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Long-term outcome in 134 patients with galactosaemia*

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Abstract. In a retrospective study 134 galactosaemic patients, born between 1955 and 1989 in the Federal Republic of Germany were traced and their long-term outcome evaluated. We investigated 83 galactosaemic patients (78 homozygotes, 5 compound heterozygotes) by clinical, psychometric and laboratory testing; 31 patients were evaluated by medical history, the remaining 20 patients had died due to sequelae of the underlying disease. In 48 out of 78 classical galactosaemia patients galactose-free therapy had been started before the 15th day, in 19 between days 15 and 56 and in 11 patients after the 56th day. Physical findings revealed that puberty was delayed in 1 out of 18 males and 6 out of 11 females. Neurological abnormalities included ataxia ($n = 6$), intention tremor ($n = 11$) and microcephaly ($n = 10$). Speech abnormalities were found in 43 out of 66 patients over 3 years of age and disturbance of visual perception and/or arithmetic deficits in 29. Intelligence declined with age, i.e., a DQ or IQ less than 85 was found in 4 out of 34 patients less than 6 years of age (12%), in 10 out of 18 between 7 and 12 years (56%) and in 20 out of 24 older than 12 years (83%). Metabolite patterns (RBC galactose-1-phosphate and UDP-galactose, plasma and urinary galactitol) did not correlate with DQ or IQ. Dietary compliance was good in almost all patients. Compound heterozygotes ($n = 5$) had normal mental and growth development and all laboratory parameters were in the normal range. The cause of the unsatisfactory outcome of well-treated galactosaemic patients with disturbances in long-term development remains unclear. This could be due to a chronic intoxication of galactose metabolites or a deficiency of UDP-galactose or galactose-containing glycoproteins or glycolipids.

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Abbreviations: G-G = classical galactosaemia; D_2-G = compound heterozygosity

Key words: Galactosaemia – Physical development – Intelligence quotient – Galactose-1-phosphate – UDP-galactose

Introduction

Classical galactosaemia (McKusick 230400) caused by galactose-1-phosphate uridyltransferase deficiency is an inborn error of carbohydrate metabolism with an incidence of 1:40,000 which leads to hepatic insufficiency and early death in newborns fed with lactose-containing breast milk or infant formula. If the surviving children are not treated the disease results in chronic liver impairment with cirrhosis and mental retardation as well as cataract formation. The latter is due to the accumulation of galactitol in the lenses as in galactokinase deficiency (McKusick 23020).

For many years it was generally considered that early diagnosed children consequently treated with lifelong galactose-free diet would develop normally. Therefore many galactosaemic children were not regularly followed up in special centres for inborn errors of metabolism; they were treated instead by practicing paediatricians after the diagnosis had been established. Hypergonadotropic hypogonadism, however, was frequently observed among female galactosaemic patients [6, 13, 15].

In 1970 the Manchester Study [18] of Komrower and Lee and in 1980 the Los Angeles Study [5] of Fishler and coworkers reported neurological impairment, speech abnormalities, dysfunction of visual perception and a subtle decline of IQ with age among treated galactosaemic patients. In each of the two publications the authors had been able to examine a representative number of 60 galactosaemic patients.

In 1987 Waggoner and coworkers [29] initiated a galactosaemia survey in the United States and Europe and presented the outcome of 350 children and adults with galactosaemia. The investigated patients showed a definite decline in intelligence quotients with age, a delay and deficit in speech development and short stat-

ure especially in girls. No correlation of declining IQ to the onset of therapy or the level of galactose-1-phosphate were found.

In the Federal Republic of Germany the report by Böhles et al. [2] drew attention to the unfavourable development in some galactosaemic patients. Since no general survey on classical galactosaemia in the Federal Republic of Germany has been reported, the German "Arbeitsgemeinschaft für Pädiatrische Stoffwechselstörungen" (APS) initiated the following study in 1989.

Methods

Children's hospitals in the Federal Republic of Germany (for list of participating centres, see below) were requested to provide information from their patients with galactosaemia and to take part in the study. After patient identification and informed consent of parents and patients had been obtained, all patients were seen by one of us (S.S.), performing clinical and psychological examinations and collecting samples for laboratory investigations on an outpatient basis.

Clinical studies included the patient's history, an actual physical and neurological examination, pubertal status, speech documentation by tape recording and measurements of developmental or intelligence quotients according to age. Blood samples from patients, parents and siblings and urine samples from patients were collected during the examination for further analysis.

