

From pediatric history. Important personalities in relation to some genetic defects – “trisomies”

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Abstract

The aim of this study is to present a short biography of some important physicians and describe the most prominent differences between trisomy 13, 18 and 21. The authors present the most prominent differences between trisomy 13, 18 and 21. The work of many important physicians, geneticists, has helped in the process of recognition of congenital anomalies. This group of famous persons includes Patau, Edwards and Down.

INTRODUCTION

The development of the fetus depends on many factors. The optimal physiological growth of the fetus requires a good genetic predisposition, healthy parents, not only the mother, and healthy surroundings. The development of the fetus is sometimes changed by spontaneous mutation, infection or by unknown mechanisms.

Some visible anomalies can be confirmed during prenatal development thanks to prenatal screening methods. A large group of diseases can be confirmed after delivery (metabolic disorders, infections, etc.) (Embleton *et al.* 1996; Kovács *et al.* 2010; Šustrova *et al.* 2004).

The consequence of a pathological impulse can be the development of a malformation (a primary defect of structure, which arises from a localized disorder in morphogenesis) or a deformation (an alteration in structure or in the shape of a certain part that has differentiated normally). Changes

in the number of chromosomes belong to the group of chromosomal anomalies with the highest occurrence rate. The most frequent anomalies are trisomy 13, 18 and 21.

The risk of trisomy is enhanced not only with the increasing maternal but also with the rising paternal age.

IMPORTANT PERSONALITIES IN MEDICINE

Klaus Patau (1908–1975)

He was born in 1908 and studied in Germany (Figure 1). During the years 1938 and 1939, he worked in London. From 1939 to 1947 he worked at the Kaiser Wilhelm Institute for Biology in Berlin. An important year in his life was the year 1948, when he emigrated to the United States, where he later obtained the American citizenship. He devoted his interest to the genetic material of the human body. In 1960 he first reported on the



Fig. 1. Klaus Patau (1908–1975).
(source: <http://4.bp.blogspot.com>)

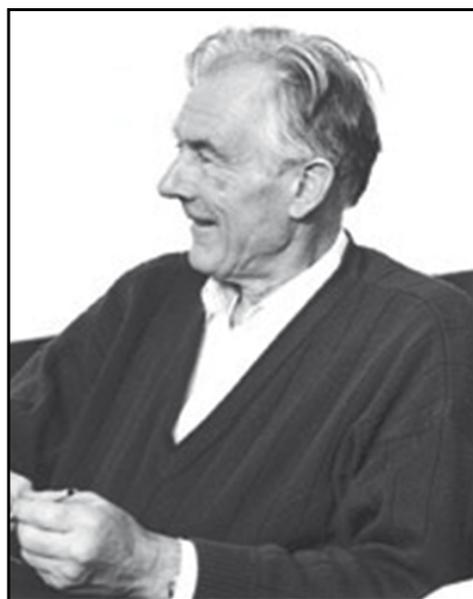


Fig. 2. John Hilton Edwards (1928–2007).
(source: <http://www.google.sk/imgres>)

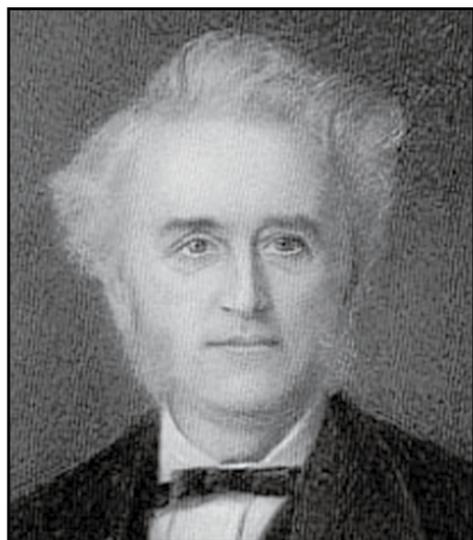


Fig. 3. John Langdon H. Down (1828–1896).
(source: <http://www.google.sk/imgres>)

presence of an extra chromosome in trisomy 13. He worked together with his wife in the Department of Genetics at the University of Wisconsin-Madison.

The name of this famous geneticist is joined with trisomy 13, although the first description of this anomaly appeared in 1656 by Thomas Bartholin.

John Hilton Edwards (1928–2007)

Born on March 26, 1928 in London, Edwards (Figure 2) was an English physician and medical geneticist. He studied at Cambridge University (1949–1952) and from 1954 to 1956 at the University of Birmingham. He achieved the membership of the Royal College of Physicians (1956), Fellowship in 1979, and became Fellow of the Royal Society in 1979.

His main interest was genetics. He is the author of the description of trisomy 18, the so-called Edwards's syndrome or trisomy E, which he discovered in 1960. He worked in Oxford, Philadelphia, and Birmingham. As Visiting Professor of Pediatrics he was working in New York and was a Staff Member of the New York Blood Center. The year 1971 was an important year in his life as he became professor of human genetics at the University of Birmingham. He died on October 11, 2007 (McKusick 2007).

All his work was focused on comparative gene mapping, on analysis of human genetic linkage and the identification of X-linked hydrocephalus.

John Langdon Haydon Down (1828–1896)

Down was born on November 18, 1828 in Torpoint in Cornwall (Figure 3). In his childhood he was interested in mathematics. His career began in London where he at the age of 18 years started to work for a surgeon in Whitechapel Road, where he had to extract teeth and to do services like washing bottles and dispensing drugs. Later he entered the pharmaceutical laboratory in Bloomsbury Square. He won a prize for organic chemistry. He died on October 7, 1896.

