Abstract

Aims—To evaluate the cognitive outcome of a cohort of children with galactosaemia in relation to genotype.

Methods—The cohort was drawn from children notified to the British Paediatric Surveillance Unit galactosaemia study which ran from 1988 to 1990. Cognitive outcome was assessed using the Wechsler Intelligence Scale for Children or the Wechsler Preschool and Primary Scale of Intelligence. Parents completed a questionnaire detailing educational status, and the attending paediatrician returned a questionnaire regarding age at diagnosis and biochemical outcome over the previous two years.

Results—A total of 45 children were genotyped: 30 were homoallelic for the Q188R mutation, the remainder being heteroallelic for Q188R with K285N (n = 4), L195P (n = 4), or other mutations (n = 7). Psychometric evaluation was available in 34 cases: mean full scale IQ was 79, verbal quotient 79, and performance quotient 82. Genotype was not related to galactose-1-phosphate (Gal-1-P) concentrations. However, children homoallelic for the Q188R mutation had significantly lower IQ scores than those who were heteroallelic (73.6 v 94.8). This difference was independent of social and demographic influences and Gal-1-P concentrations over the previous two years.

Conclusions—In children with galactosaemia, cognitive outcome appears to relate to genotype rather than metabolic control, as reflected by Gal-1-P concentrations. The value of measuring Gal-1-P concentrations routinely once successfully established on a galactosaemia diet is questionable as concentrations do not appear to affect outcome. In the UK population, homozygosity for the Q188R mutation is invariably associated with a poor outcome, and there is evidence that variability in neurocognitive outcome is at least part dependent on allelic heterogeneity.

Keywords: galactosaemia; genotype; cognitive and behavioural function; galactose-1-phosphate uridyl transferase

Classical galactosaemia is an autosomal recessive condition in which there is virtual absence of the enzyme galactose-1-phosphate uridyl transferase (GALT).

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Poster Level 1

The relationship of genotype to cognitive outcome in galactosaemia

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STATISTICS

Data were encoded for computer analysis using SPSS for Windows (version 7.5). Details of statistical tests are included in the results section. Multiple regression was carried out using the SPSS regression module.

GENETIC ANALYSIS

All samples were tested for the most common mutation, Q188R, using polymerase chain reaction (PCR) amplification of exon 6 and restriction enzyme digestion with either HpaII or MspI. The A → G transition at nucleotide c.563 creates a HpaII/MspI cutting site. A second cutting site at nt position c.443 acts as an internal control. Samples that were not homoallelic for the Q188R mutation were

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Discussion

Although the treatment for galactosaemia is theoretically simple and the median Gal-1-P level attained within this cohort indicates good adherence to dietary constraints, we are disappointed to note that the mean full scale IQ score within this group was well within the ranges described previously.6 7 Other authors have indicated that dietary control, as reflected in Gal-1-P concentrations, was a poor indicator of long term cognitive function,4 and we have further confirmed this observation. Although Gal-1-P remains the main indicator of dietary adherence, it has been recently suggested from observations in “knock out mice” that Gal-1-P might not be the only toxic metabolite involved in the pathogenesis of galactosaemic complications2; recent guidelines for the management of galactosaemia emphasise the limitations of Gal-1-P measurements for determining and influencing outcome.5

In 1993, Elsas et al suggested that being homoallelic for the Q188R mutation conferred a poorer prognosis for eventual IQ than being heteroallelic,5 although this was refuted by two later studies.10 11 We now provide further evidence for a putative genotype/phenotype effect, as children homoallelic for Q188R invariably have poor IQ results. Certainly, individuals homoallelic for Q188R show undetectable erythrocyte GALT activity, and in vitro expression analysis has confirmed a substantial or complete loss of GALT activity.12 15 The original postulation of Elsas et al requires further refinement given the large number of mutations now identified (approx. 150) in the GALT gene. Some mutations (splice site, frame shift deletions or insertions, and nonsense) in the homoallelic state or in association with a Q188R mutation would be expected to produce a severe biochemical phenotype and clinical outcome.14 In addition other mutations, namely K285N and L195P are associated with a complete loss of GALT activity and have been suggested to result in a more severe phenotype.15 16 Interestingly, although too small in number for statistical evaluation, this study gives an impression that those with a Q188R/L195P and possibly the Q188R/K285N configuration also have a poor outcome in terms of IQ consistent with these observations.

Attempts to define influences on outcome for children with galactosaemia are hampered by the rarity of the disease process and therefore the geographical spread of cases. In addition the condition seems to be particularly common in travelling families, where the gene frequency may be high relative to the general UK population. Nonetheless the progressive cognitive, speech, and educational problems in children with this condition require prospective evaluation using validated and reliable measures to determine how they may be ameliorated, if at all. Our observation of the relationship with genotype has face validity, given the background laboratory work. The detailed determination of genotype may provide a way in which groups at risk for poorer outcome may be identified and studied.
A controversial expert witness

No paediatrician relishes giving evidence to a court when it is alleged that a child’s injuries were caused by his or her parent. The task is not made easier on those occasions when the defence argument seems to owe more to wishful thinking than demonstrable fact.

Five years ago, ADC published a “Controversy” paper which discussed a particularly contentious defence argument, that of “temporary brittle bone disease”, the existence of which was frequently championed in court by a particular expert witness.¹

The argument continues: paediatricians who need to further their understanding of the legal position regarding this suggested entity would do well to read a paper published in the March 2000 issue of Family Law.² They might wish to draw the attention of solicitors (attorneys), courts, and social service departments to the paper.

This is apposite to US readers as well as those in the UK because it details a US judge’s forthright comments on evidence offered by the doctor in question as well as those already stated in a UK judgement.³

3 Re AB (Child Abuse: Expert Witnesses) 1995; 1 FLR181.
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