Ulcerative colitis • Allergies without asthma • Severe PKU	6 month history of intermittent blood in stools, diarrhoea and weight loss. Intermittent symptoms with several months of stability but at least one relapse every year during the early years of ulcerative colitis. Stable for the last 2 y.	Mesalazine PKU: diet only 1.1 g/kg/day PE from Phe-free L-amino acids	Weight: 62.5 kg Height: 170 cm (in accordance with parental height) BMI: 21.6 kg/m^2	150 mg/day	One year pre-diagnostic year: 678 μmol/L; One year post diagnostic year: 700 μmol/L	No initial changes in management, except for worse control during symptomatic periods. On diagnosis of ulcerative colitis, she resented being ill and having 2 disorders, leading to poor dietary adherence. Currently all blood Phe below 700 umol/L).
Case 4 • Eosinophilic colitis • Moderate PKU	Diagnosed age 4 y with vomiting and diarrhoea.	Mesalazine Wheat free diet PKU: diet only 0.8 g/kg/day PE from Phe-free L-amino acids	Weight z score: 2.82 Height z score: 0.43 BMI: z score: −1.12	250 mg/day	Pre-diagnostic year: 355 μmol/L; Post diagnostic year: 377 μmol/L	Initial increase of Phe levels and non-adherence to diet following diagnosis of colitis. Delayed diagnosis.
Case 5 • Cystic fibrosis • Severe PKU	Cystic fibrosis (mutations N1303K/NI3O3K). Persistent diarrhoea, marasmic face appearance, pretibial oedema, frequent chest infections.	Creon Nacl Oral rehydration Supravit Evicap Avicap Ferrosanol Pulmozyme PKU: diet + sapropterin (20 mg/kg/day) 1.34 g/kg/day PE from phe-free L-amino acids	Weight z score: -1.56 Height z score: -1.29 BMI: z score: 2.762	40 mg/kg/day	At diagnosis of PKU: Phe level = 265 μmol/L Post diagnosis of cystic fibrosis and pre sapropterin treatment: Phe ↑ 491 μmol/l Initial sapropterin treatment: blood Phe ↓ 147 μmol/L (no enteral supplements and without infections) Effect of infections on blood phe: ↑ 695 μmol/L with no protein substitute After starting protein substitute blood phe ↓ to 78 μmol/L	Mild PKU but higher blood Phe control associated with frequent chest infections 2 hospitalisations for cystic fibrosis. Mean blood Phe post diagnosis (from diagnosis to BH4 started) was 433 μmol/l. Frequent chest infections masked benefit of sapropterin. Mean blood Phe after chest infections (still on sapropterin) was 695 μmol/l; case study given L-amino acid supplement but adherence was poor as diet not commenced until 2.5 years.

Please cite this article as: A. MacDonald, et al., The challenges of managing coexistent disorders with phenylketonuria: 30 cases, Mol. Genet. Metab. (2015), http://dx.doi.org/10.1016/j.ymgme.2015.10.001

Please cite this article as: A. MacDonald, et al., The challenges of managing coexistent disorders with phenylketonuria: 30 cases, Mol. Genet. Metab. (2015), http://dx.doi.org/10.1016/j.ymgme.2015.10.001