Psychometric tests

These included Denver Developmental Screening Scale and Griffith Developmental Scale in 22 probands, Hannover-Wechsler-Intelligence Scale for Preschool Children (HAWIVA) in 10, Hamburg-Wechsler-Intelligence Scale for Children (HAWIK-R) in 42 and Hamburg-Wechsler-Intelligence Scale for Adults (HAWIE-R) in 9 probands.

Laboratory analysis

Blood samples were analysed for erythrocyte galactose-1-phosphate uridyltransferase activity according to Shin-Buehring et al. [26]. Isoelectrofocusing was performed to differentiate phenotypes [27]. RBC galactose-1-phosphate and uridine diphosphate galactose levels were measured by a radioactive dilution method [25]. Plasma galactitol and sorbitol concentrations were measured by a stable isotope dilution gas chromatographic-mass spectrometric assay as described by Jakobs et al. [10]. Urinary galactitol and galactose were measured by capillary gas chromatography [12].

Results

Patients data

A total of 25 children's hospitals and 5 practicing paediatricians participated in the study. Of galactosaemic probands, 134 could be identified, representing only a portion (about 30%–40%) of the potential total number of cases born since 1955. Of these, 31 patients or their parents refused to participate actively in the study, but allowed evaluation of their case notes. This group is referred to as "history group". Death due to the underlying disease had occurred in 20 patients (15%). Thus, complete clinical evaluations could be achieved in 83 patients (34 females, 49 males; age 9 months–33 years, mean 9.5 ± 7.1 years) and retrospective evaluations only in 31 patients (16 females, 15 males; age 9 months–27 years, mean 10.2 ± 8.8 years).

The 134 patients derived from 102 families, 75 families having one child with galactosaemia, 23 families two children with galactosaemia, three families three children with galactosaemia and one family four children with galactosaemia (two children of the latter family had already died before the diagnosis could be established in the third galactosaemic child). The patients were born between 1955 and 1989. Death related to galactosaemia occurred in four children at an age of 7–14 days, in five at 15–21 days, in ten between 4 and 9 weeks and in one severely mentally retarded child at 3 years of age.

Actual biochemical investigation confirmed that 75 patients had no measurable uridyltransferase activity and therefore had classical homozygous galactosaemia (G-G phenotype), but also that three children had some residual enzyme activity associated with "mild" galactosaemia (same phenotype G-G as in classical galactosaemia). A few patients ($n = 5$) originally diagnosed as having classical galactosaemia were found to be compound heterozygotes (Duarte 2-G). One sister of a galactosaemic male was first diagnosed at 16 years of age as being classically galactosaemic as a result of this study.

Patients' history

The *socio-economic status* of the families was normally distributed, i.e., 12 out of 78 patients with classical galactosaemia belonged to the lower social class (e.g. untrained worker), 53 to the middle social class (e.g. butcher, nurse) and 13 to the upper-middle social class (e.g. teacher, medical doctor). In five compound heterozygotes (D_2-G) three belonged to the middle social class and two to the upper-middle social class.

Complications occurred in 16 out of 78 pregnancies of patients with classical or "mild" galactosaemia (20.5%). Complications such as hyperemesis were found in 3 cases, bleeding, Shirodkar operation of the cervix uteri and tocolysis in 6, infections in 2, oedema and high blood pressure in 3, and a twin pregnancy in 2 families. In 1990 the overall risk of complications during pregnancy (including such as twin pregnancy etc.) was 34% (Yearly Report of the Working Group for Perinatology in Lower Saxony, FRG).

In 8 of the 78 pregnancies the mother took a galactose-reduced diet because of the previous birth of a galactosaemic child (see below). In 7 of the remaining 70 pregnancies the mothers avoided milk intake due to personal dislike, but consumed milk products. In 63 pregnancies the mothers had no galactose restriction, 12 pregnant women even forced themselves to drink more than one litre of milk per day in order to do "something good" for their baby.

Prenatal diagnosis was performed in two pregnancies, leading to the birth of a healthy child in one pregnancy and to a therapeutic abortion in the case of one affected fetus. Delivery was abnormal in 14 out of 78 patients (18%) with classical or "mild" galactosaemia: 9 were

born by caesarean section due to malposition of the baby, 3 were born by forceps and 2 by vacuum extraction. In 1990 the overall risk of complications during delivery was 20.9% (Yearly Report of the Working Group for Perinatology in Lower Saxony, FRG).

