J Med Genet 1993; 30: 262–264

LETTERS TO THE EDITOR

Aphasia, deafness, or mental retardation

Wilson *et al*[1] reported a new type of X linked mental retardation with 'striking aphasia' and other anomalies. I cannot find 'aphasia' indexed in three major databases.[2–4] In contrast, mental retardation occurs in 666 syndromes and deafness in 292.[4] A priori, therefore, the probability of language retardation being the result of aphasia rather than these two commoner conditions is remote. In order to establish a precedent for the use of 'aphasia' as a titular keyword, or when postulating a speech gene, it is all the more important to ensure that there is not the slightest hint of mental retardation or deafness. This was certainly not so in the cases reported.

I suspect that developmental aphasia is a rare variant of particular types of deafness. I suggested that the term 'developmental aphasia' be dropped unless peripheral ear disorders, including otitis media, can be excluded.[5] It is therefore ironic that all three cases had frequent respiratory infections, two having chronic or recurrent otitis. As for their hearing, it was not mentioned in case 1, and was said to be 'normal', at least in adolescence, in cases 2 and 3. Such cryptic information is virtually useless. To show the absence of a peripheral hearing defect a basic minimum protocol includes: (1) consistently normal pure tone audiometry, especially at high tones; (2) normal tympanometry and acoustic reflexes; and (3) no evidence that the above tests were abnormal earlier in life. This would certainly not have been true for the cases with otitis.

Even if these three criteria were fulfilled, it is still possible that unusual peripheral defects (for example, retrocochlear deafness) could be missed. It may not, of course, be easy or convenient to test such children. Nevertheless, no conclusions about rare or esoteric causes of speech or language defects can be drawn until any straightforward peripheral auditory dysfunction has been excluded.

Case 2 was said to be 'autistic'. Although autism has been associated with various syndromes (for example, rubella), most, if not all, of these syndromes also cause deafness,[6] which may in turn cause the autism.[7] Hence, like aphasia, there may be no justification for including autism in the title of another syndrome.

Another requirement for the diagnosis of aphasia is that the speech and language retardation is far below the general intellectual level, especially non-verbal IQ. Cases 2 and 3 were stated to have IQs of below 30 and 40, with no mention of which tests were used, or even if verbal or non-verbal. Verbally loaded tests like the Stanford-Binet are worse than useless since a specific verbal IQ deficit is confounded with overall low IQ. Case 1 at 3 years was said to have a developmental level of about 16 months with a vocabulary of five to 10 words. This sounds as if a standard developmental test was given, but there were no further details. To show aphasia, the language scale needs to be much lower than the other scales, otherwise aphasia and mental retardation are again confounded. Another X linked disorder was originally described as 'mental retardation-aphasia-shuffling gait-adducted thumbs, but aphasia was later reclassified as speech delay[4] or abnormality.[2] This is not surprising given that the index case[8] actually had higher verbal than non-verbal IQ (Stanford-Binet IQ 55, Raven IQ 41); hearing was not tested ('hearing appears to be grossly intact').

In view of general ignorance over the origin of language delay it is all the more important to distinguish the three rival causes, mental retardation, aphasia, and deafness. If clinical data, no matter how carefully collected, are reported in a muddled way that confounds these three causes, then readers may conclude that these distinctions are irrelevant.

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This letter was shown to Professor Wilson, who replies as follows.

Dr Gordon's argument that deafness is the explanation of 'aphasia' in our family with X linked mental retardation (XLMR)[1] is difficult to refute. Although all three of our affected males had 'normal' audiometry testing at the time of their initial evaluations for developmental delay, the actual audiograms and their timing regarding the history of chronic otitis media in two boys were not available for our review. It seems likely that significant hearing defects would have been noted by the parents or school/institutional personnel, but it is certainly true that sophisticated evaluation of hearing is worthwhile in those XLMR disorders where abnormal speech has been noted.

