Ophthalmic findings in classical galactosaemia – prospective study

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Abstract

Thirty three children with classical galacto-saemia diagnosed through newborn screening are considered. It is concluded that cataract formation has a direct relationship with poor dietary control. Erythrocyte galactose-1-phosphate (Gal-1-P) levels do not correspond to cataract formation unless many times higher than normal. The value of crystalline lens biomicroscopy is confirmed as a useful method for monitoring the dietary and biochemical control in classical galactosaemia.

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Galactosaemia results from an error of galactose metabolism caused by a deficiency of any one of the three enzymes; galactokinase, transferase, and epimerase.[1]

Galactosaemia is a rare cause of congenital cataract, but should always be considered in the differential diagnosis because of the reversibility of the condition after an early initiation of the treatment. All types of galactosaemia cause cataract due to the activation of the aldose reductase shunt and accumulation of galactitol in the crystalline lens. In classical galactosaemia galactitol also accumulates in other tissues such as the liver and the brain.

Classical galactosaemia, which has an incidence in Ireland of one in 23 000 births,[2] is due to a defective gene mapped on human chromosome 9, which is coded for the enzyme galactose-1-phosphate uridyl transferase (GPUT). It is inherited as an autosomal recessive condition.[3] GPUT deficiency causes a multi-organ illness with cataract formation, hepatomegaly, and mental retardation.[4]

We previously reported 17 children with classical galactosaemia[5] and demonstrated the importance of early diagnosis and tight biochemical control in prevention of cataract, and highlighted the importance of slit-lamp biomicroscopy.

In this study we discuss the ophthalmic findings in 33 homozygous children with transferase-deficient galactosaemia diagnosed by newborn screening and on treatment. We include the 16 out of 17 children with galactosaemia previously reported.

Patients and methods

There were 15 females and 18 males, with a mean observation time of 8·5 years (16 of them observed for 10 years). Galactosaemia was diagnosed in 13 at birth, 11 by the fourth day, four by the 11th day, two by the 20th day, one in the sixth week, one in the third month, and one in the eighth year of life. They were diagnosed as a result of a national neonatal screening programme for galactosaemia, coupled with screening for phenylketonuria, homocystinuria, and maple-syrup urine disease. The blood spot test for galactosaemia using the Guthrie card is based on the *E coli* metabolite inhibition assay, in which the inhibition of the growth of a transferase deficient *E coli* mutant by galactose is used.[6] The Beutler erythrocyte transferase assay,[7] plasma galactose, and erythrocyte galactose-1-phosphate (Gal-1-P) levels were checked in the cases which were positive on screening. High risk newborns who had older siblings with galactosaemia were put on a galactose-free diet at birth and the Beutler test and erythrocyte Gal-1-P levels were measured. Patients were monitored by the inherited metabolic and paediatric ophthalmology units after the diagnosis and introduction of a galactose-free diet. The plasma galactose and erythrocyte Gal-1-P levels were frequently assessed. The ophthalmic assessment included visual acuity, motility, retinoscopy, slit-lamp biomicroscopy, and funduscopy. The ophthalmic findings, especially the crystalline lens opacities, were compared with the mean biochemical control, as reflected by the mean erythrocyte Gal-1-P level. Comparison was also made with the dietary compliance which was assessed by the metabolic unit dietician. Five other children failed to attend for their appointments and were not included in this study.

Results

The 33 children were divided into three groups: very good, good, and fair biochemical control, on the basis of their mean erythrocyte Gal-1-P levels (Table 1). Four had no medical problems at the time of the diagnosis. Twenty two had jaundice, six had septicaemia, four had hepatomegaly with gastrointestinal disturbances. In their last review five had speech delay, four had low IQ and developmental delay (Table 2). Fifteen children had a positive family history of galactosaemia, with one or more siblings involved. Twelve children developed lens opacities in the form of posterior subcapsular, cortical, and nuclear minute opacities. One child (case 13) had familial autosomal dominant nuclear cataract which was stationary.

In the group with very good biochemical control, 13 patients had no cataract and 1 had congenital cataract (case 13). Two patients (cases 17 and 27) developed lens opacities later which were still present at the end of the study. Six other cases in this group (1, 5, 9, 10, 20, 25) with lens opacities at the beginning of the study

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cleared later. The remaining patient (case 11), a 9-year-old girl, on the diet since day 1, initially developed peripheral axial lens opacities at age 2·5 years during a 3 month period off the diet. On re-introduction of the diet, the opacities regressed completely over 6 months. Lens opacities developed 2 years later after another period of poor compliance. These regressed over a period of 3 years with tighter biochemical control.

In the good biochemical control group two had cataracts. One patient (case 4) had lens opacities at the start but they cleared later. The other (case 15), a 10-year-old boy, on the diet since day 1, developed peripheral axial lens opacities at 3·7 years following a 3 month period off all dietary restrictions. Good control was re-established and the opacities regressed totally over a 9 month period.

There were two patients in the fair biochemical control group. Case 12 showed lens opacities initially and these cleared later. Case 28 did not show any lens opacities.

All children achieved vision of 6/12 or better.

