Eur J Pediatr (1997) 156 [Suppl 1]: S39–S42

O. A. F. Bodamer · J. V. Leonard · D. Halliday

Dietary treatment in late-onset acid maltase deficiency

Abstract Late-onset acid maltase deficiency or glycogen storage disease type II (GSD II) is a rare disorder of intralysosomal glycogen metabolism, resulting in progressive myopathy that is secondary to increased muscle protein breakdown. Stable isotope studies in the postabsorptive state have confirmed that mean protein breakdown in GSD II is increased by 31% compared to control subjects, 6.86 versus 4,69 g/kg per day, that mean protein balance is reduced in GSD II –1.32 versus –1.06 g/kg per day. Indirect calorimetry has demonstrated an increase in mean resting energy expenditure in GSD II, 41.8 versus 31.2 kcal/kg per day. Compliance following the introduction of a high-protein diet is often poor due to the large quantities of protein necessary and to the high caloric intake with the consequent weight gain. Only 25% of all reported subjects with GSD II showed an improvement of muscle or respiratory function after a high-protein diet. Careful evaluation of the underlying pathophysiological changes in GSD II is necessary to develop more logical and therefore more beneficial forms of dietary treatment.

Key words Acid maltase deficiency · Glycogen storage disease · Diet · Alanine · Stable isotope

Abbreviations *GSD II* glycogen storage disease type II · *REE* resting energy expenditure

Introduction

Acid maltase deficiency or glycogen storage disease type II (GSD II) was first recognised by Pompe as a clinical entity in 1932 in a 7-month-old child, who died from sudden heart failure, with massive glycogen accumulation in almost all tissues [6]. Nevertheless it took another 20 years to characterise the biochemical defect as a deficiency of the intralysosomal enzyme α-1,4-glucosidase (acid maltase) [3, 6].

Various forms of treatment including enzyme replacement therapy have been tried with differing success [7]. Dietary treatment was tried since the 1960s, but had no effect, until Slonim and coworkers [13] in 1983 treated a 7-year-old boy with GSD II with a high-protein diet. His muscle function improved but since then there have been contradictory reports on the benefits of this treatment.

Clinical presentation

The clinical spectrum of GSD II covers a wide range of presentation with respect to age of onset, severity of symptoms and prognosis, all including varying degrees of myopathy. At either end of the clinical spectrum two phenotypes can be distinguished: the early-onset (infantile, Pompe disease) and the late-onset, slowly progressive (adult) form of presentation. Between these extremes there is a heterogeneous group of patients with juvenile or muscle variant forms [6]. To add to the complexity of the clinical spectrum, a lysosomal glycogen storage disorder has been described without obvious deficiency of α-1,4-glucosidase [6].

GSD II is an autosomal recessive disorder with an estimated frequency of less than 1 in 100,000 newborns. Around 15% of all subjects with glycogen storage disease have GSD II [6]. The gene is located on the long arm of chromosome 17q23 [6] and several different mutations have been detected. The biochemical and clinical heterogeneity is at least partly reflected in the genetic heterogeneity, but nevertheless it is not yet possible to correlate clinical and genetic findings [6].

O. A. F. Bodamer (✉) · J. V. Leonard
Medical Unit, Institute of Child Health, 30 Guilford Street, London WWC1N 1EH, UK
Tel.: 0044-171-242-9789 ext. 2614
Fax: 0044-171-813-0387

D. Halliday
MRC Human Metabolism Research Group, Imperial College School of Medicine at St. Mary's, London, UK

Table 1 Protein and glucose kinetics in GSD II and control subjects

	GSD II (juvenile) $n = 3$ (age: 13–18)	Control subjects $n = 5$ (age: 20–54)
Protein breakdown (g/kg/day)[a]	6.86 (6.2–7.51)	4.69 (4.15–5.11)
Protein synthesis (g/kg/day)[a]	5.54 (4.9–6.17)	3.63 (3.11–4.06)
Net balance (g/kg/day)[a]	–1.32	–1.06
Glucose production (mg/kg/min)[a]	2.05 (1.45–2.93)	2.20 (2.08–2.25)
REE (kcal/kg/day)[a]	41.8 (36.7–48.3)	31.2 (23.2–40.7)
	mean (range)	mean (range)

