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Non congenital heart disease aspects of Down's syndrome

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Abstract

Down's syndrome is the commonest chromosomal anomaly with an incidence of about 1:700 live births, and is often associated with various congenital anomalies. Moreover an appreciable proportion of health problems (immunological, hematological, etc) are frequently associated with this condition, and for this reason affected individuals benefit greatly from multidisciplinary management. Recent research strongly suggests that Down's syndrome is a contiguous gene syndrome, and it is unlikely that a single Down's syndrome chromosomal region is responsible for the typical phenotypic features. This review presents the most important genetic and medical features.

MeSH: Down syndrome

Introduction

Down's syndrome (OMIM 190685) is the commonest chromosomal anomaly with an incidence of about 1:700 live births. It was first described by JL Down[1] in 1866 and includes a phenotype with mental retardation; characteristic facies with oblique eye fissure, epicanthus, flat nasal bridge, protruding tongue (fig 1); short broad hands and wide space between first and second toes (fig 2); hypotonia and other associated congenital anomalies and developmental disorders. This review will only deal with non congenital heart disease aspects.

Genetics

The genetic abnormalities causing Down's syndrome are free trisomy 21 (95%) (figures 4 and 5), unbalanced translocation (4%) between chromosome 21 and other acrocentric chromosomes, most often chromosome 14 or 21 and mosaicism with two cell lines, one normal and one trisomy 21 (1%).

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Figure 1 Frontal (a) and lateral (b) appearance of a patient with Down's syndrome

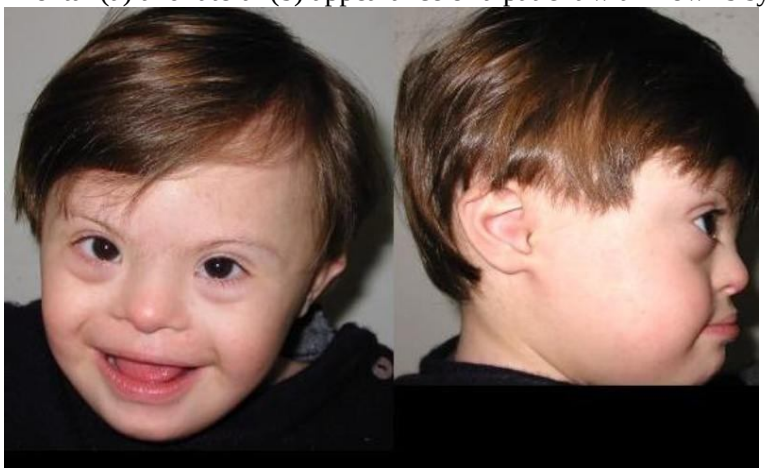

Figure 2 Typical Down's syndrome hand

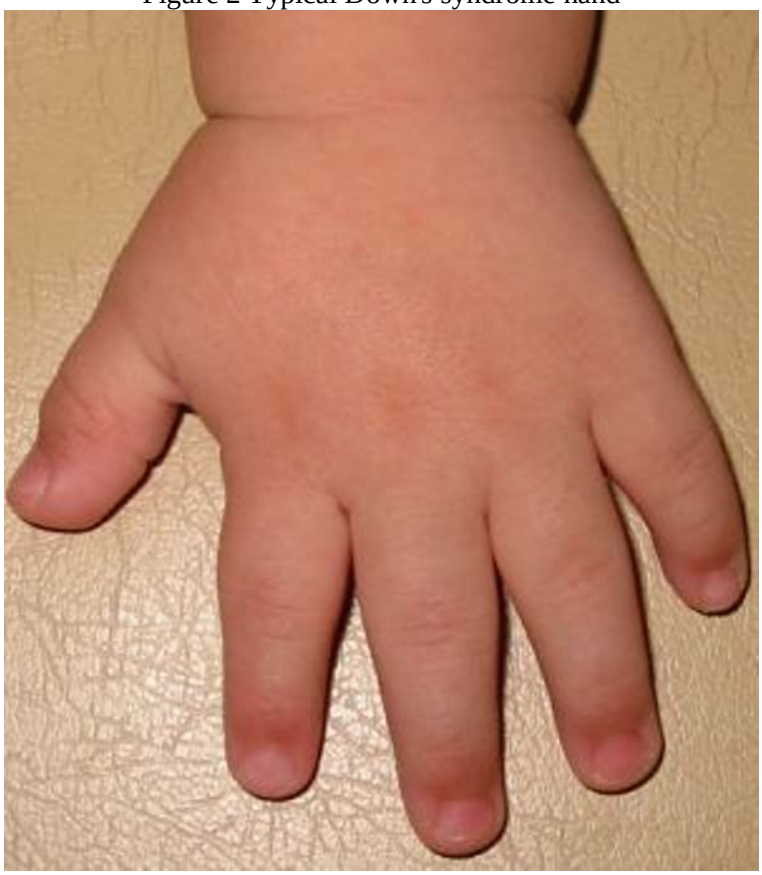

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Figure 3 Typical Down's syndrome foot

