Dietary practices in isovaleric acidemia: A European survey


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1. Introduction

Isovaleric acidemia (IVA) (McKusick 243500) is a rare inherited condition, caused by a deficiency of the mitochondrial enzyme isovaleryl-CoA dehydrogenase (EC 1.3.99.10), leading to accumulation of isovaleryl-CoA and its metabolites including free isovaleric acid, 3-isovaleryl-CoA dehydrogenase (EC 1.3.99.10), leading to accumulation of isovaleryl-CoA. This is achieved by: 1) limiting leucine intake via protein restriction [2–4]; 2) enhancement of alternative metabolic pathways using carnitine [5,6] and glycine [7,8] which conjugate with isovaleryl-CoA to produce the non-toxic compounds isovalerylglycine and isovalerylcarnitine; and 3) application of an emergency management protocol at times of metabolic stress (e.g. illness and fasting). However, partly due to IVA’s heterogeneity, its rarity, shortage of large, multi-centre longitudinal studies and long-term outcome data, there is disagreement regarding optimal dietary management. Almost all reports are from case studies or small case series only.

The first case studies of IVA reported signs of dietary protein intolerance typically with episodes of vomiting, lethargy and acidosis with ketonuria after increased intake of protein-rich foods [9,10]. Many patients maintain long term metabolic stability on dietary protein restriction only [1,11–18]. In fact, the majority of IVA case studies advise some protein restriction [1–7,9,11–14,16–19] but with wide differences in the amount of natural protein given. Some centres prescribe less than the WHO/FAO/UNU 2007 safe levels of protein intake [31] and may specifically calculate and control leucine intake supplemented with leucine-free l-amino acid supplements (LFAA) [3,5,22,23,26–29,32–35].

In September 2014, the web based E-IMD IVA guidelines [36] advocated that natural protein intake be restricted to reduce the isovaleric acid burden but should supply at least the WHO/FAO/UNU 2007 safe levels of protein intake [31]. The use of LFAA was not discussed [36] and some considered they may provide little clinical benefit and thus provide extra burden to patients and families and unnecessary expense to health services.

This paper aims to describe European practice regarding the dietary management of IVA prior to the introduction of the E-IMD IVA guidelines in 2014.

2. Material and methods

A cross-sectional questionnaire was sent to all European dietitians who were either members of the Society for the Study of Inborn Errors of Metabolism Dietitians Group (SSIEM-DG) or whom had responded to previous questionnaires on dietetic practice (n = 53). The questionnaire comprised 27 questions about the dietary management of IVA.

Results: Information on 140 patients with IVA from 39 centres was reported. 133 patients (38 centres) were given a protein restricted diet. Leucine-free amino acid supplements (LFAA) were routinely used to supplement protein intake in 58% of centres. The median total protein intake prescribed achieved the WHO/FAO/UNU [2007] safe levels of protein intake in all age groups. Centres that prescribed LFAA had lower natural protein intakes in most age groups except 1 to 10 y. In contrast, when centres were not using LFAA, the median natural protein intake met WHO/FAO/UNU [2007] safe levels of protein intake in all age groups. Enteral tube feeding was rarely prescribed.

Conclusions: This survey demonstrates wide differences in dietary practice in the management of IVA across European centres. It provides unique dietary data collectively representing European practices in IVA which can be used as a foundation to compare dietary management changes as a consequence of the first E-IMD IVA guidelines availability.
B (Germany, Switzerland, Austria), Eastern Europe (Poland), Southern Europe (Italy, Spain and Portugal), and Northern Europe (Denmark, Norway, Sweden and UK).

Clinical outcome data or patient specific data were not included in this questionnaire. Therefore, ethical approval was not required.

2.1. Statistical analysis

Data were analysed using descriptive statistics (percentage of total responses, means or medians). Prior to analysis, responses to some open answer questions were grouped or categorised according to answers received.

3. Results

Dietitians from 53 centres, representing 14 countries returned questionnaires. Fourteen of 53 centres reported they had no patients with IVA. For each country a median of 3 centres responded (range 1–14).

3.1. Patient description

In total, 140 patients with IVA were reported. Seven of 140 patients were excluded from analysis as they were not prescribed a protein restriction. Therefore 133 patients from 38 centres were on protein restriction with a median of 2 patients (range 1–17) per centre.