ARTICLE IN PRESS

Case 6 • Oesophageal stenosis • Severe PKU	Presented with dysphagia. Diagnosis by oesophageal X-ray and barium swallow test.	Treated by oesophageal dilatation	Weight loss (− 5 kg) from 53 to 48 kg Height: 163 cm BMI: from 18.77 to 18 kg/m^2	350 mg/day in infancy, but higher intake since adolescence	Long history of poor Phe control and poor dietary adherence. At the time of symptoms, blood Phe slightly improved. Post recovery he returned to poor dietary adherence with poor metabolic control (Phe level > 1200 μmol/L)	No extra PKU issues due to co-existent condition.
Case 7 • Acute lymphoblastic leukaemia • Severe PKU	One month pre-diagnosis: symptoms were weakness, pallor, and skeletal pain. On presentation, he had hepatosplenomegaly, anaemia (Ht 22%, Hb 7.8 g/dl, RBC 2.7×10^6/μl), leucocytosis (23.7×10^3/μl), haemorrhagic diathesis (PLT 9×10^3/μl).	Treatment of ALL according to the protocol: ALL IC – BFM 2009 treatment. Drugs included: encorton, Ara-C, dexamethasone and Methotrexate. PKU: diet only 1.74 g/kg/day (varied from 0.29–2.35 g/kg/day) PE from Phe-free L-amino acids Supplemented with glucose polymer and 50% fat emulsion. Sapropterin treatment was considered but declined because of potential effect of MTX on DHPR reductase.	Weight increased during glucocorticoid therapy but decreased during periods of food refusal and vomiting	7–12 mg/kg/day (200–300 mg/day)	One year pre-diagnostic year: 450 μmol/L; Post diagnostic year: 406 μmol/l Second year of treatment: 313 μmol/L	Blood Phe control was difficult in the first period of ALL treatment based on encorton and dexamethasone (cytoreduction phase, beginning of Protocol II) and later during intensive treatment with methotrexate, which was complicated by stomatitis, food refusal and vomiting. Attaining energy and protein requirements was difficult with vomiting and stomatitis. Enteral tube feeding was refused. Parents required psychological support.
Case 8 • Breast cancer • Severe PKU	Breast cancer identified at age 38 years. Classical history of breast tumour diagnosed as breast carcinoma after biopsy.	Treated by surgery and additional chemotherapy 6 cycles of FED (5-Fluorouracil-Epirubicin--Cyclophosphamide every three weeks	Weight lost at the beginning of the treatment (70 to 65 kg) Height: 168 cm	380 mg/day	Phe control deteriorated during cancer treatment but returned to previous levels at end of treatment	The cancer specialist prescribed high protein supplements and Phe levels increased (1600 μmol/L). the Phe levels returned to 900 μmol/l after better collaboration between cancer and metabolic teams.
Case 9 • Breast cancer • Severe PKU	Breast tumour on clinical examination at preconception visit at 29 years of age (adenocarcinoma T2N0M0).	Age 29–33: 5-Fluorouracil-Epirubicin--Cyclophosphamide Surgery; Tamoxifen PKU: no diet	N/A	Pre pregnancy diet (age 29 years): 300 mg/day (5.5 mg/kg/day)	Pre-pregnancy year: 1438 μmol/l Post pregnancy 1422 μmol/L	Pregnancy delayed for 4y, due to breast cancer therapy). Good Phe control (blood Phe < 360 μmol/l) during pregnancy. Anaemia and iron deficiency during pregnancy, treated with IV iron infusion and oral iron. Delivery at 41 weeks + 5 days (caesarean section). Birth weight 3040 g.
Case 10 • Huntington's disease • Moderate PKU	Poor co-ordination, jerky movements and unsteady gait. Eventual inability to walk, talk and swallow. Rigidity. Seizures. Sleep problems. Wheelchair bound from age of 12 years.	Gastrostomy Melatonin Botulinum toxin injections Seizure control medication PKU: 1 g/kg/day PE from Phe-free L-amino acids	Weight: 44 kg at aged 18 years.	30 g/day natural protein supplemented with L-amino acid supplement (administered via gastrostomy)	Pre-diagnostic year: 400 μmol/L. Post diagnostic year: 610 μmol/L	Social issues, it was first considered that clumsiness was related to poor Phe control and so delayed diagnosis of Huntington's. Father's diagnosis was post case study diagnosis. Blood Phe rarely measured post diagnosis as not seen as a priority.
Case 11 • Type I diabetes mellitus • Mild/moderate PKU	Polydipsia, polyuria, high blood sugar, weight loss at aged 3 years.	Insulin Normal diet	Age 22: Height: 179.5 cm Weight: 70 kg	Normal diet.	Pre-diagnostic year: 229 μmol/l; Post diagnostic year: 288 μmol/L	Normal diet in adulthood, diet restrictive as a child with two conflicting dietary treatment regimens. Diabetes was considered the priority condition. Attended 2 different hospitals for management.
Case 12 • Type I diabetes mellitus • Severe PKU	Polydipsia, polyuria, high blood sugar. Diagnosis at aged 13.8 years.	Insulin + diabetes regimen	Weight: 68 kg Height: 161 cm BM : 26.2 kg/m^2	Relaxed diet	Usual metabolic control (900–1000 μmol/L). Successful pregnancy with strict metabolic control. Return to usual Phe levels after delivery	No extra PKU issues due to co-existent condition.