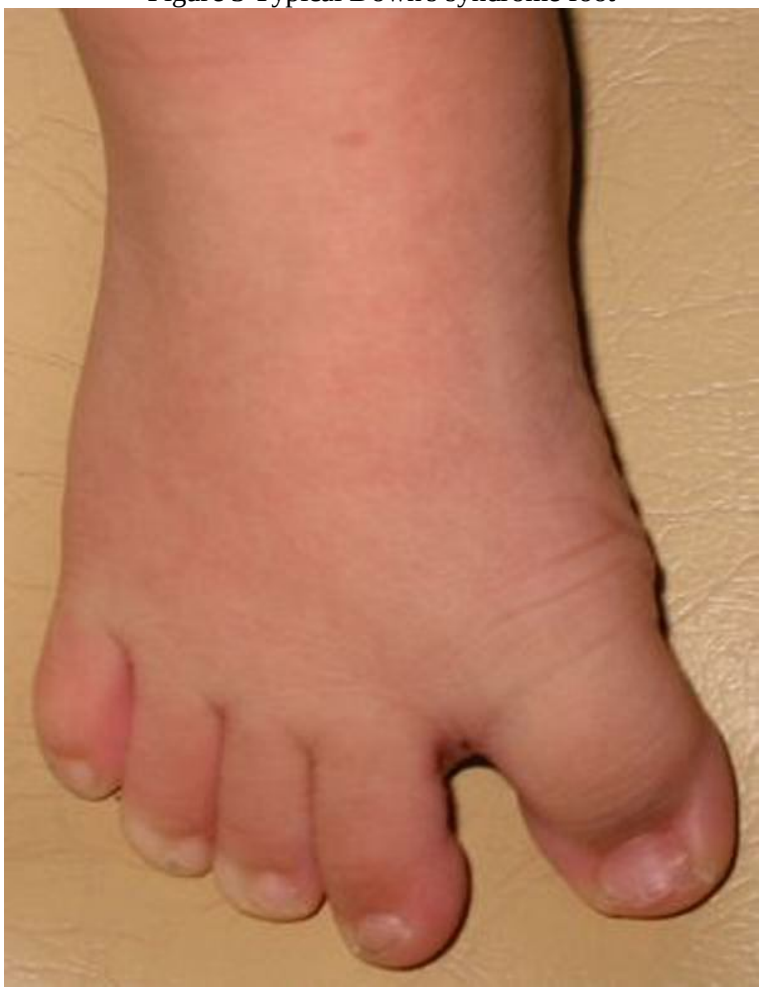


Figure 4 Trisomy 21 classical karyotype

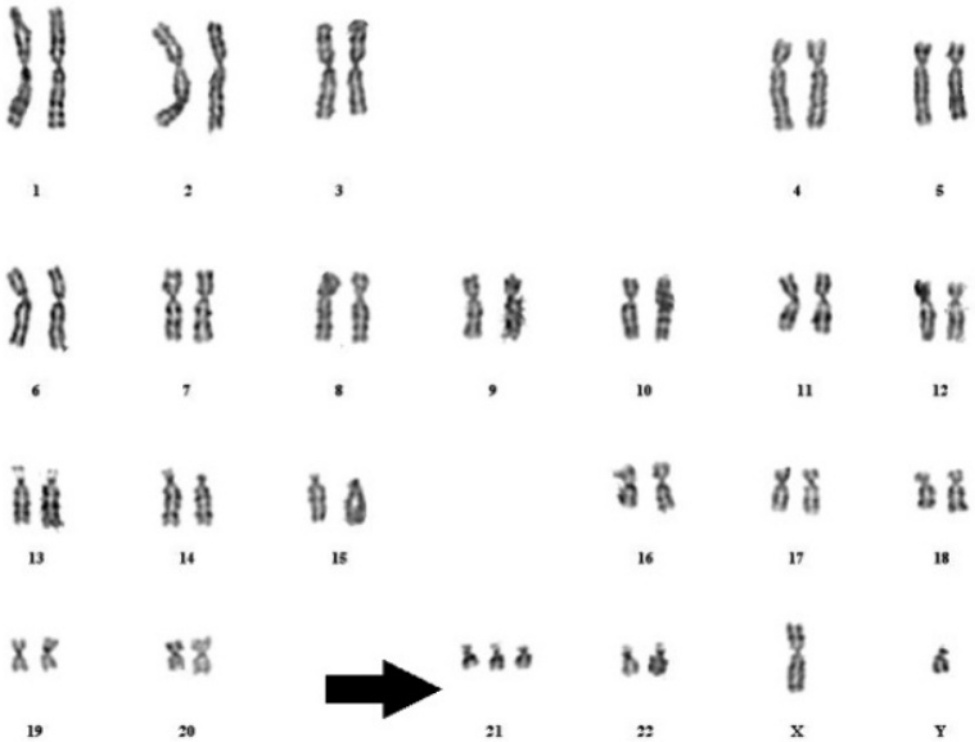
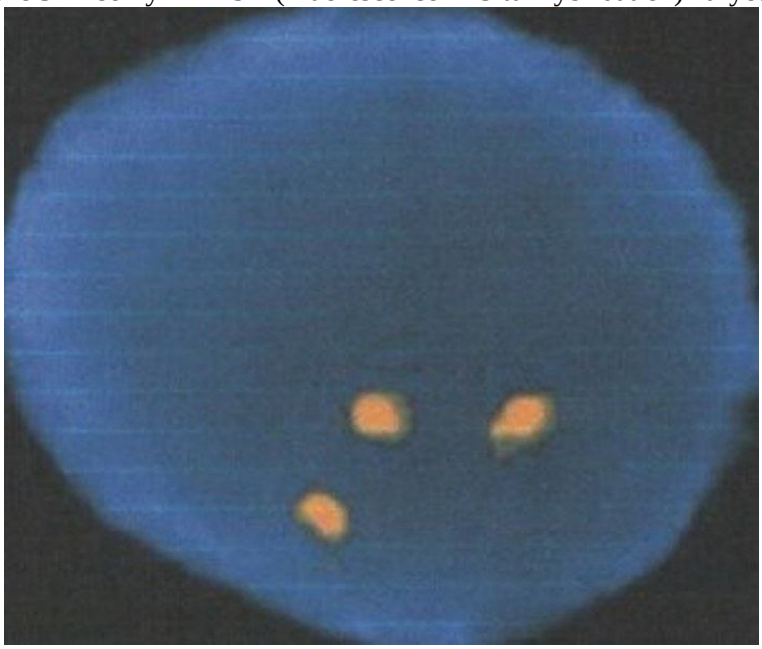


Figure 5 Trisomy 21 FISH (Fluorescence In Situ Hybridation) karyotype



Chromosomal analysis is important in order to exclude translocation as this has implications for genetic counselling since one of the parents may have a balanced translocation.

Origin of free trisomy 21

The availability of highly informative DNA markers has allowed the parental origin of the extra chromosome 21 and the meiotic/mitotic origin to be determined. Some studies[3,4] have been conducted on this topic with these results:

1. Errors in meiosis that lead to trisomy 21 are overwhelmingly of maternal origin; only about 5% occur during spermatogenesis.
2. Most errors in maternal meiosis occur in meiosis I and the mean maternal age associated with these is 32 years. Thus, meiosis I errors account for 76 to 80% of maternal meiotic errors and 67 to 73% of all instances of free trisomy 21.
3. Maternal meiosis II errors constitute 20 to 24% of maternal errors and 18 to 20% of all cases of free trisomy 21. The mean maternal age is also advanced.
4. In rare families in which there is paternal nondisjunction, most of the errors occur in meiosis II. The mean maternal and paternal ages are similar to the mean reproductive age in western societies.
5. In 5% of trisomic individuals, the supernumerary chromosome 21 appears to result from an error in mitosis. In these cases there is no advanced maternal age and there is no preference for which chromosome 21 is duplicated in the mitotic error.

