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Dietary Management of Non-Pyridoxine Responsive Homocystinuria

Introduction

- Non-pyridoxine Homocystinuria, an autosomal recessive inherited amino acid disorder, is caused by deficiency of cystathionine β-synthase (CBS).
- Without treatment, increased plasma concentrations of homocysteine, methionine and other sulphur containing metabolites and low concentrations of plasma cysteine, cystathionine and serine occur.
- It is characterized by developmental delay/intellectual disability, ectopia lentis and/or severe myopia, skeletal abnormalities (excessive height and length of the limbs) and thromboembolism.
- Treatment strategies aim to lower plasma total homocysteine, and may use drugs (betaine) or diet (low methionine diet) or a combination of both.
- There is little information about dietary practices in non-pyridoxine responsive homocystinuria across Europe.

Methods

- A questionnaire consisting of closed and open ended questions about dietary management of non-pyridoxine responsive homocystinuria was distributed to dietitians through the SSIEM-DG network.
- Questionnaires were returned from 28 centres (Table 1).

Table 1: Contributing Countries

	No. centres From each country	No. subjects on treatment (diet and drug)
Belgium	1	2
France	1	2
Germany	4	23
Netherlands	3	19
Norway	1	2
Portugal	2	4
Switzerland	2	5
UK	14	106
TOTAL	28	163

Results

- Data was collected on 163 patients with non- pyridoxine responsive homocystinuria.
- 85% (n=139) were white European, 4% (n=6) Indian, 4% (n=6) Pakistani, 4% (n=7) Black Caribbean/African and 3% (n=5) Arabic.
- Overall, 60% (n=97) of patients (58 UK; 39 non UK) were on a methionine/intact protein restriction (Figures 1&2).
- Newborn screening was uncommon (25% of centres).

Subject Demographics

Figure 1: Number of subjects on diet

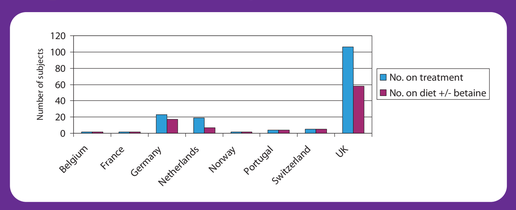
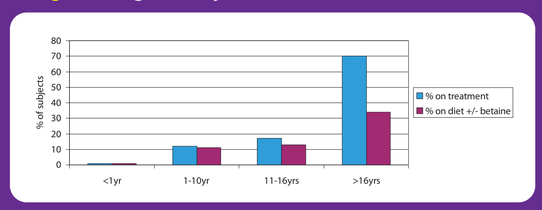


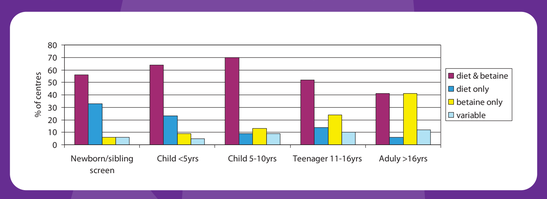
Figure 2: Age of subjects



Treatment Choice

- The most common choice of treatment by centres was a combination of diet and betaine (Figure 3).
- Treatment choice was determined by patient age (46%), problematic experience with diet alone (39%), previous good experience with diet alone (32%), and 21% of centres considered betaine to be efficacious without diet therapy.

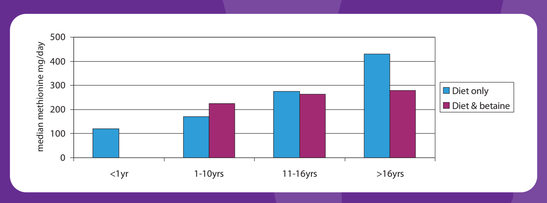
Figure 3: Choice of treatment by centre



Methionine intakes

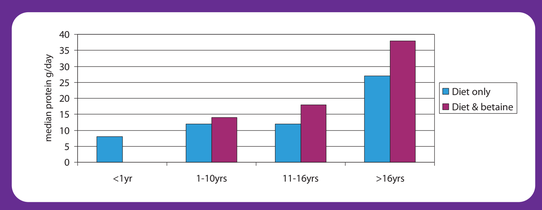
- Methionine intake increased with age in patients on diet only
- Only 36% (n=10) of centres used the methionine analysis of foods to allocate intact protein allowance. The rest used intact protein analysis.
- Of the centres using methionine analysis, 9 used methionine exchanges (6 UK; 3 non UK).
- All the 6 UK centres used 20 mg exchanges whilst 2 non-UK centres used 10 mg exchanges and 1 non-UK centre used 10 mg for fruit, 20 mg for vegetables and 80 mg for starches.