Exchange transfusion was necessary in 28 out of 78 patients (36%) due to hyperbilirubinaemia and/or a septicaemia-like clinical picture.

Diagnosis

The primary diagnosis was established by abnormal newborn screening in only 3 out of 78 classical or "mild" galactosaemic patients and by clinical symptoms in only 31 including those born before newborn screening for galactosaemia was introduced nationwide in the Federal Republic of Germany in 1978. A further eight infants were diagnosed by clinical symptoms before the result of a positive newborn screening was known. However, 24 further infants were first diagnosed by positive newborn screening although clinical symptoms of galactosaemia had already been present from day 3 on.

In 10 out of 18 G-G cases with a previous galactosaemic sibling, the diagnosis was not established until the birth of the second or third affected sibling. In three of the remaining eight pregnancies the mother had taken a galactose-free diet and in five cases a galactose-reduced diet.

All five D_2-G cases were diagnosed as having classical galactosaemia due to positive newborn screening results without displaying any clinical symptoms.

Treatment

In order to evaluate the outcome and long-term effects of treatment, the patients were divided into four groups according to the initiation of galactose-free diet (Table 1). Treatment was started during the 1st day of life in only 6 G-G patients (group 1), between days 2 and 14 (group 2) in 42 G-G patients and in one D_2-G patient, between the 3rd and 8th week (group 3) in 19 G-G and in three D_2-G patients, and after the 8th week (group 4) in 11 G-G patients and one D_2-G patient.

Dietary compliance as assessed by parental interview, reports from the pediatricians, dietetic questioning during study evaluation and laboratory controls such as RBC galactose-1-phosphate or blood galactose concentration was good in 58 out of 78 probands, fair in 18 and poor in 2 probands. Urinary or plasma galactose concentrations as routine control parameters for dietary compliance were used in all participating children's hospitals; RBC galactose-1-phosphate in only a few.

Table 1. Age at initiation of diet ($n = 114$)

Group	Age at initiation of diet	Phenotype		
		Examined		Historical Group
		G-G	D_2-G	
1	1st day	6	0	3
2	2nd–14th day	42	1	17
3	3rd–8th week	19	3	9
4	Over 8th week	11	1	2
		78	5	31

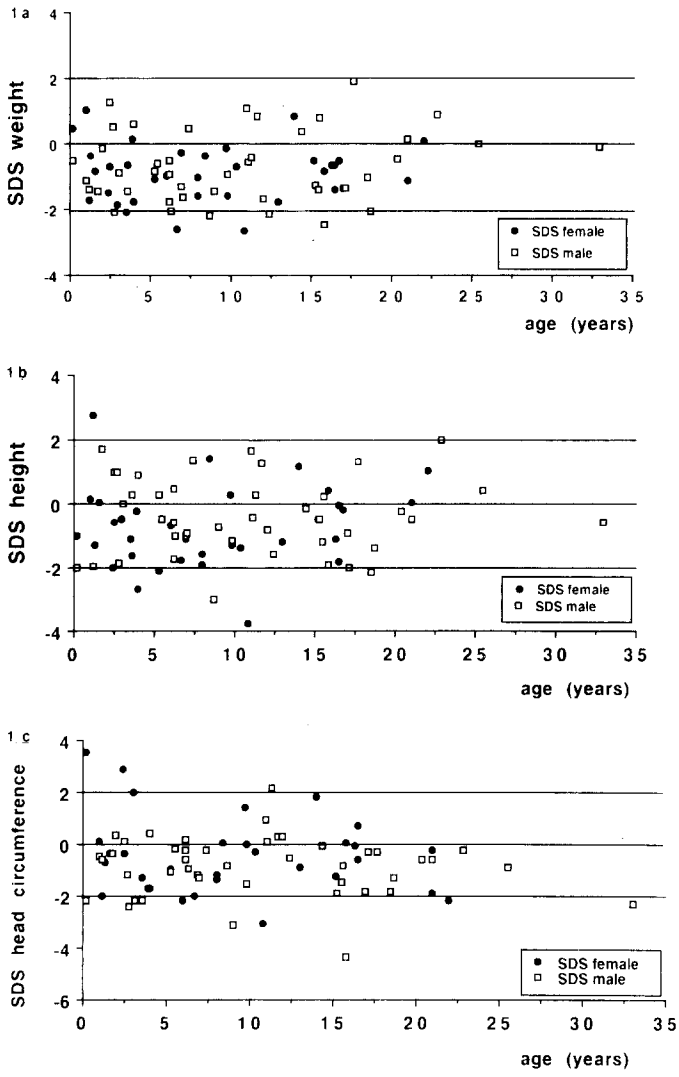

Fig. 1. Weight (**a**), height (**b**) and head circumference (**c**) in 78 galactosaemic probands at time of evaluation (standard deviation scores (SDS) according to Prader [24])