(continued on next page)

ARTICLE IN PRESS

Please cite this article as: A. MacDonald, et al., The challenges of managing coexistent disorders with phenylketonuria: 30 cases, Mol. Genet. Metab. (2015), http://dx.doi.org/10.1016/j.ymgme.2015.10.001

Table 2 (*continued*)

Subject number/co-existent condition (s)	Symptoms/outcome of co-existent condition	Treatment	Growth	Phe-tolerance mg/day	Annual blood Phe (μmol/L) control pre and post diagnosis of co-existence condition (s)	Issues of management
Case 13 • Type I diabetes mellitus • Severe PKU	Polydipsia, polyuria, high blood sugar.	Insulin Controlled carbohydrate intake PKU: diet only 0.6 g/kg/day PE from Phe-free L-amino acids	Weight z score: 1.22 Height z score: 0.48	Unknown	One year pre-diagnostic year: 618 μmol/L; Post diagnostic year: 552 μmol/L	2 conflicting dietary treatment regimens. Difficulty combining low Phe diet with controlled carbohydrate intake. Good blood Phe control.
Case 14 • Type I diabetes mellitus • Severe PKU	Blood glucose fluctuations before planning pregnancy HbA1C = 9.1% before pregnancy. No diabetes –related microvascular/macrovascular complications.	Admission for starting insulin pump therapy, 2 months before preconception diet for PKU Commenced low Phe diet for pregnancy Was "off diet" since the age of 5y	NA	Pre pregnancy diet : Phe intake- 680 mg/day (11 mg/kg/day)	Pre-pregnancy year: 1109 μmol/L/post pregnancy 979 μmol/L	Good blood glucose and phe control (blood Phe constantly <360 μmol/l) during pregnancy. Monthly clinical monitoring. HbA1C: 6.8–7.3% during pregnancy. Delivery at 37 weeks +4 days (no caesarean section). Birth weight 3130 g.
Case 15 • Grave's disease • Mild/moderate PKU	22 year old treated with Sapropterin. Preconception she was on strict diet and stopped Sapropterin but developed weight loss and diarrhoea. The diet was stopped and BH4 recommenced. She also developed amenorrhoea, thought to be related to hyperthyroidism, but she was pregnant [21].	She was treated by propranolol and she continued Sapropterin during her pregnancy with a successful outcome.	Weight: 53 kg Height: 165 cm	1500 mg of Phe with Sapropterin treatment with a Phe level of 650 μmol/L	Successful treatment of hyperthyroidism and normal outcome of pregnancy	Symptoms associated with co-existent condition masked pregnancy.
Case 16 • Autoimmune hepatitis Type 2 (LKM+) • Mild PKU	At diagnosis, cutaneous and scleral icterus, hypo colic faeces with hepatomegaly and altered coagulation profile.	Intravenous corticosteroid therapy (methyl prednisolone) followed by oral prednisolone therapy Normal diet	Normal growth and weight gain	Normal diet	One year pre-diagnostic year: <200 μmol/L; Post diagnostic year: 173 μmol/L	No extra PKU issues due to co-existent condition.
Case 17 • Alopecia universalis • Mild PKU	Rapid hair loss, baldness within 40 days, and loss of eye lashes, eye brows. Within 3 months of start of MTX injections, there was hair re-growth of eyebrows, eyelashes and wisps of hair on head. After 6 months hair grew back (after increased dose of MTX).	Dermovate cream, high dose prednisolone for 6 days, biotin supplementation Treatment for 1.5y with Methotrexate injections PKU: diet + Sapropterin (start dose 20 mg/kg/day) 0.9 g/kg/day PE from Phe-free L-amino acids The PE decreased to 0.5 g/kg/day	Height + 0,94 SD, weight + 2,67 SD (start of treatment)	With Sapropterin: Phe 1750 mg/day (35 g/day protein). Pre-re Sapropterin protein: 17 g/day).	With MTX blood Phe within target range. Mean Phe in treatment period: 268 μmol/L	Patient blood Phe remained within target range with MTX, low Phe diet and sapropterin. MTX stopped after 18 months because case declined further injections.
Case 18 • Congenital hypothyroidism • Severe PKU	Elevated TSH.	L-thyroxin PKU: diet only 1.4 g/kg/day PE from Phe-free L-amino acids	Weight z score: 0.06 Height z score: −0.39 BMI: z score: 0.40	25 mg/kg/day	Mean blood Phe 180 μmol/L (18–486)	When thyroxin dose increased, it lowered blood Phe (by >100 μmol/l) and so diet Phe intake was increased by 50 mg/day.
Case 19 • Congenital hypothyroidism • Mild PKU	Elevated TSH.	L-thyroxin PKU: diet only 0.3 g/kg/day PE from Phe-free L-amino acid	Weight z score: 1.44 Height z score:1.41	Minimal protein restriction and diet stopped at age of 3y	Mean blood Phe 294 μmol/L	Good blood Phe control as PKU was very mild. Blood Phe varied between 48 and 240 μmol/l. The caregivers struggled with measurement of controlled Phe intake when on diet therapy. The caregivers are also not adherent in administering the L-thyroxin.

