Imprinting and Angelman’s syndrome

The revision of the conclusions of two recent reports of Angelman’s syndrome\(^1\) by Professor Hall\(^3\) is correct in pointing out the consistency of the observations with those expected owing to genetic imprinting. However, the importance of the results is underestimated even in this revision. The essential observation made was that the maternal transmission of pericentric inversions of chromosome 15 (inv(15)(p11q13)) resulted in offspring with Angelman’s syndrome, while the mothers carrying the inversion were unaffected. Whereas the authors of the original reports postulated that the inversion ‘unmasked’ a recessive gene for the condition transmitted by the father, the role of imprinting in this parentally determined susceptibility was highlighted by Professor Hall, who predicted that the mothers would have to have inherited the rearrangement from their fathers to be unaffected. On first appraisal, this conclusion contradicts what is known about imprinting on chromosome 15, that the area deleted to yield Angelman’s syndrome or Prader-Willi syndrome is identical, not only in cytogenetic (15q11–13)\(^4\) but also in molecular terms,\(^5\) dependent only on the parent of origin of the deleted chromosome (AS maternal, PWS paternal). If this were true, then the paternal inheritance of the rearrangement by the probands’ mothers in these cases should have resulted in maternal Prader-Willi syndrome.

The pathological effect of imprinting apparently results from the production of nullisomy at a locus when a genetic event removes a functioning allele, the homologue of which has been rendered inactive owing to the imprinting process.\(^6\) In the 15q11–13 region, several (a minimum of two) such loci must exist, inactive alleles occurring on both paternal and maternal chromosomes, in order to produce the discrete phenotypes. The pericentric inversions should be interpreted in this light, while adhering to the assumption implicit in the previous assessments: that, as the mothers express the rearrangement in a non-mosaic manner in their somatic cells, they probably inherited the inversion. Firstly, if the inverted segment has led to incapacitation of the 15q11–13 region, and as it is being inferred that the individual loci giving rise to Prader-Willi and Angelman’s syndromes are distinct, it may be concluded that the locus (loci) for the former is located more distally, beyond the breakpoints in these cases. If there is indeed a submicroscopic deletion associated with the inversion, then the status of the rearranged segment is crucial. If the rearranged segment is not inactivated, which would be more consistent with viability, then the pathological consequences are mostly attributable to the deletion. In this case, the locus (loci) for Angelman’s syndrome are within the deleted segment, and the Prader-Willi locus (loci) may be proximal or distal to this. Furthermore, the rearrangement could indeed be inherited from grandparents. It is also possible that further genetic events have taken place in the Angelman patients. The final possibility is that the other cases in fact have loci nullisomic owing to imprinting, but that the deletion is sufficiently small that compensatory mechanisms to prevent the development of Prader-Willi syndrome are effective.

Whatever the molecular event, the main conclusion which may be drawn is that, apart from the last possibility, these cases confirm the independence of the Prader-Willi and Angelman loci, suggest that if multiple loci govern Angelman’s syndrome they are within a relatively restricted stretch of DNA uninterrupted by Prader-Willi loci, and confirm the importance of imprinting in the region. In short, the loci for Prader-Willi and Angelman’s syndromes may be distinguishable using the DNA of these patients, and the chromosomal status of the maternal grandparents must be ascertained, a point stressed by Professor Hall.

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5 Donlon TA. Similar molecular deletions on chromosome 15q11.2 are encountered in both the Prader-Willi and Angelman syndromes. Hum Genet 1988;80:322–8.

Clinical geneticists frequently receive enquiries from colleagues, particularly in obstetrics, about the possible teratogenic risk to the unborn child of chemical and physical agents in a pregnancy. The editor and a number of the contributors to this multi-author text have established centres with a multidiscipline team for enquiries of this nature, many of which come directly from the couples/women concerned. This text is said to be a result of the new approaches and clinical tools which developed.

The book is divided into four main sections covering Drugs in pregnancy, Poisoning and radiation in pregnancy, Genetic and obstetric considerations, and the Organization and operation of teratogenic information services.

Particularly well written and succinct are the chapters on Ionizing and nonionizing (sic) radiation in pregnancy and Genetic aspects, which covers clinical genetics and genetic counselling.

One of the interesting aspects of the text is the chapter on Nonmedical drug and chemical use in pregnancy. The inclusion of this as a separate topic reflects the frequency of enquiries of this nature by the clientele. The rarity of such enquiries from personal experience in the United Kingdom probably reflects a difference in attitude rather than the magnitude of the problem.

One chapter, Teratogenic information sources, reviews in some detail other textbooks on reference sources including computer databases, an unusual practice for a textbook.

One of the important points mentioned in the introduction of many of the chapters, but explored in detail in the chapter The way women perceive teratogenic risk, is the fact that many women overestimate the degree of risk with the majority of teratogenic exposures in utero.

There are, I am afraid, a few criticisms. Having read the text through rather than 'dipping into it' at random, there is repetition of material, both in the introductions of the various chapters, as well as in the topics covered in the individual chapters, something that editors of multi-author texts should be wary of.

The index does not cross reference items and topics in enough detail. For example, if one wanted to look up epilepsy and anticonvulsants, these are covered in numerous sections of the book, but one is required to look up the individual anticonvulsants one by one to find the relevant material. The use of a hierarchical index with highlighting in the main section would have been helpful.

The text also suffers from being parochially North American in its terminology and listing of centres with experience and interest in this topic. In addition, while the reader can usually get the sense of what the authors are attempting to convey, on many occasions this requires the ability to understand what might be politely called 'neologisms' or more correctly 'North Americanisms'.

While this book might well appeal to obstetricians, paediatricians, and clinical geneticists who deal with enquiries of this nature, I am afraid the drawbacks outlined, when the cost is taken into account, might not make it a first choice for the reference bookshelf. For that price, I would expect the last word!

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