Physical development

Out of 78 galactosaemic patients, 9 (3 females, 6 males) had body weights below −2 standard deviation scores (SDS) (Fig. 1a) and 6 (4 females, 2 males; Fig. 1b) had body lengths below −2 SDS [24]. Bone age was not routinely examined.

Interestingly, 10 (3 females, 7 males; Fig. 1c) out of 78 galactosaemic patients were microcephalic with a head circumference below −2 SDS. These ten probands had no peripartal complications and the head circumference at birth was normal in nine (in one case it was not reported), thus excluding prenatal brain damage resulting in microcephaly.

Cataracts had developed in 15 patients with reversible clouding of the lenses after initiation of galactose-

free diet; 6 children had mild persistent cataracts. A 33-year-old man was blind due to cataract formation. One proband had never been examined ophthalmologically, but was clinically unaffected.

Puberty, assessed according to Tanner et al. [28], was delayed in 1 male out of 18 over 12 years of age (confirmed by hormone analysis) and in 5 out of 11 females over 12 years of age. The latter had primary amenorrhoea and hypergonadotropic hypogonadism. Only one of these females was hormonally substituted with oestrogens and gestagens. Of the 78 galactosaemic probands, 58 were prepubertal. The results of the hormone analysis will be reported elsewhere.

Neurological development

Actual neurological examination was normal in 49 out of the 78 galactosaemic probands and in all five D_2-G cases. Severe clumsiness was present in 12 cases, 11 had intentional tremor, 3 had mild ataxia and 3 severe ataxia including the twins described by Böhles and coworkers in 1986 [2]. The age of onset of ataxia was 9–14 years. One patient had familial epilepsy with grand mal seizures and one was blind due to cataracts. A correlation between neurological disturbances and onset of therapy was not found.

Among 31 galactosaemic patients of the history group, 20 gave no information concerning neurological status. Normal neurological development was reported in seven patients and three had seizures. One was blind due to cataract formation.

Speech abnormalities were observed in 43 out of 66 examined probands over 3 years (65%): 15 had isolated dyslalia, 9 multiple dyslalia, 9 dyspraxia, 7 dysgrammatism and one stuttered. Speech therapy was given to 21 patients including 2 children in whom dietary treatment had been initiated during the 1st day of life.

Of 31 galactosaemic patients of the history group, 12 had speech abnormalities and 5 of these received speech therapy. The status of speech development was not known in the remaining 19 cases.