[a] Kg lean body mass as measured by body impedance measurement

Pathophysiology

Excess glycogen in the cytosol is taken up into lysosomes where it is hydrolysed by α-1,4-glucosidase or in the absence of the enzyme it will accumulate [6]. Glycogen metabolism in general is not affected but protein metabolism within the skeletal muscle in subjects with GSD II is impaired [6]. Mechanical stress in muscles causes enlarged lysosomes to rupture, releasing their contents into the cytosol finally digesting muscle fibres [7]. This is not a uniform process in all groups of muscles, showing significant intra- and inter-individual differences [6, 7]. The increase in protein breakdown has been shown in various studies in comparison to healthy subjects using both radioactive and stable isotope tracers [2, 14].

Metabolic studies

The first isotope study was done by Umbleby and coworkers [14] in 1989. The effects of a high protein diet on leucine and alanine turnover in five adult patients with GSD II were measured by employing radioactive tracer techniques. There was no significant reduction in protein turnover after a high protein diet in GSD II compared to control subjects, who were on normal diet. However, alanine production was significantly reduced on the high protein diet, but this could be explained by a compensatory decrease in carbohydrate intake [14].

Studies at Great Ormond Street Hospital

In a preliminary study done by our group we measured, in addition to leucine and glucose kinetics, resting energy expenditure (REE), using stable isotope techniques and indirect calorimetry in three subjects with juvenile GSD II and five healthy control subjects [2].

Methodology

Leucine and glucose turnover were measured by a primed constant infusion technique using 1-^{13}C leucine and (6,6)-D_2 glucose as tracers following an overnight fast [1, 10]. After a prime of 0.1 mg/kg 1-^{13}C bicarbonate, 0.5 mg/kg 1-^{13}C leucine and 2.5 mg/kg (6,6)-D_2 glucose, a constant infusion with 1-^{13}C leucine (0.5 mg/kg/h) and (6,6)-D_2 glucose (2.5 mg/kg/h) for 4 h was started. Blood for stable isotope enrichment was taken before the prime and every 15 min during the last 2 h of the infusion from an indwelling cannula on the contralateral hand. The blood samples were centrifuged immediately and the plasma stored at –70° C until analysed by GC-MS (Incos XL, Finnigan). Additional blood samples were taken for glucose and amino acid concentrations in blood. Breath samples for enrichment in $^{13}CO_2$ were taken using a Douglas bag and the breath transferred to vacutainers and stored until analysed on an IRMS (Delta S, Finnigan).

Carbon dioxide production, oxygen consumption, respiratory quotient and resting energy expenditure were measured continuously, using a Deltatrac I (Datex) while the subject was resting on a bed for 45–60 min Lean body mass was measured by using a bioelectrical impedance meter [8].

Calculations of glucose and leucine turnover rates as well as protein synthesis and breakdown rates were done using established mathematical models [1, 10].

Results

Three subjects with the juvenile form of GSD II (aged 13–18 years) and five healthy volunteers (aged 20–54 years) were studied. Two of the subjects with GSD II had

