LEADING ARTICLE

DOWN'S SYNDROME — Factors Influencing Its Incidence

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Down's Syndrome caused by trisomy of chromosome 21 is the best recognized and most frequent human chromosomal syndrome; accounting for 15-25% of severely mentally handicapped children of school age. "Regular" trisomy comprises some 95% of cases of Down's Syndrome. Approximately 1% of cases are mosaics (this estimate is minimum since some mosaics probably remain undetected, particularly among phenotypically normal parents of trisomic offsprings); the remainder are the result of translocation.

Parental and Meiotic Origin of the Extra Chromosome 21

Chromosomal trisomy in Down's Syndrome is most frequently the result of non-disjunction of chromosomes 21 during meiotic divisions in gametogenesis. It may occur during the first meiotic division - as a failure of homologous chromosomes to separate - or during the second division - as a failure in separation of chromatids. As a result of the introduction of banding techniques, chromosomes 21 were often found to show polymorphism in such features as the size of the satellites, the stalks of the satellites, and of the centromeric region. It was therefore possible to determine the parental origin and meiotic origin of the extra chromsome in most cases. Mikkelsen(1) found that in about 80% of the cases, the origin of the extra chromosome was maternal and, in the remaining 20% of the cases, paternal. As regards the tracing of the meiotic division in which non-disjunction occurred, it was more frequent in the first meiotic division, particularly in the mothers, less so in the fathers; the proportions of the first to second division for mothers and for fathers were 4:1 and 2:1 respectively. Furthermore, the proportion of males to the total number of cases was found to be dependent on whether non-disjunction was maternal or paternal. If it was maternal, the ratio was 0.55; if paternal, 0.43.

Maternal Age and Incidence at Birth

The incidence of Down's Syndrome in the general population as quoted in most countries is of the order of 1 in 600-800 LIVE-BIRTHS. Penrose(2) established that the risk of having a Down's Syndrome child increased with the MOTHER'S AGE, and this forms the basis for prenatal screening. Data from a New York State Study(3) showed that the frequency of 21-trisomic children rose from a low of 1 in 1925 births among mothers aged 20 years to a high of 1 in 110 in women aged 40 years. The estimated rates of Down's Syndrome were 1/1205 at maternal age of 25; 1/885 at 30; 1/365 at 35; and 1/32 by the age of 45 years. The risk figures increased exponentially from 35 years onwards by almost threefold every 5 years.

The basis for the correlation between late maternal age and non-disjunction remains unresolved. It has long been thought that the maternal age effect on non-disjunction may be due to some aspect of ageing effect on the ovum. An important distinction between oogenesis and spermatogenesis relates to the timing of meiosis in the life of the subject. Oogenesis begins in late foetal life of the female or at about the time of her birth. The process is arrested, however, before the first meiotic division is completed. By or before the end of her foetal life, all the ova that a female is ever going to have are already produced and have reached this stage of meiosis (the dictyotene). They remain in this stage until puberty, and from puberty onwards will ripen at the rate of one a month (or more in multiple pregnancies) until the menopause. The consequence of this arrangement is that the later in a woman's life that an ovum is fertilised, the longer that ovum has remained, in a sense, 'frozen'. Consequently, the ovum fertilised in a woman of 40 is 20 years older than one fertilised in a woman of 20. It may be assumed that the retention of the primary oocyte in the resting stage of the first meiotic division for so long is directly connected with what is known as the maternal age effect. The longer the period of the resting stage, the higher is the risk of exposure to deleterious factors, which may cause damage to those mechanisms of the cells which control regular separation of chromosomes in a dividing cell. Hormones, an endogenous factor, may also play a role in non-disjunction. A variety of hormones influence oocyte maturation. The increased risk of chromosomal aberrations in older women may be connected with less efficient hormonal control as a woman approaches climacterium. No maternal age effect was ever found in transmitted translocation trisomies and mosaics. Most chromosomal mosaics arise as a result of post-fertilization mitotic non-disjunction and so the lack of a maternal age effect is not surprising.