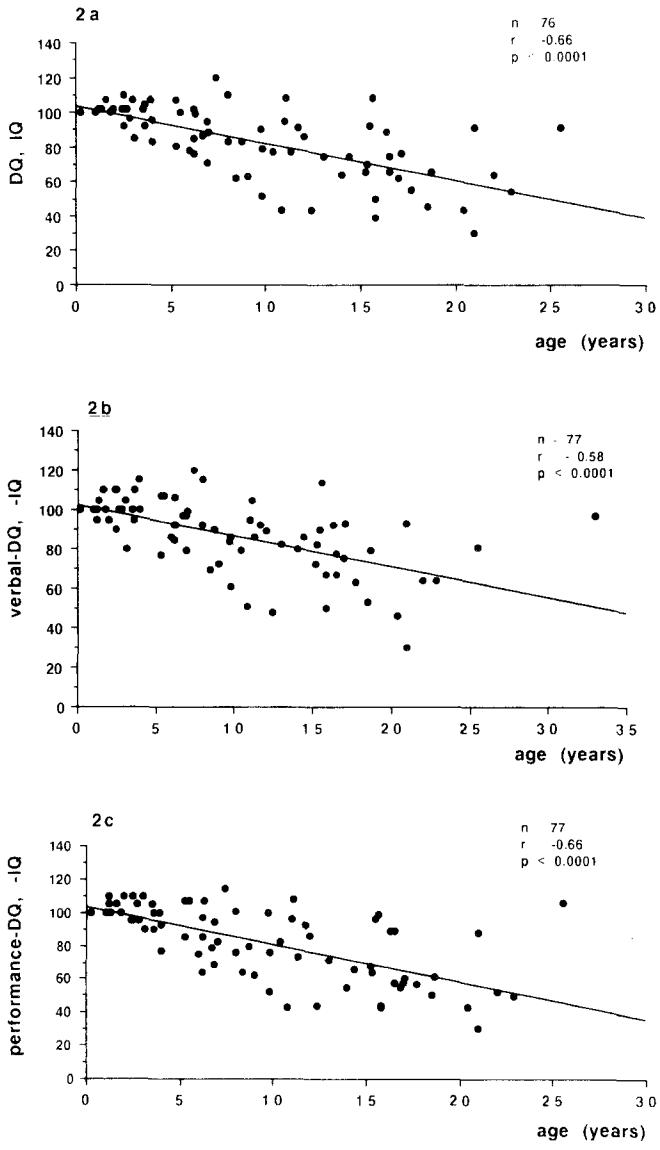

Fig. 2. Developmental Quotient (DQ) or Intelligence Quotient (IQ) in 76 galactosaemic patients (**a**), verbal DQ or IQ ($n = 77$) (**b**) and performance DQ or IQ ($n = 77$) (**c**) in relation to age

Psychometric testing

The actual psychometric tests during this study were performed by the same examiner in 83 probands with G-G and D_2-G forms. Out of 78 G-G patients, 76 received a complete testing. No performance IQ was available in the blind galactosaemic adult and no verbal IQ in a heavily stuttering patient.

The results revealed a decline in DQ or in IQ with age in classical galactosaemics ($r = -0.66$) (Fig. 2a). A DQ or IQ < 85 was found in 4 out of 34 patients under 6 years of age (12%), in 10 out of 18 patients aged between 7 and 12 years (56%) and in 20 out of 24 patients over 12 years of age (83%). Altogether, 34 out of 76 probands had a DQ or IQ < 85 (45%). The decline was similar when the evaluation of verbal IQ ($r = -0.58$) (Fig. 2b) or performance IQ ($r = -0.66$) (Fig. 2c) was separately performed.

There was no significant correlation between mean DQ or IQ and the initiation time of dietetic treatment for all patients tested (Fig. 3). This held true for those patients over the age of 4 years in whom more differentiated psychometric tests could be performed (not shown). Only those patients whose treatment had started after the 8th week of life (group 4) exhibited lower mean DQ or IQ levels. In the majority of patients the actual psychometric testing was performed for the first time. This lack of routinely performed psychometric tests was also evident in the 31 patients of the history group: 18 had not had IQ tests at all, 1 had an IQ > 100, 5 an IQ between 85–100 and 7 an IQ < 85.

Disturbance of visual perception was found in 29 out of 66 probands over 3 years of age (44%) which showed no correlation to the time of therapy initiation. Calculation deficits were observed in 29 out of 66 over 3 years of age (44%), again without any correlation to the start of

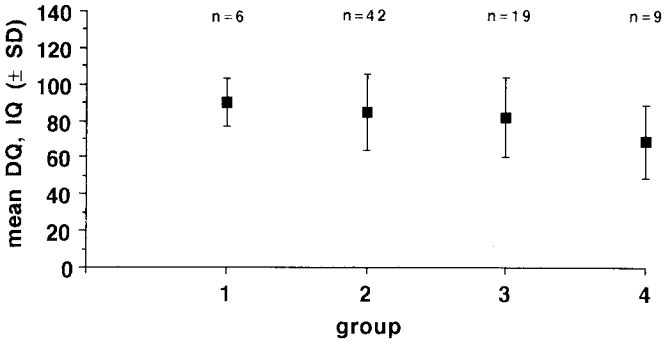

Fig. 3. Mean Developmental Quotient (DQ) or Intelligence Quotient (IQ) in relation to age at initiation of diet ($n = 76$) (also see Table 1)