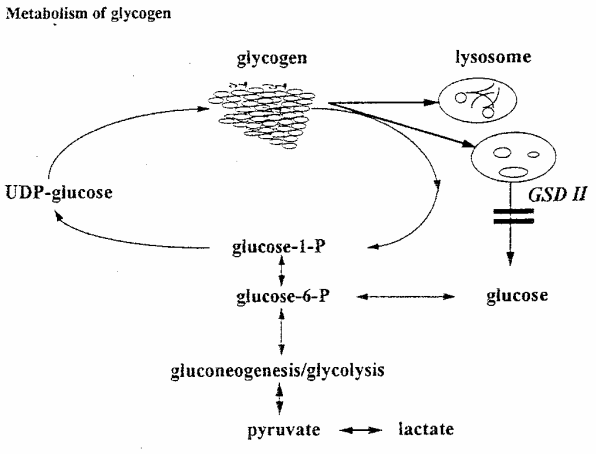

Fig. 1 Metabolism of glycogen

Table 2 Dietary intervention in GSD II

	Type of study	No. of subjects	Diet	Outcome
Slonim et al. [13]	Case report	1 patient (6 years)	high-protein (25%–30% protein)	Improved muscle funct.
Margolis and Hill [9]	Case report	1 patient (55 years)	high-protein (1.6 g/kg)	Improved resp. funct.
Isaacs et al. [7]	Case report	1 patient (33 years)	high-protein (35% protein)	Improved muscle funct.
Umbleby et al. [15]	Leucine turnover (radioactive tracer)	1 patient (33 years)	high-protein (21% protein)	No change
Umbleby et al. [14]	Alanine/leucine flux (radioactive tracer)	5 pat. (42–50 years) 5 cont. (25–57 years)	high-protein (16%–22% protein)	No change
Padberg et al. [12]	Muscle strength pulmonary function	5 adult patients	high-protein	No change
Demey et al. [4]	Case report	1 patient (27 years)	high-protein (17% protein)	Improved resp. function
Ferrer et al. [5]	Case report	1 patient (21 years)	high-protein (37% protein)	No change
8 publications since 1983	5 case reports 3 studies	16 patients 5 controls	high protein diet (16%–37% protein)	4/16 patients improved

a waddling gait, one had severe respiratory dysfunction, requiring overnight ventilation. The results for protein turnover, glucose production rate and resting energy expenditure are given in Table 1.

Conclusion

Muscle wasting and weakness in GSD II seem to be caused by increased muscle protein breakdown. This is also reflected in increased resting energy expenditure, as the increase in protein breakdown is highly energy consuming. However protein balance remained negative, despite a secondary increase in protein synthesis. Therefore dietary treatment has to aim at reducing this increase in protein breakdown towards normal levels, improving the net protein balance.

Dietary treatment

Low carbohydrate diets, fructose, vitamin A supplementation and ketogenic diets proved to be of no benefit for subjects with GSD II [6, 7]. Slonim et al. [13] observed an early rise and fall in plasma branched-chain aminoacid concentrations following a protein load in one young patient with GSD II. They concluded that this was due to protein utilisation occurring within the muscle as an alternate source of energy, resulting in a state of relative protein deficiency, muscle wasting and weakness [13]. They proposed a high-protein diet and observed an improvement of muscular function in a 7-year-old boy after 12 months on a high-protein diet (25%–30% of total calories) [13]. Since then the reports in the literature about the benefits of high-protein diets have been contradictory. From our own experience it is first difficult for the patients to increase their protein intake by either taking additional protein supplements or eating more meat and eggs. Secondly the patients usually gain considerable weight which reverses part of the potential benefits of the diet as respiratory function becomes impaired through an increase in oxygen consumption and carbon dioxide production with an increase in respiratory work.

Since 1983 there have been eight reports in the literature examining the benefits of a high-protein diet in subjects with GSD II (Table 2). From 16 reported subjects with GSD II only 4 (25%) showed either an improvement of respiratory function or skeletal muscle function. The remaining 75% did not show any signs of improvement even after long periods on very high amounts of protein (> 30% of protein). A recent report highlighted the possible advantages of branched-chain amino acid enriched diets [11].

Outlook

Further careful evaluation of the pathophysiology in GSD II is necessary so acceptable dietary treatment can be developed. Alanine as the key amino acid linking both protein and glucose metabolism within the muscle or insulin whose known effects on muscle protein metabolism are thoroughly documented are the most likely candidates for future novel approaches.