Case 20 • Adrenocortical deficiency • Severe PKU	Weight loss, dehydration, hypotonic, poor feeding hyponatraemia, hyperkalemia, hypochloraemia, Increase of ACTH, high rennin, and cortisol deficiency.	Cortico-steroid therapy: Fludrocortisone, Deflazacort, sodium chloride PKU: diet only 1.1 g/kg/day Phe-free L-amino acids	Weight z score: −0.57 Height z score: −2.60 BMI: z score: 1.29	75 mg/kg/day but was only 30 mg/kg/day immediately after diagnosis of condition.	Pre-diagnosis: 657 μmol/L; Post diagnosis: 61 μmol/L Blood phe at PKU diagnosis was 3022 μmol/L	Unable to reduce blood phe levels at diagnosis after 5 days of infant Phe-free L-amino acid formula. Infant lost 12% of birth weight. Post treatment, blood phe was controlled.
Case 21 • Partial adrenal insufficiency • Severe PKU	Obesity and hypertrichosis Hyperandrogeny Increase of ACTH and mild cortisol deficiency.	Continuation of strict diet, and treatment of partial adrenal insufficiency by hydrocortisone Requires continuing treatment for adrenal insufficiency	Normal growth and weight gain	320 mg/day	250–350 μmol/L No change with co-existent disease	Normalisation of adrenal insufficiency with treatment. No extra PKU issues due to co-existent condition.
Case 22 • Down syndrome • Severe PKU	Characteristic facial features. Intellectual disability. Feeding difficulties.	PKU: diet only 2 g/kg/day PE from Phe-free L-amino acids	Underweight at 3.5 years	225 mg/day	Mean blood Phe 247 μmol/L (30–1350) 1 y post diagnosis 296 μmol/L (104–1008)	Feeding difficulties ↑ workload for parents who already have another child with PKU.
Case 23 • Rearrangement of chromosome material between chromosomes 9 and 12. • Autistic spectrum disorder. • Moderate PKU	Poor social interaction, little eye contact, difficulty understanding instructions, limited speech. Dislikes change. Insists on routine. 1:1 support at school.	Movicol PKU: diet only 2.3 g/kg/day PE from Phe-free L-amino acid	Weight z score: 0.812 Height z score: 0.597 BMI: z score: 0.666	250 mg/day (13 mg/kg/day)	One year pre-diagnostic year: 195 μmol/L (range 130–460); Post diagnostic year: 193 μmol/L (range 160–310)	Meal times have to be consistent (i.e. same daily food choices) as dislikes change. Diet particularly restricted due to unwillingness to try new foods.
Case 24 • Chromosome 19 p13.3 μ-deletion on chromosome 12 • Severe PKU	Developmental delay with dysmorphic features. Hypotonia, hypospadias.	Physiotherapy PKU: diet only 2.3 g/kg/day PE from Phe-free L-amino acid	Weight z score: 0.308 Height z score: −0.175 BMI: z score: 0.558	225 mg/day (20 mg/kg/day)	Pre-diagnostic year: 256 μmol/L (range 30–1030); Post diagnostic year: 189 μmol/L (range 30–440)	Additional appointments at physiotherapy and child developmental centres. Came to UK at 4.9 months. Had early high fluctuating blood Phe levels; was unclear if this contributed to developmental delay until further investigations performed.
Case 25 • Stickler syndrome • Mild PKU	Intellectual disability, severe myopia, skeletal abnormalities, dental caries.	PKU: diet only 1.38 g/kg/day PE from Phe-free L-amino acid	Age 26 years Weight: 56.5 kg; Height: 159.5 cm BMI: 22.2 kg/m^2	28 mg/kg/day	One year pre-diagnostic year: 278 μmol/L; Post diagnostic year: 362 μmol/L	No extra PKU issues due to co-existent condition.
Case 26 • Chiari 1 malformation (Ch1) • Mild PKU	No symptoms. Condition diagnosed by routine MRI imaging.	Sapropterin: 10 mg/kg/day Minimal low Phe diet. No Phe-free L-amino acid supplements	Normal growth and weight gain	2000 mg/day	One year pre-diagnostic year: <300 μmol/L; Post diagnostic year: 300 μmol/L	No extra PKU issues due to co-existent condition.
Case 27 • Dysmorphic syndrome: non-specified • Severe PKU	Hearing impairment, hydronephrosis, retinal dystrophy, feeding difficulties.	Tube fed until the age of 4 y. PKU: diet only 1.3 g/kg/day PE from Phe-free L-amino acid	Weight z score: −0.53 Height z score: −2.51 BMI: z score: 1.96	200 mg/day (3 mg/kg/day)	Mean blood Phe last year of care = 380 μmol/L	Nutritional support by tube feeding.
Case 28 • Dysmorphic syndrome: non specified Severe PKU	Dysmorphic, cleft lip and palate, developmental delay, episodes of encephalopathy, seizures.	Anti-convulsion medication Gastrostomy tube feeding PKU: diet only 1.7 kg/kg/day PE from Phe-free L-amino acid	Weight z score: −1.16 Height z score: −1.8 BMI: z score: 0.12	250 mg/day	Mean blood in last year of care = 482 μmol/L	Feeding difficult with extreme food faddiness. Intermittent refusal of child to allow carer to administer feed through gastrostomy and unable to administer appropriate nutritional support. Difficulty in achieving Phe concentrations within target ranges.