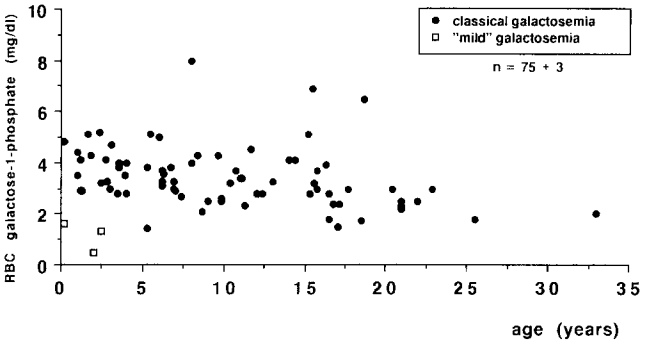

Fig. 4. RBC galactose-1-phosphate concentration in relation to age in 75 patients with classical galactosaemia and 3 patients with "mild" galactosaemia

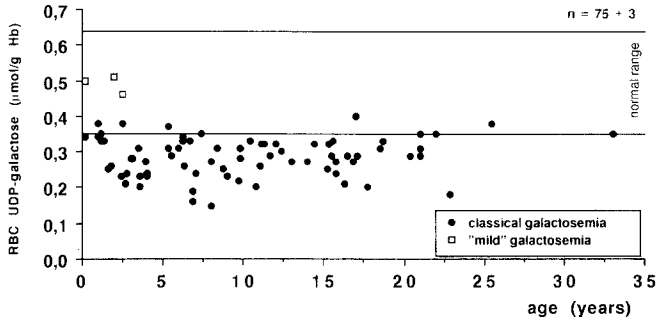

Fig. 5. RBC UDP-galactose concentration in relation to age in 75 patients with classical galactosaemia and 3 patients with "mild" galactosaemia

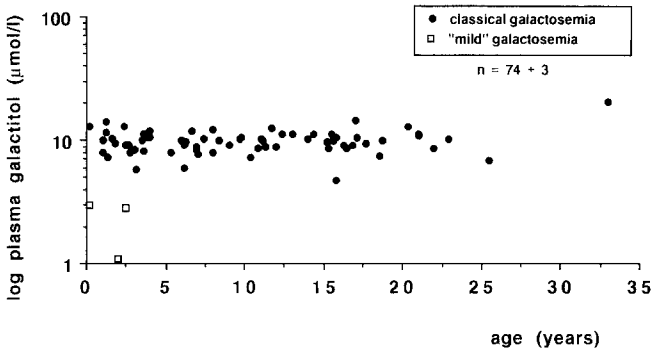

Fig. 6. Plasma galactitol concentration in relation to age in 74 patients with classical galactosaemia and 3 patients with "mild" galactosaemia

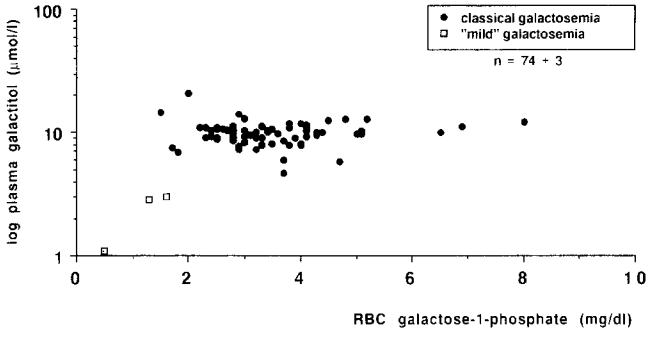

Fig. 7. Plasma galactitol concentration in relation to RBC galactose-1-phosphate concentration in 74 patients with classical galactosaemia and 3 patients with "mild" galactosaemia

dietetic therapy. Out of 31 patients of the history group, 7 were described to have calculation deficits and 3 to have disturbance of visual perception.

School achievement. At time of the study none of the 78 galactosaemic probands attended college. Out of 78, 3 attended high school, 15 secondary school, 11 elementary school and 16 schools for the mentally handicapped. Seven attended preschool, 10 kindergarten and 16 were below kindergarten age.

The school achievements of the healthy siblings were one or two degrees higher in 22 out of 78 cases and similar in 11 patients. In 45 cases there were no healthy siblings.

Laboratory analysis

RBC galactose-1-phosphate uridyltransferase activity was zero in 75 out of 83 analysed blood samples (G-G phenotype), 3 had "mild" galactosaemia (uridyltransferase activity 0.79–2.0 µmol/h per gramme Hb, normal range: 20–35, homozygous phenotype G-G) and 5 were compound heterozygotes (uridyltransferase activity 4.3–5.5 µmol/h per gramme Hb, phenotype D_2-G).