He is best known for his description of a relatively common genetic disorder that is now called Down syndrome.

CHARACTERISTICS OF TRISOMIES 13, 18 AND 21

Trisomy 13, Patau's syndrome, is the least common and most severe of the viable autosomal trisomies. In most cases, the affected child dies within the first month; only 10 % survive beyond the first year.

Trisomy 18, Edwards's syndrome, results from no disjunction during the first or during the second meiotic stage. The extra chromosome 18 is in 90–97 % of maternal origin (Embleton *et al.* 1996).

Trisomy 21, Down's syndrome is characterized by the presence of supernumerary chromosome 21, known as trisomy 21. It is a common chromosomal aberration in humans. It occurs in three forms: free trisomy, translocation or mosaic trisomy (Šustrova *et al.* 2004).

The risk factors for the disease are not fully known. The following situations have been implicated in its occurrence: a higher age of the mother, environmental factors – radiation and additive substances – tobacco, alcohol, drugs, etc. increase the likelihood of occurrence of Down's syndrome (Kovács *et al.* 2010).

In the clinical picture, in most cases the newborn presents the typical somatic signs at birth (Table 1), though the presence of individual signs may differ.

Tab. 1. The most prominent differences between Trisomy 13, 18 and 21.

Trisomy	Trisomy 13	Trisomy 18	Trisomy 21
incidence	1 in 5 000 live births	1 in 300 live births	1 in 700 live births
head and neck	<ul style="list-style-type: none"> • microcephaly, • holoprosencephaly, • anomaly of the pupils, • microphthalmia, • anophthalmia, • colobomata, • hypertelorism, • abnormal and low set ears, • cleft of the lip and/or palate 	<ul style="list-style-type: none"> • microcephaly, • anencephaly, • hypo/hypertelorism, • monophthalmia, • small hypoplastic nose, • cleft of the lip and/or palate, • occipital prominence, • small mouth, • low set ears 	<ul style="list-style-type: none"> • eyes – slanted eye slits, epicanthus, Brushfield spots on the iris, • nose – wide root, short, • tongue – enlargement of the size with typical slide from the oral cavity, fissured, • teeth – anomalies of number and shape, • ear – stored below and dysplastic, • fontanelle – delayed closure, • neck – short and wide
cardiovascular system	<ul style="list-style-type: none"> • atrial septal defect, • ventricular septal defect, • patent ductus arteriosus, 	<ul style="list-style-type: none"> • atrial septal defect, • ventricular septal defect, • patent ductus arteriosus, • double outlet right ventricle 	<ul style="list-style-type: none"> • atrial or ventricular septal defect, • complete atrio-ventricular septal defect, • patent ductus arteriosus
extremities	<ul style="list-style-type: none"> • crossing of fingers of hands and feet, • clenched fists, • rotation of thumbs, • polydactylia, • rocker bottom feet, • palm – transverse furrow 	<ul style="list-style-type: none"> • crossing of the 2nd finger across the 3rd and the 5th across the 4th finger, • rocker bottom feet, • prominent heel, • clinodactylia, • polydactylia, • palm – transverse furrow 	<ul style="list-style-type: none"> • hypermobility of joints, • central disorder of muscle tonus – a significant reduction in muscle tension, • lack of Moro reflex, • fingers – short, wide, dysplasia of the middle part of the little finger in hands, • palm – wide, transverse furrow
others	<ul style="list-style-type: none"> • pre- and postnatal hypotrophy, • mental retardation 	<ul style="list-style-type: none"> • pre- and postnatal hypotrophy, • mental retardation 	<ul style="list-style-type: none"> • mental retardation

DISCUSSION

We present three very important geneticists from the history of previous centuries, Patau, Edwards and Down, who confirmed the most frequent chromosomal abnormalities. Even nowadays, the contribution of all three physicians presented has an impact on the clinical work of pediatricians caring for children with dysmorphic features.

The clinical presentation of the anomaly of the number of chromosomes in trisomy 13, 18 and 21 is somewhat different. During physical investigation, it is very useful to know the most prominent features (Table 1). There are also slight differences in the form of congenital changes of organs, which require detailed knowledge of anatomy and embryonic development (Holománová & Brucknerová 2000; 2001; 2002; 2003). In all forms of the described trisomies, there is an increased frequency of prenatal and perinatal asphyxia and the prognosis is not very optimistic.

On establishing the differential diagnosis, we have to think also about congenital infection. Congenital infection can be assumed when the following manifestations

are found on physical examination: microcephaly/macrocephaly, low birth weight, growth retardation, stigmatization, dysmorphism, enlargement of the liver and spleen, hearing loss, congenital anomaly of organs. The final diagnosis is confirmed by serologic investigations. An unknown metabolic disease can present with dysmorphic features, severe convulsions, enlargement of the liver and spleen, hypoglycemia, anemia, metabolic acidosis, etc.

The care of a child with genetic abnormality must be multidisciplinary, involving genetic counseling, assessment by a general practitioner for children, by a surgeon, cardiologist, neurologist, speech therapist, special educator, audiologist, ophthalmologist, otorhinolaryngologist, immunologist, physiotherapist and orthopedist. It requires also the awareness of both parents.

CONCLUSION

The physiological course of the development of the fetus can be changed due to infection and anomalies in the shape and number of chromosomes. Also genetic predisposition to some diseases can play an important

role. Mostly the actual reason is unknown. The probability of the occurrence of prenatal and perinatal neonatal asphyxia is very high.

We present only three very important names of physicians who by their enthusiastic and seminal accomplishments contributed considerably to the realm of knowledge in pediatrics. We pay tribute to their achievements.

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