Figure 4: Methionine intake (information available in n=32 subjects)



Intact protein intake

Figure 5: Natural protein intake (information available on n=53 subjects)

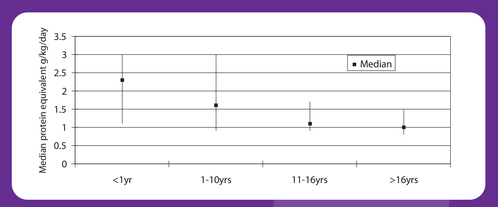


- Natural protein gradually increased with age.

Methionine-free protein substitute

- 94% (n=91/97) of all patients on dietary restriction were taking a methionine-free protein substitute (formula).
- The median protein equivalent in g/kg/day prescribed from both dietary protein (methionine) and protein substitute decreased with age (Figure 6).

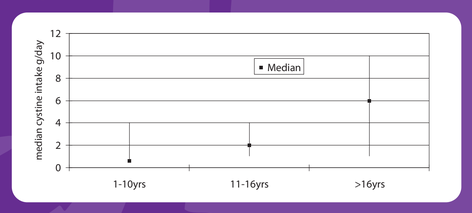
Figure 6: Median protein equivalent for the different age bands from both dietary protein (methionine) and protein substitute



Cystine supplementation

- 46% (n=13; 10 UK, 3 non-UK) of centres advocated additional cystine supplements only if plasma concentrations were lower than the reference range; and only one centre gave it routinely.
- 16 subjects from 8 centres were taking cystine supplements.

Figure 7: Dose of cystine (n=16 subjects)



Other prescribed supplements

Table 2: Other supplements prescribed

Supplement	Number of centres	%
Essential fatty acids	3*	11
LCP's	6**	21
Low protein foods	26	93
Low protein milks	24	86
Vitamins & minerals	21#	75

*1 of 3 in protein substitute. **3 of 6 in protein substitute. #7 of 21 in protein substitute

Biochemical indices

- Although the recommendations for blood homocystine/homocysteine (free/total) concentrations did not vary with age, there was little consensus between centres about the recommended blood concentrations they were aiming for (Figure 8).
- There was also wide variation in the frequency of blood monitoring (Figure 9).

Figure 8: Total homocysteine treatment aims by centre (n=25 centres)

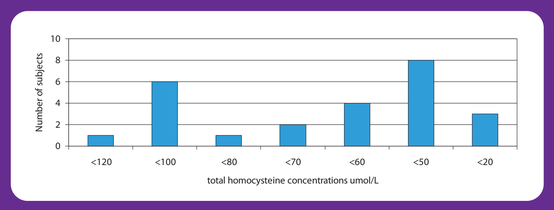
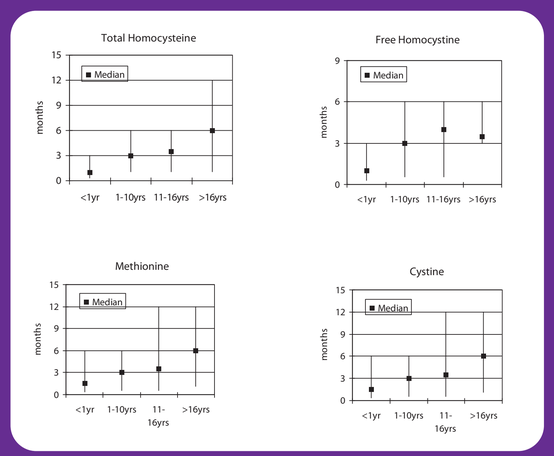


Figure 9: Frequency of blood monitoring



- 89% (n=25) of centres routinely measured total homocysteine
- 39% (n=11) free homocystine

Conclusion

- In non-responsive pyridoxine HCU, the use of methionine restricted diet was used less frequently with increasing age, with over half of adult patients on a normal diet.
- The total protein intake and treatment aims were highly variable.
- There is a need for European consensus guidelines on the management of non-responsive pyridoxine HCU.