Origin of translocation trisomy 21

It is well know that de novo t(14;21) trisomies have originated in maternal germ cells[5,6]. In de novo t(21;21) Down's syndrome the situation is different: in most cases the t(21;21) is an isochromosome (dup21q) rather than the result of a Robertsonian translocation caused by a fusion between 2 heterologous chromatids. About half were of paternal and half of maternal origin. In the 3 de novo t(21;21) true Robertsonian trisomy 21 cases, the extra chromosome 21 was maternal.[6–8]

Mapping

Detailed analysis of DNA is still under way, but an area of approximately 5 Mb between loci D21S58 and D21S42 has been identified that is associated with mental retardation and most

of the facial features of the syndrome. In particular, a subregion that includes D21S55 and MX1 (interferon-induced protein), the latter being located in band 21q22.3, has been associated with mental retardation and several morphologic features, including oblique eye fissure, epicanthus, flat nasal bridge, protruding tongue, short broad hands, clinodactyly of the fifth finger, gap between first and second toes, hypotonia, short stature, Brushfield spots, and characteristic dermatoglyphics.[9] Additional phenotypic characteristics may map outside the minimum critical region. A "phenotypic map" was constructed[10] that included 25 features and assigned regions of 2 to 20 Mb as likely to contain the genes responsible. This study provided evidence for a significant contribution of genes outside the D21S55 region to the Down's syndrome phenotypes, including the facies, microcephaly, short stature, hypotonia, abnormal dermatoglyphics, and mental retardation. The results strongly suggest that Down's syndrome is a contiguous gene syndrome and make it unlikely that a single Down's syndrome chromosomal region is responsible for most of the Down's syndrome phenotypic features.

Gastrointestinal Anomalies

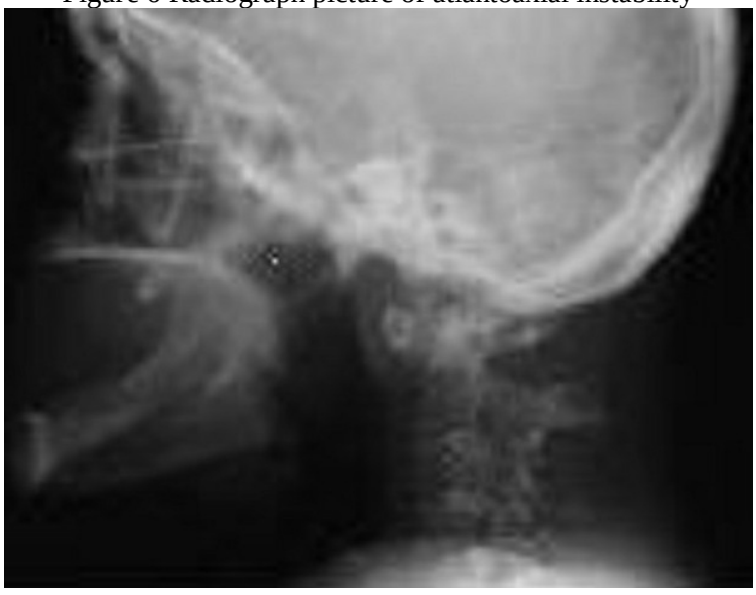
Gastrointestinal anomalies are frequently associated with Down's syndrome (12%) and the more common are duodenal atresia, annular pancreas and Hirschsprung disease. Anorectal anomalies are often associated with Down's syndrome.[12] An high percentage of Down's syndrome subjects may have celiac disease (7-16%) and screening for coeliac disease with antigliadin and antiendomysial antibodies should be performed in all Down's syndrome children after the start of gluten diet.[13] The higher incidence of gastrointestinal problems may be due to anatomical, functional, or nutritional disorders, and may significantly affect the growth and development of Down's syndrome children.

Central Nervous System

Atlantoaxial instability

This is due to increased mobility at the atlantoaxial joint, probably due cervical vertebral or ligaments anomalies. It is recognised in about 15% of cases[14] and is usually asymptomatic and diagnosed by cervical spine radiography (fig 6). Symptomatic instability results from subluxation with injury of the spinal cord and neurological manifestations.

Figure 6 Radiograph picture of atlantoaxial instability



Epilepsy

Epilepsy occurs in about 5-10% of Down's syndrome individuals. The treatment is standard.[15]

Autism

Autism is probably not one single condition, but is instead a common cluster of symptoms, with a number of different causes. Some children with Down's syndrome may meet the criteria for autism. The differential diagnosis is important and indeed, many signs are part of syndrome and not due to autism.

Alzheimer's disease

Alzheimer disease is a condition that affects older people with or without Down's syndrome. Down's syndrome is associated with early onset Alzheimer's disease, and one type of brain change linked to Alzheimer's disease, brain plaques, are associated with abnormalities in a gene on chromosome 21.