(continued on next page)

Please cite this article as: A. MacDonald, et al., The challenges of managing coexistent disorders with phenylketonuria: 30 cases, Mol. Genet. Metab. (2015), http://dx.doi.org/10.1016/j.ymgme.2015.10.001

ARTICLE IN PRESS

ARTICLE IN PRESS

Table 2 (*continued*)

Subject number/co-existent condition (s)	Symptoms/outcome of co-existent condition	Treatment	Growth	Phe-tolerance mg/day	Annual blood Phe (μmol/L) control pre and post diagnosis of co-existence condition (s)	Issues of management
Case 29 • Autistic syndrome • Mild PKU	Intellectual disability, behaviour spectrum disorders.	No phe-free L-amino acid supplement	Normal growth and weight gain	Normal	One year pre-diagnostic year: <240 μmol/L; One year post diagnostic year: 240 μmol/L	All BH4 disorders excluded No issues related to PKU management.
Case 30 • Psychotic behaviour • White matter disease • Mild/moderate PKU	Behaviour disturbance, anxiety, suicide attempts Normal IQ. Brain MRI: white matter hypersignal in posterior regions (posterior periventricular).	Minimal PKU treatment Phe levels <600 μmol/L No improvement of psychiatric behaviour with BH4 treatment (with complete normalisation of Phe levels) Psychiatric treatments: Alprazolam; Sertraline	Normal growth Weight: 58 kg, Height: 167 cm BMI : 20.8 kg/m^2	1200 mg/day	350–450 μmol/L	Moderate improvement of behaviour with psychiatric treatments only. No extra PKU issues due to co-existent condition.

Please cite this article as: A. MacDonald, et al., The challenges of managing coexistent disorders with phenylketonuria: 30 cases, Mol. Genet. Metab. (2015), http://dx.doi.org/10.1016/j.ymgme.2015.10.001

PKU. The patient was first treated with sapropterin, but after repeated chest infections and higher blood Phe concentrations, eventually began a low Phe diet. In Grave's disease, amenorrhea attributed to hyperthyroidism, masked a maternal PKU pregnancy for 12 weeks [21]. One co-existent condition (Chiari 1) was diagnosed following a routine scan for PKU.

3.2.3. Impact on dietary treatment and nutritional status

Some patients required conflicting diet therapy (n = 5), nutritional support (n = 7) and five had additional feeding problems associated with the co-existent condition. In conditions such as T1DM and cystic fibrosis, the ability to restrict/control carbohydrate intake or increase protein from natural sources was challenging. One patient with breast cancer was given high protein sip feeds leading to poor Phe control. Three patients had particular difficulty in taking their Phe-free L-amino acid supplement mainly because of mouth ulcers, stomatitis, and delayed introduction of protein substitute (associated with delayed commencement of low Phe diet). Ten (33%) patients had weight loss and 3 (10%) had poor weight gain. Three patients required nutritional support via a gastrostomy and one subject refused tube feeding. One patient developed obesity associated with the co-existent condition.

