Aphasia, deafness, or mental retardation

Wilson et al.\(^1\) reported a new type of X linked mental retardation with 'striking aphasia' and deafness. I cannot find 'aphasia' indexed in three major databases.\(^2,3\) 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 carefully ruled out.

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 diagnosis was given, but there are 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\(^8\) or abnormality.\(^9\) This is not surprising given that the index case\(^\ast\) 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 'developmental aphasia' 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.

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)\(^{10}\) 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, it is possible that their 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 reported.

We used the term 'aphasia' in our title to emphasize our clinical impression that there was a dissociation between the degree of speech problems and cognition.\(^{11}\) 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 distinct 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.\(^{12}\) Such disorders will guide us to the genes that account for male predominance and familial aggregation in language development.

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.\(^{13}\) 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\(^{14}\) may also prove non-specific, but are worth pursuing in view of the open road to gene characterisation. Supporting our 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, or the lumbosacral junction, than if it includes the thoracic, cervical, or occipital spine.\(^{12}\) A fourth study appeared to confirm this\(^1\) but on further analysis\(^2\) 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\(^2\) 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 later 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\(^3,4\) 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 cranio-caudal 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.\(^5\) In the curiously tall male, female embryos are growth retarded at the time of neurulation\(^6\) and this may, by changing the rate of neural tissue growth, affect neural folding and canalisation in different ways.

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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\(^5\) Hall JL. Neural tube defects, sex ratios, and X inactivation. Lancet 1986;i:8134.


**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.


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 of this importance, the article on the fragile X syndrome (Brown and Jenkins) would have been a dandy squib had it appeared in volume 1. Fortunately, the unstable CGG mutation was described just in time for it to appear in 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 correlations, but this is not sad news. It is a reassuring reminder that the order for molecular genetics is being placed in the right hands. For me, the future looks bright.

ANDREW WILKIE


*Genes and Phenotypes* presents a rather forbidding title to what is, in fact, a very user-friendly introduction to the subject. This volume is a first step and places emphasis on the genetic control of development. It does not attempt to cover the whole field of molecular medicine, but focuses on the human genome. It does an excellent job at covering the basics and putting it into a historical perspective. N. J. Wald, University of Edinburgh.