We used the term 'aphasia' in our title to emphasise our clinical impression that there was a dissociation between the degree of speech problems and cognition.[2–6] This was particularly evident in the older male who had a large sign language vocabulary—perhaps 'expressive aphasia' would have been a better term. I disagree strongly with Dr Gordon's opinion that mental retardation should be accepted as the cause of speech delay based on the use of keywords in databases. A long and current battle in the US concerns separation of mental retardation into specific causal entities, many with distinctive behavioural and neuropsychiatric phenotypes. One particularly instructive example is Williams syndrome in which chronic otitis media, hyperacusis, and a dissociation between language and cognitive function have all been noted.[3,4] Such disorders will guide us to the genes that account for male predominance and familial aggregation in language impairment.[5,6]

Progress in the delineation of XLMR has been remarkable over the past decade and it would seem negligent not to mention abnormal speech when it is striking to the clinical observer. Many of these observations may not hold up, as suggested by Paul *et al*[2] when they performed language assessments of fragile X syndrome adults in a blind fashion with controls having comparable degrees of mental retardation. Although the numbers of patients were small, their lack of discrimination contrasted with many clinical reports of specific language abnormalities in fragile X syndrome. The speech abnormalities mentioned in six other XLMR disorders[1] may also prove non-specific, but are worth pursuing in view of the open road to gene characterisation. Supporting Dr Gordon's view that abnormal speech in XLMR reflects either deafness or mental retardation is the conservation of human X chromosomes when compared to those of non-human primates with limited speech capacity. On the other hand, unusual evolutionary variation of a gene responsible for XLMR and abnormal speech might help explain our remarkable linguistic facility.

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Sex differences in the location of a spina bifida lesion

Three studies have shown that in patients with spina bifida the ratio of males to females is greater if the lesion includes only the lumbar or sacral region than if it includes the thoracic, cervical, or occipital spine.[1–4] A fourth study appeared to confirm this[5] but on further analysis[6] this was not found to be the case (J G Hall, personal communication). We sought to clarify the effect using data from Oxford.

Two series were studied: (1) derived from a survey of spina bifida births in 1965 to 1972

to women normally resident in Oxfordshire[7] and (2) spina bifida births and terminations of pregnancy in 1973 to 1987 among women booking for their antenatal care at the John Radcliffe Maternity Hospital, Oxford. Information on the site of the lesion was available from hospital records and necropsy reports on 184 cases of spina bifida in the earlier series and 103 in the later series. The sex ratio was 0·67 (49/73) in cases of spina bifida confined to the lumbar or sacral region and 0·54 (58/107) in those with higher lesions, but this difference was not statistically significant ($p = 0·18$, one tail test).

The table summarises the results from the four published studies on the subject, our own data, and two other studies[8,9] of spina bifida where information on fetal sex and spinal location was not included in the original publication but has been provided to us by the authors. Using standard methods to combine the results from all seven studies yielded an overall statistically significant increase in sex ratio among those with low lesions (Mantel-Haenszel, $p < 0·01$). Because there is considerable heterogeneity between the studies in both the overall sex ratio and in the proportion of low lesions, it is not possible to estimate reliably the magnitude of the effect. The between study differences in proportion of low lesions are probably related to the accuracy with which the site of the lesion was determined. If x ray or necropsy examination were used the lesion may be found to be more extensive than on clinical examination. The between study differences in sex ratio are likely to be the result of chance.

Following the original observation of sex differences in the spinal location, explanations have been suggested which relate to the fact that the neural tube is formed by neural folding in a craniocaudal direction followed by canalisation in the sacrum. If female fetuses are less developed at a specific gestational age because on average they are conceived later in the cycle, they may be more susceptible to higher lesions from a gestation specific insult.[10] In the curly tail mouse, female embryos are growth retarded at the time of neurulation[1] and this may, by changing the rate of neural tissue growth, affect neural folding and canalisation in different ways.[5,11]

Whatever the explanation, information on the site of the lesion now needs to be included in epidemiological studies of spina bifida which are aimed at elucidating the aetiology of this disorder.