3.2.4. Impact on social disease burden and adherence

Most patients attended additional hospital appointments, commonly under different specialist teams, and even different hospitals. Seven families required extra emotional support from their PKU teams, particularly with increasing severity of co-existent conditions. Some caregivers found the treatment demands of a co-existent condition challenging particularly if they had other children with PKU. Dietary adherence deteriorated in 5 cases after the diagnosis of a co-existent condition.

4. Discussion

The presence of a co-existent condition was not uncommon in PKU. This paper describes 30 cases with PKU with 21 heterogeneous co-existent conditions and 2 children with dysmorphic syndromes with unknown causes, considerably adding to the cases previously reported. Autoimmune, endocrine and gastro-intestinal disorders were common co-existent conditions. It was evident that the presence of overlapping neurological symptoms associated with PKU delayed the diagnosis of the second condition in 2 cases. In several cases, the co-existent condition adversely affected blood Phe control, growth and nutritional status in PKU. It also complicated an already difficult dietary treatment and even influenced choice of medication or treatment options. Some co-existent conditions required their own complex management plan. In contrast, other co-existent conditions had little impact on either PKU care or blood Phe control but it was clear that this was influenced by the severity of PKU or less strict therapy in adult patients with PKU.

In some conditions, it was particularly difficult to control blood Phe levels. In the subjects with inflammatory bowel disease, corticosteroid treatment was associated with increase in blood Phe concentrations and frequent adjustments in dietary Phe intake. This therapy is known to inhibit protein synthesis [22]. In the child with cystic fibrosis, the initial blood Phe concentrations on newborn screening did not require treatment. Blood Phe levels only increased to within treatment range following control of malabsorption. Frequent chest infections worsened blood Phe control and delayed dietary treatment led to poor acceptance of the Phe-free L-amino acid supplement.

Conflicts between co-existent conditions and PKU caused dilemmas in drug management choice. The use of methotrexate was an important drug treatment option in the management of two conditions: acute lymphoblastic leukaemia and alopecia universalis. Methotrexate acts as a mild immunosuppressant that exhibits anti-inflammatory activity. It may increase blood Phe concentrations associated with a decrease in protein synthesis [23]. Methotrexate (MTX) is also reported to inhibit dihydropteridine reductase (DHPR), an enzyme in the regeneration of BH4, and induces hyperphenylalaninemia [24,25]. In the case of alopecia universalis, MTX and sapropterin were successfully used together: blood Phe concentrations remained within target range and there were no adverse reactions but in the case of acute lymphoblastic leukaemia, the use of sapropterin with MTX was avoided.

There was a considerable increase in the burden of care for the families as a consequence of additional medical investigations and hospital appointments. A small number of co-existent conditions required frequent lengthy hospital admissions. There was sometimes limited comprehension of the treatment requirements of PKU by other medical professionals causing anxiety for caregivers. Some caregivers had more than one child with PKU or other children with the same co-existent conditions and their workload and potential effect on the quality of family life was huge but unmeasured. It is possible that some parents suffered from guilt, marital stress and even grief on the diagnosis of two serious conditions particularly with a second genetic condition [26].

There were several study limitations. Not all cases of PKU with a co-existent condition could be reported due to consent issues or missing data. In addition, patients were not specifically screened prospectively to identify potential co-existent conditions but rather clinicians at each centre reported any known conditions that may have impacted on PKU management or control. As a consequence, there is likely to be other cases of co-existent conditions that are not reported here. Also consistent long term outcome data was not collected for each patient.

It is clear in PKU with life-threatening or life-limiting co-existent disease that blood Phe control may take a lower priority to the treatment demands and effects of the co-existent condition. However, achieving acceptable blood Phe control should remain a key goal and it may be inappropriate and even unethical to abandon treatment, even when patients have poor prognosis or poor neurological outcome. If PKU management is sub-optimal, it is uncertain how much high blood phe levels will impact on the immediate symptom control and patient comfort (abrupt increases in blood Phe concentrations may cause irritability, anxiety and decrease mood [27]) and lower tolerance of additional procedures and treatments. Health professionals should still aim to optimise dietary treatment and in the subgroup of patients who are BH4 responsive, consider using sapropterin to help ease dietary management and ultimately treatment burden.