Actual RBC galactose-1-phosphate levels were 3.36 ± 1.25 mg/dl, range 1.3–8.0 mg/dl, $n = 78$ (normal range: 0–0.3). There was a slight decline with age (Fig. 4). No correlation with DQ or IQ values was observed. A lower level for galactose-1-phosphate was found for 3 children with "mild" galactosaemia (0.5, 1.3 and 1.6 mg/dl, respectively).

Actual RBC UDP-galactose levels were 0.29 ± 0.07 µmol/g Hb, range 0.15–0.51 µmol/g Hb, $n = 78$ (normal range: 0.35–0.65). Out of 78 patients, 65 had UDP-galactose concentrations below the normal range. No decline in the concentration with age was found (Fig. 5). There was no significant correlation to IQ performance. Normal UDP-galactose levels were found in three children with mild galactosaemia (0.46, 0.50 and 0.51 µmol/g Hb, respectively). Galactose-1-phosphate concentrations and UDP-galactose levels had a weak inverse correlation ($r = -0.425$).

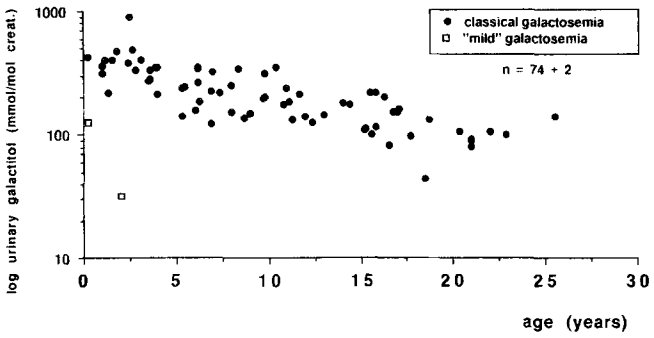

Fig. 8. Urinary galactitol concentration in relation to age in 74 patients with classical galactosaemia and 2 patients with "mild" galactosaemia

Plasma galactitol concentrations in classical galactosaemia were 9.9 ± 2.2 µmol/l, range 4.7–20 µmol/l, $n = 74$ (normal range: 0.08–0.86). There was no correlation with age (Fig. 6), galactose-1-phosphate levels (Fig. 7) or UDP-galactose levels, but an expected correlation with the uridyltransferase activity. In the three children with "mild" galactosaemia there was only a slight increase in plasma galactitol (1.08, 2.85 and 2.98 µmol/l plasma, respectively).

Urinary galactitol levels in classical galactosaemia were 228 ± 134 mmol/mol creatinine, range 44–897 mmol/mol creatinine, $n = 74$ (normal range: 9–80 with an inverse relationship with age). This decline with age could also be seen in the galactosaemic patients although it was still tenfold higher than the normal range (Fig. 8). Two children under 2 years of age with so-called "mild" galactosaemia had low urinary galactitol concentrations (32 and 128 mmol/mol creatinine, respectively).

Urinary galactose levels as a control of short-term dietetic compliance were only mildly elevated in 2 out of 75 patients examined.

Compound heterozygosity

All five D_2-G probands, aged 4 months–8 years, had DQ or IQ scores > 100. Clinical examinations, RBC galactose-1-phosphate levels (0.1–0.3 mg/dl), UDP-galactose levels (0.4–0.6 µmol/g Hb), plasma galactitol levels (0.13–0.62 µmol/l) and urinary galactitol excretion according to age (6–74 mmol/mol creatinine) were all within the normal range.

Discussion

Unexpected results in reports on classical galactosaemia [2, 4, 5, 18, 29] have thrown shadows upon the opinion that this is a manageable disease. A review by Komrower [17], a Lancet editorial [1] and a report by Gitzelmann and Steinmann [7] provided further evidence that there could be "some clouds over galactosaemia". Therefore, this detailed study was initiated in order to evaluate the long-term outcome of German patients with classical galactosaemia.

As estimated from the German birth rate (approximately 600000 children per year for the last 30 years), about 12–15 galactosaemic children must have been born yearly in former Federal Republic of Germany. In this study we were able to trace 134 galactosaemic children, who reflect only 30%–40% of the hypothetical total number of patients. It is conceivable that a large number of patients had probably died without the correct diagnosis and that yet another group of patients was lost to follow up and may now present unrecognised with signs of hypergonadotropic hypogonadism or ataxia.

