Molecular Genetics and Metabolism 116 (2015) 242–251

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 9 October 2015

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

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.

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