The numbers of centres and patients in each geographical grouping were: Western Europe Group A, n = 14 centres, 44 patients; Western Europe Group B, n = 6 centres, 24 patients; Eastern Europe, n = 1 centre, 8 patients; Southern Europe, n = 4 centres, 9 patients; and Northern Europe, n = 13 centres, 48 patients. In the 133 IVA patients presentation age was: neonatal, n = 81 (61%); late, n = 48 (36%), and unknown, n = 4 (3%). Patients were distributed in the following age ranges at the time of questionnaire completion: <1 y (n = 7), 1–10 y (n = 71), 11–16 y (n = 31) and >16 y (n = 24).

3.2. Total protein prescription

All centres distributed by region and age range are presented in Fig. 1. Total protein intake (g/kg/day) in almost all centres (32 of 38, 84%) met WHO/FAO/UNU safe levels of protein intake [31].

Twenty centres (53%) prescribed total protein prescription according to the WHO/FAO/UNU safe levels of protein intake [31], and 15 centres (39%) used the countries national reference protein intake as a guide for protein prescription. The median total protein prescription (g/kg/day) with and without LFAA is given in Table 1.

The following criteria were used by all centres for adjusting protein prescription: quantitative plasma amino acid profiles, growth and severity of IVA. Protein prescription was a combined decision between medical doctors and dietitians in 24 centres (63%), medical doctors only in 11 centres (29%) and a dietitian’s decision only in 2 centres (5%). One centre did not answer this question.

3.3. Natural protein prescription

The median natural protein prescription (g/kg/day) compared with WHO/FAO/UNU safe levels of protein, with and without LFAA is given in Table 2. In Fig. 2, natural protein prescription is presented by region and age. Almost half of the centres (n = 18; 47%) prescribed natural protein intakes below WHO/FAO/UNU 2007 safe levels of protein intake [27] in at least one age range. However, the use of LFAA in 12 (66%) centres improved protein intake allowing safe levels to be achieved. Five of 38 centres (13%) prescribed a low protein diet (without LFAA) that did not provide safe levels of protein intake [27] in patients above 11 y (centres from France n = 2; UK, n = 2; and Italy, n = 1).

Ten centres (26%) reported avoiding animal protein as part of the natural protein allowance. Seven of these centres used LFAA to supplement natural protein intake.

3.4. Prescription of LFAA

LFAA were used routinely to supplement protein intake by 23 of 38 (61%) centres (Fig. 3). The amount of LFAA prescribed per kg is given in Table 1. The median percentage of total protein provided by LFAA was over 40% (range 17–82%) in all age groups. The numbers of centres prescribing LFAA declined from 10 years of age [aged 0 to 12 months, 67% (n = 4 centres); 1 to 10 y, 67% (n = 18 centres), 11 to 16 y, 50% (n = 9 centres) and >16 y of age, 43% of centres (n = 6 centres)].

None of the UK centres prescribed LFAA for IVA. Centres within countries that varied in their approach to using LFAA were Austria, Belgium, France, Germany, Italy and Netherlands.

LFAA were given in divided doses throughout the day mixed with water/fruit juice or as a puree. The preferred LFAA were for: infants, a leucine-free infant formula supplemented with carbohydrate, fats, vitamins and minerals, and patients over 1 y, a leucine-free L-amino acid supplement (powder/liquid) containing carbohydrate, vitamins and minerals. LFAA without added vitamins and minerals were rarely used.

3.5. Nutritional support

Only 8 of 133 patients (6%) were given tube feeds (for neurological dysfunction and feeding difficulties). Of this group all had gastrostomy tubes and 3 of 8 were on nocturnal enteral feeds only.

The majority of centres (34 of 38; 89%) used special low protein foods such as low protein pasta but the amount varied according to individual patient needs and the dietary practices of local centres. Seventy-four percent (28 of 38 centres) prescribed a low protein milk replacement instead of cow’s milk. Only 11% (15 of 133) of patients were given additional energy supplements.

3.6. Monitoring

All centres monitored weight, height, quantitative plasma amino acids and nutritional blood markers. The frequency was age dependent (3–12 monthly) with infants and young children (pre-school age) assessed more frequently. Nutritional markers included: quantitative amino acids, zinc, selenium, haemoglobin, ferritin and vitamins B12 (and plasma MMA), D, A and E. Some centres reported monitoring essential fatty acids (23 centres; 60%), but at infrequent intervals.