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*Sex ratio (male/female) according to spina bifida location in seven studies.**

Study	Low lesions	High lesions
London[1,2]	3·00 (15/5)	0·42 (10/24)
Madrid[3]	1·26 (110/87)	0·67 (2/3)
Glasgow[4]	1·67 (10/6)	0·21 (5/24)
Vancouver[5]	0·76 (95/125)	0·86 (37/43)
Cambridge[8]†	0·94 (32/34)	0·55 (18/33)
Grand Rapids[9]‡	0·96 (76/79)	0·66 (21/32)
Present study	0·67 (49/73)	0·54 (58/107)

* A 'high' lesion is defined as one including the thoracic, cervical, or occipital region; a 'low' lesion is below this.
† When the sensory, rather than cutaneous, level is used they are 1·53 (23/15) for below L3 and 0·57 (27/47) for higher lesions. Five were unclassifiable because of widely asymmetrical levels (G M Hunt, personal communication).
‡ H V Toriello, personal communication.

BOOK REVIEWS

All titles reviewed here are available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add 15% to the value of the order for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (Mastercard, Visa, or American Express) stating card number, expiry date, and full name.

Molecular Genetic Medicine. Volume 2. Ed T Friedman. (Pp 233; $55.00.) New York: Academic Press. 1992.

In my (favourable) review of the first volume of this new book series (*J Med Genet* 1992;**29**:519), I made a plea for more articles about the practical applications of molecular genetic medicine. I was pleased to find that volume 2 adequately answers this need.

There is a great art (which means that a little luck is needed) to choosing appropriate topics for a review series such as this. For instance, the article on the fragile X syndrome (Brown and Jenkins) would have been a damp squib had it appeared in volume 1. Fortunately, the unstable CGG mutation was described just in time: it provides a dramatic finale to a good review of the events leading up to its discovery. Naturally, one would look elsewhere to find out the latest news on genotype/phenotype correlation, but attempts by series such as this to describe the up to the minute situation can easily backfire. This is illustrated by the less successful article 'The impact of molecular biology on the diagnosis and treatment of hemoglobin disorders' (Berg and Schechter). The first half is a standard summary of globin mutations, which can be found elsewhere. The second half launches into locus control regions, globin switching, transcriptional factors, and—confusion. The story will have changed by next year, and those who need to be bang up to date will be better served by following the original publications.

Three of the other five articles will be of particular interest to the geneticist. I was surprised to learn from 'The molecular genetics of Down syndrome' (Holtzman and Epstein) that expression levels of some chromosome 21 genes in this condition are greater than normal by more than the predicted factor of 1·5. Such deregulation of expression dosage may be important in the pathogenesis of the condition. 'Mammalian X chromosome inactivation' (Gartler *et al*) is a scholarly review that summarises basic biological knowledge of the process. The candidate gene for the X inactivation centre (XIST) is not described in detail, a sensible decision as its significance is still unclear. However, of all the articles, I found 'Molecular analysis of mutation in the human gene for HPRT' (Lambert *et al*) the most interesting, probably because of my previous ignorance of the subject. The existence of both positive and negative HPRT selection systems, together with PCR/sequencing technology, make possible the rapid characterisation and comparison of HPRT mutations in both the germline and the soma, currently a unique situation, with important lessons for mutation detection of other genes, oncology, and gerontology. In fact the mutational spectrum in different contexts is generally remarkably uniform, 10 to 15% being gross deletions. A notable exception is that neonatal cord blood T cell mutants comprise 85% deletions: speculatively, this may be related to the massive recombinase mediated somatic gene rearrangements that take place during thymic differentiation of T lymphocytes.

The final two articles 'Hepatitis B virus biology and pathogenesis' (Chisari) and 'Regulatory genes of human immunodeficiency viruses' (Wong-Staal and Haseltine) are no doubt good too. I have to admit that virology became too complicated for me some time ago, and I did not read them in detail.

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Genome Analysis: Genes and Phenotypes. Volume 3. Ed Kay E Davies, Shirley M Tilghman. (Pp 174; $40.00.) New York: Cold Spring Harbor Laboratory Press. 1992.

Genes and Phenotypes presents a rather forbidding title to what is, in fact, a very user