Incidence at Amniocentesis

It is important to note that the above rates relate only to the incidence of Down's Syndrome AT BIRTH, but not the true incidence AT CONCEPTION. The most extensive data available on maternal age specific rates for Down's and other chromosomal syndromes comes from the European Collaborative Study(4). The results of prenatal diagnosis in 52,965 pregnancies were collected in which foetal chromosome analysis by amniocentesis was undertaken because the mother was 35 years of age or over. 1,200 foetal chromosome aberrations were detected including 613 cases of trisomy-21 Down's Syndrome (51% of total abnormalities). The maternal-age-specific rates for Down's Syndrome at amniocentesis increased from 1 in 256 at age 35 to 1 in 75 at age 40, and 1 in 23 at age 45. The rates for all chromosome aberrations increased from 1

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in 82 at age 35 and peaked at 1 in 10 at age 47. The form of the exponential increase in rates as a function of maternal age is similar in the 5 major chromosomal sydnromes, namely trisomies 21, 13 and 15, XXY Klinefelter's Syndrome and the triple-X Syndrome, implying the same maternal age contribution to the occurrence of non-disjunction in each. 2 similar studies in USA had produced comparable risk figures(5,6). Obviously, for the purpose of genetic counselling, parents should be given the risk figures both at birth and at amniocentesis, and not only of trisomy 21 but of all chromosomal aberrations.

Spontaneous Abortions and Foetal losses

While these results AT AMNIOCENTESIS confirm the value of offering prenatal diagnosis to older mothers, it is also obvious that the rates of abnormality for the most severe aberrations are substantially higher than those to be expected AT DELIVERY. Foetuses with extensive chromosomal defects tend to abort before amniocentesis. Cytogenetic surveys of early abortuses show that the overall contribution of chromosomal abnormalities among spontaneous abortions is as high as 50-60%(7,8). Trisomy 21 itself accounts for 3% of all abortions(9). Some affected pregnancies will be lost by abortion or stillbirth between the time of amniocentesis and delivery. For Down's Syndrome the rate at birth is about 30% less than the rate at amniocentesis and for trisomies 13 and 18 the reduction is estimated to be 43% and 68% respectively(10). Thus, one should realize that live-born children with chromosomal aberrations constitute only the tip of the iceberg of chromosomally abnormal conceptuses, since chromosomal aberrations, in the overwhelming majority of cases, are not compatible with life. Tissue cultures established from abortuses with trisomy 21 have shown decreased rate of growth and multiplication of cells(9). This apparently arises from disturbances in the development of the placenta, which in cases of trisomy 21 reveals growth retardation and hypoplasia. Thus, impairment of the placenta may be a direct cause of spontaneous abortion and foetal death. Trisomy 21 is compatible with life apparently because it involves the smallest autosome in the human karyotype, carrying a relatively small amount of genetic material. In spite of that, a substantial proportion of trisomy 21 conceptuses (80%) fail to survive(9).

Genetic Fitness

NATURAL SELECTION also operates postnatally. The main reason why in Down's Syndrome there is an overwhelming majority of isolated (rather than familial) cases is due to the fact that the condition involves an almost complete reduction of genetic fitness, the fertility of affected individuals being near to zero. Otherwise, the incidence of Down's Syndrome would be much higher. If a person with trisomy 21 were able to produce offspring, the theoretical risk of that offspring being affected would be as high as 1 : 2.

Paternal Age Effect ?

The problem of relative effect of paternal and maternal age was studied by Penrose(11) and Jenkins(12). Both came to the conclusion that only maternal age was of importance, paternal age being of no significance. However, recent studies have shown that in about 20% of cases, the non-disjunction of chromosome 21 occurred in the father. This has reawakened interest in the possibility that increasing PATERNAL AGE may be associated with an increased risk of Down's Syndrome. Based on 60 cases of cases of trisomy 21 from 5,014 pregnancies recorded in the DFG Amniocentesis Register collected in the Federal Republic of Germany, Stene et al. found a significant excess of cases conceived to fathers age 41 years and above, compared to the number expected assuming no paternal age effect(13). This observation could not be confirmed in a similar study from New York State Chromosome Registry based on 98 cases of trisomy 21 in 10,427 pregnancies(14), nor in the European Collaborative Study based on 161 cases in 13,299 pregnancies(4). The results of Stene et al. are likely to be due to statistical fluctuation and small sample size. Paternal origin of the extra chromosome 21 does not imply paternal age dependence. There is no justification for recommending amniocentesis on the basis of increased paternal age alone. This view also fits with the biological circumstances relating to spermatogenesis. Sperms are produced throughout male adult life from puberty onwards. As a result, the sperm of a man of 40 that fertilizes an ovum is of recent production, no older than that of a man of 20. The absence of the equivalent resting stage in the meiotic cycle of spermatogenesis may explain the lack of paternal age effect in contrast to the remarkable maternal age effect. Factors other than age may account for the aneuploidy in which genetic or chromosomal marker studies have implicated paternal meiosis.