3.7. Drugs treatment

Most centres reported using carnitine (37 centres, 97%) and glycine (29 centres, 76%) as a standard treatment approach. Nitrogen scavenger...
Table 1

Descriptive statistics comparing centres (using/not using LFAA) for dietary prescription of: total protein (g/kg), natural protein (g/kg), LFAA (g/kg) and % of protein provided by LFAA compared with total protein prescription.

Table 2

Comparison of natural protein and total protein with WHO/FAO/UNU [2007] safe levels of protein intake for all centres.

Table 3

Comparison of natural protein and total protein with WHO/FAO/UNU [2007] safe levels of protein intake for all centres.
The IVA E-IMD guidelines [36] recommend that natural protein intake should be restricted to reduce the isovaleric acid burden but ought to supply at least the safe levels of protein intake advocated by WHO/FAO/UNU 2007 [31]. They emphasise that over-restriction of natural protein could lead to catabolism and metabolic instability [42]. From case reports, patients are able to maintain metabolic stability when consuming at least the WHO/FAO/UNU safe levels of protein/leucine intake although some younger patients have tolerated double this amount [1,14,15,24]. In IVA, there are no reported differences in leucine/protein prescription for age, growth rate and severity of disorder. There are also no case reports describing protein intake in adolescents and adults or for patients with the milder 932C-T mutations. Although in our cohort some of the older patients, in particular, were prescribed less than safe levels of protein intake, it is possible that their actual natural protein intake was higher but we did not collect this data.

Leucine is an essential amino acid; it plays an important role in the regulation of metabolism, promotes global protein synthesis by signalling an increase in translation [43,44], promotes insulin release [45] and inhibits autophagic protein degradation [46]. Over restriction will lead to anorexia, triglyceride lipolysis [47], weight loss [48], and amino acid imbalance. Leucine provides 10% of the amino acid content of animal protein but only 6% of vegetable protein [49]. In this study, almost one third of centres used only low biological food sources to provide natural protein intake. This may potentially lead to leucine deficiency, which has been reported in IVA children [50].

Generally, in IVA, emphasis has been placed on protein intake but maintenance of energy intake may be as important as protein restriction. In an early study, Millington et al. [51] demonstrated that the turnover of endogenous protein, rather than dietary protein intake, is the main cause for the production of toxic metabolites in IVA. He suggested that suppression of endogenous catabolism is more effective than exogenous dietary protein restriction. Therefore, although there was low use of tube feeding (8 of 133 patients) in this survey, overall evidence would suggest that attention should be paid to adequate energy intake when patients are both stable and during metabolic stress.

There are some limitations in this survey. Initially participant interpretation of some questions was inconsistent, but all answers were quality checked with individual participants until we were certain data was interpreted correctly. No data was collected about patient clinical outcome, disease severity or detailed information about drug treatments which may have impacted on centres practices with protein prescription. Also data was collected about dietary prescriptions rather than actual dietary intake.

There remains much to be done to define the optimum dietary management of IVA considering all age groups and disorder severity. The prescription of median natural protein intake was below safe levels of protein intake when centres were giving LFAA. Overall, there may be ‘over restriction’ of natural protein and unnecessary use of LFAA creating a diet that is burdensome and expensive [51,52], particularly in older patients who have fewer episodes of metabolic instability. It is also important that further guidelines should differentiate dietary management for the “classic” IVA and the “mild” phenotype [52]. This study provides baseline data from a large cohort of IVA patients and will help enable the development of controlled trials to further investigate dietary management and help standardise treatment.

**Author’s roles**

All authors were involved in data collection, interpretation of data, critical revision of the paper for important intellectual content and final approval of the version to be published. Alex Pinto was involved in quality check of data, data analysis and writing of the manuscript. Anne Daly was involved in data analysis and manuscript development. Sharon Evans was involved in questionnaire design, collection of data and manuscript development and Anita MacDonald was involved in questionnaire development, interpretation of data and writing of the manuscript.

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**Conflict of interest**

Alex Pinto has received an educational grant from Cambrooke Therapeutics and grants from Vitaflo, Merck Serono and Biomarin to attend scientific meetings.

Anita MacDonald has received research funding and honoraria from Nutricia, Vitaflo International and Merck Serono. She is a member of the European Nutrition Expert Panel (Biomarin), member of Sapropterin Advisory Board (Biomarin), member of the Advisory Board entitled ELEMENT (Danone-Nutricia), and member of an Advisory Board for Arla and Applied Pharma Research.

Anne Daly has undertaken evaluation work for the nutritional companies – Vitaflo Ltd, Nutricia Ltd and Metax.

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