In conclusion, it is essential to investigate for co-existence of other disorders when the clinical history is not completely consistent with PKU. Integrating care is a challenge as this may require a wide spectrum of healthcare professionals. It requires strict consideration of compatibility of dietary treatment and drug management. Treatment should be closely co-ordinated to ensure that patients and caregivers receive the clinical and social support they require. Having a better understanding of the issues associated with co-existent conditions and PKU will hopefully lead to the development of strategies to aid more effective care.

Conflict of interest

MacDonald A, Belanger-Quintana A, Blau N, Burlina A, Cleary M, Coskum T, Feillet F, Gizewska M, Muntau AC, Trefz FK, van Spronsen F are members of the EPG, an advisory board to Merck Serono.

MacDonald A, Ahring K, Belanger-Quintana A, Dokoupil K, Gokmen Ozel H, Lammardo AM, Robert M, Rocha JC, van Dam E, van Rijn M have participated in the European Nutritionist Expert Panel in PKU (ENEP), an Advisory Board to Merck Serono.

Additionally, Giżewska M has participated in strategic advisory boards for Nutricia Advanced Medical Nutrition, and has received speaker honoraria from Merck Serono and Nutricia Advanced Medical Nutrition; MacDonald A has received research funding and honoraria from Nutricia, Vitaflo International and Merck Serono, and has participated in advisory boards to Nutricia and Arla; Bélanger-Quintana A has received speaker honoraria from Merck Serono; Burlina A has

Please cite this article as: A. MacDonald, et al., The challenges of managing coexistent disorders with phenylketonuria: 30 cases, Mol. Genet. Metab. (2015), http://dx.doi.org/10.1016/j.ymgme.2015.10.001

ARTICLE IN PRESS

participated in advisory boards to Nutricia; Muntau AC has participated in advisory boards to Arla, has received lecture fees from Merck Serono and has received research funding from Vitaflo, Merck Serono and Nutricia.