Discussion

Classical galactosaemia is a rare cause of cataract, 1–3% of all cataracts in different reports.[8] The

Table 1 Number of children in each group based on biochemical control

Biochemical control	Mean erythrocyte Gal-1-P		Number of patients (case no)
	µg/ml packed cells	µmol/l	
1 Fair	>70	>208	2 (12, 28)
2 Good	45–70	134–208	8 (4, 8, 14, 15, 18, 19, 29, 31)
3 Very good	<45	<134	23 (rest)

Table 2 Ophthalmic and systemic findings in 33 children

Biochemical control	Patients	Mental state (present)	Initial medical problems	Lens opacities		
				First	Mid term	Late
Very good: 23	1		S	+		
	2		J, V, WL			
	3		J			
	5		J, HG, M	+		
	6					
	7	SD	J			
	9	SD	I, J	+		
	10			+		
	11		S		+	
	13			cong cataract		
	16		S			
	17	SD	H, I, J, V		+	+
	20	<IQ, DD	J	+		
	21		J			
	22		HG, J, V			
	23	<IQ, DD	HG, J, V			
	24		HG, J			
	25		HG, J, S	+		
	26		J			
	27	<IQ, DD			+	+
	30		SA			
	32	<IQ, DD	P			
	33		J			
Good: 8	4		HIV and Hnep	+		
	8					
	14	SD	HG, J, V, WL			
	15		J		+	
	18		J			
	19		J			
	29		J			
	31		J, M, S			
Fair: 2	12		HG, J, S	+		
	28	SD	J			

Cong cataract=congenital cataract; DD=developmental delay; HG=haemorrhage from cord; H=hepatomegaly; Hnep=hydronephrosis; I=irritable; J=jaundice; M=meningitis; P=premature; S=septicaemia; SM=small for age; SD=speech delay; V=vomiting; WL=weight loss.

most common type, classical galactosaemia with the transferase deficiency, is a multi-organ illness. It appears with acute early signs 1 to 7 days after a lactose containing milk diet. Mild to severe vomiting, diarrhoea, lethargy, hypotonia, formation of minute lens opacities, jaundice, hepatomegaly, and infection with Gram positive micro-organisms are early presenting signs. Severe complications are advanced cataract formation, mental retardation, and neurological sequelae.[9] Transferase deficiency and activation of the aldose reductose shunt with eventual overproduction of dulcitol or galactitol have been proposed as being responsible for an increased osmolarity in the crystalline lens and other tissues. The mechanism responsible for the diabetic cataract is similar.[10]

Recent studies have shown a decreased level of uridine diphosphate galactose in the liver biopsy, erythrocytes, and skin fibroblasts. It has been speculated that this is responsible for late complications, especially neurological sequelae.[11] This supports the hypothesis of a subgroup with only neurological complications, and a low IQ in spite of being on a galactose-free diet since birth.[12] Cataract has not been reported in these. The severity of the presenting signs and the cataract depends on the severity of galactosaemia, age at the time of diagnosis, and the date of the initiation of treatment.[13] In a review of 55 galactosaemic children referred to our metabolic unit, nine of 55 babies with untreated galactosaemia died within 17 days of birth, two of them on the eighth day.[14] In contrast two children in this study in whom treatment started at the age of 12 weeks (case 1) and 8 years (case 31), had a favourable outcome.

Mean erythrocyte Gal-1-P had been used as a monitor reflecting the biochemical control but does not correlate with cataract formation. The test is not widely available and laboratory techniques differ. The test needs to be repeated frequently, even monthly. Even with regular testing and using the same laboratory criteria as in our study, fluctuation of Gal-1-P makes it an unreliable marker. This is thought to be due to an endogenous production of Gal-1-P, as a result of unsuspected absorption from fruits, medication, or other unknown factors. Measurement of uridine diphosphate galactose has been suggested as a better indicator of the biochemical control. Urinary galactitol is also a possible marker which is currently being investigated. Reports of heterozygote cases of transferase deficiency who had cataract suggest that there are other mechanisms involved.[15][16] Four of the 23 obligate heterozygote parents of children in our previous study showed lens opacities. This also emphasises the role of galactosaemia as a cause of presenile cataract.[17]

Poor dietary compliance causes early and late complications as described. On three occasions, when cases 11 and 15 were off their diet, lens opacities developed, and on a tighter dietary control they cleared. Two patients (cases 17, 27) who had normal Gal-1-P levels developed crystalline lens opacities and when tighter dietary control was introduced the opacities gradually resolved.

The rate of formation of lens opacities in our

study does not correlate with the erythrocyte Gal-1-P level. Our ophthalmic assessment with portable slit-lamp biomicroscopy helped us to exclude cases of congenital cataract and diagnose lens opacities which were already overlooked in the younger age group and enabled us to advise the metabolic unit about the poor dietary control.

Our findings in this larger group of patients with a mean follow up of 8·5 years (16 with 10 years, 17 with more than 7 years) reinforces our previous study of the usefulness of slit-lamp biomicroscopy. We also believe that the mean level of erythrocyte Gal-1-P does not correspond with the formation of lens opacities. Newer biochemical measurements are yet to be introduced.

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