Immune System

Some children with Down's syndrome have immune system disorders which, if not treated, can lead to serious chronic illness and poor health. Because these children are at higher risk for chronic hepatitis, the hepatitis B immunization is recommended along with the standard immunisation protocols.[16] Moreover the immune system in children with Down's syndrome matures more slowly, predisposing to a higher incidence of upper respiratory tract infections.

Endocrine Related Problems

Thyroid disease

The most common endocrine disorder in people with Down's syndrome concerns the thyroid gland. About 15% of these individuals have problems of hypo or hyper thyroidism.[17] The reason for this is uncertain but is believed to be related to the propensity of these individuals to develop autoantibodies.

Diabetes

The prevalence of insulin-dependent diabetes mellitus in Down's syndrome patients is higher than in the general population. This has been lifestyle related but may also be autoantibody mediated.

Stature

Many children with chromosomal disorders, including Down's syndrome , have small stature. Special growth charts have been developed for children with Down's syndrome . Treating children with Down's syndrome with human growth hormone is controversial, both for stature benefits and for possible risks accompanying growth hormone therapy.

Reproductive problems

Down's syndrome male are usually not fertile and this is probably due to low testosterone levels. In female, ovarian dysfunction is probably responsible for the fertility problems with additional involvement of the hypothalamic-pituitary-ovarian-adrenal axis.[18]

Eye Anomalies

Individuals with Down's syndrome have a higher incidence of functional and structural abnormalities of the eyes. Several ocular anomalies have no functional significance (e.g. Brushfield's spots, epicanthal folds, etc), but there are some important anomalies (e.g.

congenital glaucoma, cataracts, nystagmus, refractive errors, etc) that have important functional and therapeutic significance.[19] Myopia is found in 30% of school aged children, strabismus in 27% and cataracts in 15%.[20]

Skin Conditions

There are no disorders of the skin or nails that occur only in people with Down's syndrome, however several conditions are more common than in general population. Some morphological conditions, such as loose skin at the back of the neck, fissured tongue, and changes in skin color due to cutis marmorata and acrocyanosis, may be seen in infants. Others, such as fungal infections, seborrheic dermatitis, cheilitis, and so on are common problems that can be easily identified and treated. Less common conditions, including alopecia areata, vitiligo and severe atopic dermatitis are described.

Ear, Nose and Throat

Children with Down's syndrome have a higher incidence of chronic otitis media than other children, with more anatomic anomalies of the eustachian tube.[21] This is shaped differently and collapses more easily. These individuals may also have external ear canal stenosis, which causes hearing loss by collapse of the canal and by cerumen that obstructs more easily. The reported incidence[22] of hearing loss is between 38-78% but an aggressive approach can greatly diminish this value.[21] Many children with Down's syndrome have also enlarged tonsils and adenoids and the surgical approach to this problem is controversial.

Orthopaedic Problems

There are certain characteristics of the muscles and bones of Down's syndrome children that contribute to musculoskeletal problems. Individuals with Down's syndrome appear to have differences in their bones and in the structure of their connective tissue and, in addition, their muscle tone can be low with hypotonia. Other than atlantoaxial instability that was discussed before, the most common musculoskeletal disorders includes genu valgum, hip instability, pes planus, scoliosis and frequent joint dislocation.

Haematology

Leukemia

The reported relative risk for acute leukemia in Down's syndrome patients ranges 10-20 times higher than for non-Down's individuals.[23] Leukemia in patients with Down's syndrome occurs mostly during the first 4 years of life and it has been assumed that the increased risk of leukemia extends into adulthood.[24] Little is known about the mechanism leading to the increased risk of leukemia in these individuals. Several genes on chromosome 21 have been found to be disrupted in leukemia. Since only a small proportion of Down's syndrome patients develop leukemia, non-genetic factors may also be of importance. The trisomy 21 predisposition to leukemia seems to be just the first hit in the multistep process leading to leukemia.[25]

Oral and Dental Development

Individuals with Down's syndrome often have smaller jaws and palate, with poor alignment of the jaws. The size, surface, and position of the tongue may also be different. They also have a higher incidence of clefting of the soft palate, which can affect swallowing and speech. No specific delay in teeth eruption is present.

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Conclusion

Down's syndrome is one of well known congenital conditions but it presents with a complex clinical profile. This review presents the most important genetic and medical features and places emphasis on the need for a multidisciplinary medical approach to these individuals.

Further sources

Associazione Italiana Persone Down: www.aipd.it
National Down's syndrome Society: www.ndss.org
National Down's syndrome Congress: www.ndsccenter.org
Down's syndrome Health issue: www.ds-health.com

Acknowledgments

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