Our results confirm previous observations [1, 4, 5, 17, 29]. In well-treated classical galactosaemia there was a significant decline in IQ with age. Speech development, visual perception and arithmetic calculation were impaired in the majority of the examined probands. School achievements were one or two steps below the grades achieved by healthy siblings. These unsatisfying results did not depend on age at initiation of diet except for those diagnosed after the age of 8 weeks.

There was also a high degree of microcephaly, partly in conjunction with intention tremor, and mild to severe ataxia which appeared at age 9–14. These signs are suggestive of a neurodegenerative disease [2, 11, 19].

Not much is known about neurohistological findings in early diagnosed and consequently treated galactosaemic patients. Histopathological brain examinations of late-treated patients revealed cortical neuronal degeneration and atrophy of the cerebellum and basal ganglia [3, 8]. White matter was demyelinated and sclerosed. Pigmentation of pallidum and substantia nigra was decreased explaining the choreoathetotic movement disorder in the index case of Haberland et al. [8]. Cerebroside levels of cerebral white matter were slightly reduced [3].

Pathomechanisms responsible for the degeneration of brain cells during postnatal life in galactosaemic patients are as yet unknown. A self-intoxication via high galactose-1-phosphate levels generated by endogenous galactose production or by the pyrophosphorylation pathway during pre- and postnatal life has been discussed in ovarian failure [7, 9]. Recently, however, a reduction in intracellular levels of UDP-galactose has been reported [21] as confirmed in this report. Contradictory reports on UDP-galactose concentrations [16] are probably due to different analytical methods, i.e. enzymatic [20] or HPLC [22]. Our radioactive dilution method [25] may include other UDP-sugars. A recent report of a deficiency of glycolipids in brain and lymphocytes may explain some of the clinical abnormalities seen in patients with classical galactosaemia [23].

Interestingly, two identical twins of our study treated from day 7 on developed severe progressive ataxia in combination with severe mental retardation and microcephaly or widening of the CSF-containing spaces at age 9 [2]. Their dietary compliance as well as RBC galactose-1-phosphate values were very satisfactory. The mechanism for this timing of brain damage is unclear.

Physical growth (i.e. height and weight) of the majority of the examined probands was, contrary to a previous report [29], within the normal range of ± 2 Standard

Deviation Scores. Thus the nutritional requirements had been fulfilled by the dietetic treatment. Most parents were well informed concerning the galactose content of the daily food. Dietary compliance was good in almost all galactosaemic patients. As a consequence, the galactose-1-phosphate levels of the majority of patients were within the expected range of appropriately treated children showing a sharp decrease of galactose-1-phosphate during the first months of life.

It seems to be that a residual galactose-1-phosphate uridyltransferase activity (1%–15%) is sufficient to metabolise galactose without major clinical consequences as seen in three children with "mild" galactosaemia and in five with compound heterozygosity. All of these children showed elevated levels of galactose-1-phosphate and galactose only during the first periods of life and were therefore detected by newborn screening. Their UDP-galactose levels were higher and their plasma and urinary galactitol concentrations lower than those of patients with classical galactosaemia. They had normal mental and physical development. It is therefore concluded that patients with "mild" galactosaemia do not require a dietary regimen as strict as in classical galactosaemia.

Various clinical and biochemical abnormalities observed in classical galactosaemia could not be prevented or corrected by galactose restriction therapy. It may be possible that substitution with uridine as reported by Kaufman and coworkers [15, 20] could help to ameliorate symptoms of the disease. Obviously, it would take many years to prove the benefits of this therapy.

From these observations it is obvious that the long-term treatment of galactosaemic patients in the Federal Republic of Germany has so far been unsatisfactory. It is therefore suggested that galactosaemic patients be more closely followed up by paediatric metabolic centres in order to monitor treatment and evaluate their outcome. In addition, only a large prospective collaborative study will help to clarify whether the unsatisfactory outcome of galactosaemic patients is due to a chronic intoxication of galactose metabolites already during prenatal life or due to a deficiency of galactose-containing glycoproteins and/or glycolipids, or perhaps due to an over-restrictive galactose-free diet. The results of our study could be the basis for prospective trials in the management of galactosaemia.

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