Environmental Factors

The probable role of many ENVIRONMENTAL FACTORS, such as X-rays, chemicals and viruses, in causing chromosomal aberrations has not yet been proven in humans. Uchida et al. noticed an increased frequency of Down's Syndrome babies born to mothers exposed to X-ray irradiation(15). However, the incidence of both Down's Syndrome and maternal exposure to diagnostic irradiation of the abdomen correlate with maternal age. Virus-induced disturbance of chromosomal segregation has been suggested to account for the clustering of births of 21-trisomic infants following epidemics of infectious hepatitis(16). A number of studies have shown an increased frequency of chromosomal aberrations in spontaneous abortions of contraceptive pill users(17). Mothers of Down's Syndrome patients had been on contraceptive pills more often than controls(18). The effect may be associated with an increase in the androgen/oestrogen index. This argument could also help to explain the higher incidence of Down's Syndrome babies among older women since the production of oestrogen is decreased in older women, and the relative effect of androgens increased. The contraceptive pills may also change the sex ratio in Down's Syndrome. There seems to be an excess of females among children with Down's Syndrome born to mothers who use contrceptive pills, whereas in most other unselected series, more males than females with Down's Syndrome have been registered(19). More effective and efficient treatment of threatened abortion in recent years may interfere with this process of natural selection in the prenatal period. A history of threatened abortion is not a contraindication to amniocentesis but is rather an additional indication that the pregnancy may be at risk of foetal chromosome abnormality. Persistent bleeding in the first trimester occurs in 26% of mothers carrying a trisomic 21 foetus compared with 1% in controls(20).

Prenatal Diagnosis: Problems and Future Strategies

The ultimate aim in reducing the birth incidence of Down's Syndrome and other chromosome aberrations is to identify the causes of chromosomal non-disjunction and develop strategies effective in primary prevention. This possibility seems remote in the foreseeable future, and the only option available is PRENATAL DIAGNOSIS and therapeutic termination of affected pregnancies. Following the discovery in 1966(21) that foetal chromosomes could be made available for analysis through the culture of foetal cells present in amniotic fluid, diagnostic amniocentesis in the second trimester became the most efficient basis for the prevention of Down's Syndrome. For moral, practical, and economic reasons, the selection of patients for amniocentesis must be based on estimates of the empirical risk of producing offsprings with chromosomal

aberrations, taking into account the risk of the procedure itself. From this point of view, pregnant women aged 35 or older are judged to be at sufficiently high risk. Foetal loss attributable to amniocentesis is about 0.3% in units doing at least 100 amniocenteses per year(4).

However, prevention of Down's Syndrome by offering amniocentesis to older women has not been found to be a particularly sensitive screening procedure. Results of foetal chromosome analysis of the West of Scotland Prenatal Diagnostic Service from 1976-81(4) showed that the impact on overall reduction of affected births was below expectation. Only about 25% of mothers 35 years and older had prenatal diagnosis to exclude this serious disorder. A more recent study reports that about 5% of all pregnancies occur in women aged 35 and older and 20% of all Down's Syndrome are found in this age group(22). The use of age alone as a screening test, therefore, excludes the possibility of detecting the 80% of all Down's Syndrome occurring in pregnant women younger than age 35. If the objective is to diagnose 50% of all foetuses with Down's Syndrome, one would have to screen all pregnancies in women above 30. This would be unrealistically expensive and too many pregnancies would be put at procedural risk. More sensitive and specific screening tests are clearly required to complement the existing prenatal diagnostic techniques.