References

[1] J. Almirall, M. Fortin, The co-existence of terms to describe the presence of multiple concurrent diseases, J. Comorbid. 3 (2013) 3–9.
[2] R. Gijsen, N. Hoeymans, F.G. Schellevis, D. Ruwaard, W.A. Satariano, G.A. Van den Bos, Causes and consequences of comorbidity: a review, J. Clin. Epidemiol. 54 (2001) 661–674.
[3] L.G. Greeves, H.L. McCarthy, A. Redmond, D.J. Carson, Coexistence of cystic fibrosis and phenylketonuria, Ulster Med J. 66 (1997) 59–61 (24).
[4] D. Concolino, M. Rapsomaniki, E. Disabella, S. Sestito, M.G. Pascale, M.T. Moricca, G. Bonapace, E. Arbustini, P. Strisciuglio, Co-existence of phenylketonuria and Fabry disease on a 3 year-old boy: case report, BMC Pediatr. 0 (2010) 32.
[5] R.O. Fisch, J.M. Horrobin, Down's syndrome with phenylketonuria, Clin. Pediatr. (Phila) 7 (1968) 226–227.
[6] A. Tokatli, T. Coşkun, C.N. Kocabaş, I. Ozalp, S. Balci, Classical phenylketonuria associated with Goldenhar's syndrome. A case report, Turk. J. Pediatr. 36 (1994) 153–156.
[7] T. Patiroglu, E. Unal, F. Kardas, M.A. Ozdemir, M. Karakukcu, O. Sayilmaz, Phenylketonuria with acute myeloblastic leukemia in a 9-year-old boy: reporting a rare case, J. Pediatr. Hematol. Oncol. 33 (2011) e256–e257.
[8] J.M. Marques, Phenylketonuria with familial hyperglycinuria, J. Inherit. Metab. Dis. 17 (1994) 641.
[9] D.R. Webster, J. Wallace, PKU and diabetes: help requested, J. Inherit. Metab. Dis. 18 (1995) 649.
[10] T. Coşkun, I. Ozalp, G. Tekinalp, Hereditary fructose intolerance in a patient with phenylketonuria, Turk. J. Pediatr. 33 (1991) 181–184.
[11] O. Søvik, H. Boman, Co-occurrence of vitamin D-dependent rickets type 1 and phenylketonuria, Acta Paediatr. 97 (2008) 665–667.
[12] H.S. Kalkanoğlu, D. Anadol, E. Yilmaz, T. Coşkun, Phenylketonuria and cystic fibrosis in the same patient, Pediatr. Int. 42 (2000) 92–93.
[13] C. Wang, C.S. Camfield, C.V. Fernandez, T. Hurley, K. Campbell, Successful neurological outcome of a child with classical phenylketonuria and acute lymphoblastic leukemia: a 7-year follow-up, Am. J. Med. Genet. A 143A (24) (2007) 3324–3327.
[14] L. Lucaccioni, B.C. Schwahn, M. Donaldson, C. Giacomozzi, Central precocious puberty in a 3 year-old girl with phenylketonuria: a rare association? BMC Endocr. Disord. 14 (2014) 38.
[15] B. Büyükgebiz, Y. Eroğlu, A. Büyukgebiz, True precocious puberty associated with phenylketonuria, J. Pediatr. Endocrinol. 7 (1994) 361–363.
[16] K.S. Roth, R.M. Cohn, P. Berman, S. Segal, Phenylketonuria and Duchenne muscular dystrophy: a case report, J. Pediatr. 88 (4 Pt. 1) (1976) 689–690.
[17] R. Minami, K. Olek, P. Wardenbach, Phenylketonuria in a patient with cystinuria, Humangenetik 28 (1975) 319–324.
[18] J.U. Leititis, M. Stahl, W. Tackmann, H. Wick, A. Wildberg, Homozygous hypobetalipoproteinaemia and phenylketonuria, Eur. J. Pediatr. 144 (1985) 174–176.
[19] M.M. Parks, N.F. Schwilk, Bilateral lamellar cataracts in the case of phenylketonuria, Am. J. Ophthalmol. 79 (1975) 479.
[20] T. Yilmazer, A.H. van Gennip, N.G. Abeling, I. Ozalp, T. Coşkun, H.D. Bakker, Phenylketonuria and glycogen storage disease type III in sibs of one family, Turk. J. Pediatr. 44 (2002) 49–53.
[21] F. Feillet, A.C. Muntau, F.G. Debray, A.S. Lotz-Havla, A. Puchwein-Schwepcke, M.B. Fofou-Caillierez, F. van Spronsen, F.F. Trefz, Use of sapropterin dihydrochloride in maternal phenylketonuria. A European experience of eight cases, J. Inherit. Metab. Dis. 37 (2014) 753–762.
[22] S.J. Steiner, J.D. Noe, S.C. Denne, Corticosteroids increase protein breakdown and loss in newly diagnosed pediatric Crohn disease, Pediatr. Res. 70 (2011) 484–488.
[23] N. Boukhettala, J. Leblond, S. Claeyssens, M. Faure, F. Le Pessot, C. Bôle-Feysot, A. Hassan, C. Mettraux, J. Vuichoud, A. Lavoinne, D. Breuillé, P. Déchelotte, M. Coëffier, Methotrexate induces intestinal mucositis and alters gut protein metabolism independently of reduced food intake, Am. J. Physiol. Endocrinol. Metab. 296 (2009) E182–E190.
[24] N. Blau, A.C. Curtius, L. Kierat, D. Leupold, E. Kohne, Hyperphenylalaninemia caused by dihydropteridine reductase deficiency in children receiving chemotherapy for acute lymphoblastic leukemia, J. Pediatr. 115 (1989) 661–663.
[25] J.C. Netter, J.L. Dhondt, F. Rance, M. Petrus, Early neurotoxicity of high-dose of methotrexate and tetrahydrobiopterin deficiency, Arch. Fr. Pediatr. 48 (1991) 719–722.
[26] D.G. Olsen, Parental adjustment to a child with genetic disease: one parent's reflections, J. Obstet. Gynecol. Neonatal. Nurs. 23 (1994) 516–518.
[27] A.E. ten Hoedt, L.M. de Sonneville, B. Francois, N.M. ter Horst, M.C. Janssen, M.E. Rubio-Gozalbo, F.A. Wijburg, C.E. Hollak, A.M. Bosch, High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria: a randomised, double-blind, placebo-controlled, crossover trial, J. Inherit. Metab. Dis. 4 (2011) 165–171.

Please cite this article as: A. MacDonald, et al., The challenges of managing coexistent disorders with phenylketonuria: 30 cases, Mol. Genet. Metab. (2015), http://dx.doi.org/10.1016/j.ymgme.2015.10.001