Acknowledgement Part of this work has been supported by a grant from the "Deutsche Forschungsgmeinschaft" Bo 11/93-1 (OAF.B).

References

1. Bier DM, Leake RD, Haymond MW, Arnold KJ, Gruenke LD, Sperling MA, Kipnis DM (1977) Measurement of "true" glucose production rates in infancy and childhood with 6,6-Dideuteroglucose. Diabetes 26: 1016–1023
2. Bodamer OAF, Leonard JV, Halliday D (1995) Protein, glucose kinetics in juvenile and adult patients with Glycogen Storage Disease Type II. Monatsschr Kinderheilkd 143: 909

3. Cori GT (1957) Biochemical aspect of glycogen deposition disease. Mod Probl Paediatr 3:344–358
4. Demey HE, Van-Meerbeeck JP, Vandewoude MF, Prove AM, Martin JJ, Bossaert LL (1989) Respiratory insufficiency in acid maltase deficiency: the effect of high protein diet. JPEN J Parenter Enteral Nutr 13(3):321–323
5. Ferrer X, Coquet M, Saintarailles J, Ellie E, Deleplanque B, Desnuelle C, Levade T, Lagueny A, Julien J (1992) Myopathy in adults caused by acid maltase deficiency. A trial of treatment with high protein diet. Rev Med Interne 13(2):149–152
6. Hirschhorn R (1995) Glycogen storage disease type II: acid α-glucosidase (acid maltase) deficiency. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic and molecular bases of inherited disease, vol. II. McGraw Hill, New York, pp 2443–2464
7. Isaacs H, Savage N, Badenhorst M, Whistler T (1986) Acid maltase deficiency: a case study and review of the pathophysiological changes and proposed therapeutic measures. J Neurol Neurosurg Psychiatry 49:1011–1018
8. Jebb SA, Murgatroyd PR, Goldberg GR, Prentice AM, Coward WA (1993) In vivo measurement of changes in body composition: description of methods and their validation against 12-d continuous whole body calorimetry. Am J Clin Nutr 58(4):455–462
9. Margolis ML, Hill AR (1986) Acid maltase deficiency in an adult. Evidence for improvement in respiratory function with high-protein dietary therapy. Am Rev Respir Dis 143(2):328–331
10. Matthews DE, Motil KJ, Rohrbaugh DK, Burke JF, Young VR, Bier DM (1980) Measurement of leucine metabolism in man from a primed, continuous infusion of L-[1-^{13}C] leucine. Am J Physiol 238:E473–E479
11. Mobarhan S, Pintozzi RL, Damle P, Friedman H (1990) Treatment of acid maltase deficiency with a diet high in branched-chain amino acids. JPEN J Parenter Enteral Nutr 14(2):210–212
12. Padberg GW, Wintzen AR, Giesberts MA, Sterk PJ, Molenaar AJ, Hermans J (1989) Effects of a high-protein diet in acid maltase deficiency. J Neurol Sci 90(1):111–117
13. Slonim RA, Coleman MA, McElligot JN, Hirschorn GU, Ladabie RM, Mrak R, Evans OB, Shipp E, Presson R (1983) Improvement of muscle function in acid maltase deficiency by high protein diet. Neurology 33:34–38
14. Umpleby AM, Trend PStJ, Chubb D, Conaglen JV, Williams CD, Hesp R, Scobie IN, Wiles CM, Spencer G, Sonksen PH (1989) The effect of a high protein diet on leucine and alanine turnover in acid maltase deficiency. J Neurol Neurosurg Psych 52:954–961
15. Umpleby AM, Wiles CM, Trend PS, Scobie IN, Macleod AF, Spencer GT, Sonsken PH (1987) Protein turnover in acid maltase deficiency before and after treatment with a high-protein diet. J Neurol Neurosurg Psychiatry 50:587–590