An association between foetal Down's Syndrome and low maternal serum alpha-foetoprotein levels (MSAFP) has been demonstrated(23). More recently, the unconjugated oestriol in maternal sera of Down's Syndrome pregnancies has also been found to be reduced compared with unaffected pregnancies(24). Unconjugated oestriol is said to be independent of maternal age, and largely independent of MASFP, so permitting greater sensitivity. Furthermore, second trimester maternal serum human chorionic gonadotrophin levels in Down's Syndrome pregnancies have been found to be twice normal(25). Ultrasonographic detection of abnormal foetal movement patterns and measurement of foetal femur length have been described as possible screening methods. The reliability of all these screening tests needs further evaluation. These findings suggest that it may be possible to construct a table of risks, incorporating all these features including maternal age, which might be used to select mothers with the greatest risk for prenatal diagnosis. Second-trimester amniocentesis for foetal chromosome analysis may well be replaced in the future by first-trimester chorionic villous biopsy (CVS)(26). It is cheaper and provides much earlier results, and thus in cases of positive diagnosis allows for early termination, which for the patient is much less distressing than late termination following amniocentesis.

If the approach of prenatal screening of pregnancies at high risk of chromosome abnormalities is to become effective, it must receive greater support from obstetricians. What is also needed is a more determined effort to inform the community about the availability of prenatal diagnosis. Adequate facilities for testing pregnancies either by amniocentesis or CVS should be made available. If it is regarded as important to avoid the birth of severely handicapped children with chromosome abnormalities, then prenatal diagnosis should be made more freely available to those who want it.

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Book Review

CLINICAL ELECTROCARDIOGRAPHY

B L Chia
2nd edition 1988 . PG Publishing .

In 1985. Professor Chia sliced through the confusion in the minds of junior doctors who found it difficult to grasp the essentials of electrocardiography by publishing the first edition of his book. There is no doubt about the success of the book which appealed not only to medical students. nurses and junior doctors but also to experts in fields other than cardiology who had a desire to refresh themselves. if not. re-learn. the principles of clinical electrocardiography. And in just three years. the author thought it necessary to review the first edition.

The seven chapters of the book comprising one hundred pages are nicely divided into the normal ECG. Ischaemic heart disease. miscellaneous conditions (where Grusin patterns are mentioned). cardiac arrhythmias. supraventricular arrhythmias. ventricular arrhythmias and the various heart blocks.

Each chapter has very well-illustrated ECGs to try and explain the variations in wave forms. There are also excellent simple line diagrams to highlight the shapes of various complexes. Throughout the chapter but somewhere hidden among the paragraphs are "pearls of wisdom" regarding diagnosis of the various rate. rhythm and morphological changes that accompany physiological and pathological changes of the heart. The book would definitely have enhanced value if these "practice points". as it were. were highlighted in boxes. or at the page margins or collected together at the end of each chapter or formed into a separate chapter on its own.

This book is highly recommended for the clinician's personal bookshelf rather the library.

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SKILLS & MANAGEMENT IN FAMILY MEDICINE

Dr E K Koh, Dr L G Goh and Dr P Kee
1988. PG Publishing

This book should have come onto the local scene much earlier. There is a great deal of practical advice that every doctor can benefit from. No doctor, specialist or otherwise, can afford to treat a patient in isolation away from his family unit.The psychosocial support of relatives is essential and should be properly harnessed by the doctor to benefit his patient in certain vexing situations. Doctors do well to address the brains and hearts of patients and not only their bodies or parts thereof.

The art of Medicine in Singapore, as would be in any other country. is very complex. The multi-religious, multilingual and multicultural context is not always easily understood by locally-trained doctors who in their training were more interested in Medicine as a science, than in the art of the vocation. Certain colloquial terminology in different musical dialects do not have English equivalents, To communicate is essential and two-way communication is ensured only if the language nuances and expressions are fully understood.

There is no doubt that the front-line doctor is all-important in the overall health care system in Singapore. It took a long time before training requirements were realised to be profitable to doctors undertaking such roles. Being left to themselves to find the relevant experience in the hospital system should now be history. Those doctors interested in this vocation of family medicine should receive the proper guidance and training to fit them for the responsibility. They cannot just drift into this position. Neither should they be left in the cold, having sometimes fallen off the specialist-training ladder.

The three authors, all very senior in the profession, have put together a very comprehensive 265-page book that is based on years of general family practice. Each of its 21 chapters is very well-written and easily readable, even at bedtime. There are case illustrations and appropriate quotes at opportune moments, Culture and Medicine is a chapter every doctor should read so that there is a better understanding of the different races as patients. Medical Ethics and the Law too contains good advice to ensure continuing practice.

There are pearls of wisdom to be found throughout the book. Using them would hopefully result in a more satisfying and gratifying practice and more satisfied and grateful patients even if they had to die. All of have to go one day, anyway.

DR CHEE YAM CHENG