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Commentary

THE IMPACT OF GENETIC DISEASES ON NEONATAL AND PEDIATRIC CARE

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ABSTRACT

The impact of genetic diseases on the pediatric population in clinical practice is remarkable and their prevalence has rapidly increased in the last 50 years. A wide diffusion of modern diagnostic techniques has implemented early diagnosis and consequently the precocious start of effective support therapies which have determined an increased survival rate and quality of life. The percentage of genetics anomalies in children hospitalized is really high and amounts to at least 50% of hospital pediatric admissions. Over 5% of stillborn babies, without other known causes, have genetic disorders, and it goes up to 50% in the case of visible malformations.

1. Main text

The impact of genetic diseases on the pediatric population in clinical practice is remarkable and their prevalence has rapidly increased in the last 50 years. A wide diffusion of modern diagnostic techniques has implemented early diagnosis and consequently the precocious start of effective support therapies which have determined an increased survival rate and quality of life (1).

The percentage of genetics anomalies in children hospitalized is really high and amounts to at least 50% of hospital pediatric admissions. Over 5% of stillborn babies, without other known causes, have genetic disorders, and it goes up to 50% in the case of visible malformations. Furthermore, the majority of fetal malformations or genetic abnormalities leads to arrest of the intrauterine growth and early prenatal loss (2). Genetic causes are recognized in about 50% of spontaneous abortions, mainly Turner syndrome (X chromosome monosomy) and polyploidies (3).

In view of this considerable evidence, a general extended dissemination of knowledge about the genetic bases and features of diseases is critical. Although the prevalence of genetic diseases in the pediatric population has probably not increased in terms of absolute value, there has been a substantial change in the relative frequency of these diseases, mostly due to the development of active surveillance systems, infection prevention and control.

Improved neonatal cardiopulmonary resuscitation and ventilation techniques have also played an important role in reducing perinatal death in babies with cardiopulmonary or airway malformations. In other words, the general decline in neonatal and pediatric morbidity and mortality (due to reduction of infections and malnutrition) has yielded a relative increase of morbidity and mortality from genetic diseases. In terms of pediatric morbidity, genetic diseases account for a substantial proportion of admissions in children's hospitals: children with special needs represent a considerable percentage of the total expenditure on pediatric health, about 70-80% in USA in 2017. They have a three times higher probability of hospitalization, compared to other children, and their permanence in pediatric departments lasts between five to eight times longer. In almost 35% of cases, these hospitalizations are preventable and are generated by health care system deficiencies, medical mistakes or misdiagnosis. Medical mistakes are preventable events and are more common during assistance to people with disabilities, especially in the pediatric group.

A correct medical management of children with suspected or confirmed genetic disease begins during prenatal period: the approach has to be based on the cooperation between gynecologist and neonatologist in order to provide adequate diagnosis and assistance to the newborn baby and to accurately communicate with the parents-to-be.

Prenatal diagnosis is the identification of birth defects before the delivery and is a routine practice in most European countries.

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According to data from the European Surveillance of Congenital Anomalies (EUROCAT), 64% of birth defects could be diagnosed before birth, although it varies widely from 94% success rate for anencephaly and 87% for omphalocele to as low as 27% for the transposition of great vessels. For chromosomal anomalies, the sonographic detection rates range from 5.7% (Klinefelter syndrome) to 78.6% (triploidy); for Down syndrome it was 26.4%, and 19.9% for cardiovascular malformations (11% for isolated cases and 40% for multiple malformations). Intrauterine growth restriction is a very common and non-specific prenatal sign associated with many different malformative conditions (4).

Prenatal screening for malformations influences the stillbirth rate, as early diagnosis leads to termination of pregnancies. Surgical correction of defects during the first days of life can also reduce neonatal mortality (5). Some prenatally diagnosed malformations require immediate postnatal intervention: for example, neonates with congenital diaphragmatic hernia need to be managed with intubation and mechanical ventilation from the first breaths in order to manage respiratory insufficiency and to prevent entrainment of air into the intestines with further compression of the lungs and heart (6). In any case, the evidence of a major malformation at birth has to be completed by a careful analysis of all phenotypes that may reveal other major and/or minor malformations and lead to the diagnosis of a more complex polymalformative condition (7).

In neonates with Pierre-Robin Sequence that require resuscitation measures, endotracheal intubation is usually difficult or impossible because of the micrognathia and glossoptosis. Infants with PRS should be evaluated by a multidisciplinary team to prevent airway obstruction and feeding issues. Positioning resolves airway obstruction in a large percentage of cases. In the correct position, most children will also be able to feed normally (8). In other cases, placement of a nasopharyngeal tube is indicated (9).

Furthermore, neonates with genetic diseases may show other problems during the first days of life. Hypotonia and poor feeding in newborns can be the first signs of genetic conditions like Prader-Willy syndrome, Angelman syndrome, neuromuscular congenital diseases and others. If poor feeding is associated with a cleft palate in newborns with non-specific morphologic abnormalities, a genetic investigation for 22q11.2 deletion is suggested (10). Moreover, difficult feeding in cases of newborns with hypoglycemia and omphalocele can be a warning bell for neonatologists to search for other clinical signs of Beckwith-Wideman syndrome. Babies with Down syndrome are often adequate for gestational age, but they usually present hypotonia, retardation of growth, poor feeding, and relative macroglossia. Congenital heart defects, hypothyroidism, and gastrointestinal malformations are frequently associated to this syndrome and raise the need of specific assistance.

During the neonatal period, a large variety of rare genetical conditions (not diagnosed with prenatal screening, due to very low incidence) can provide warning signals requiring careful analysis of clinical features. Signs and symptoms need to be evaluated in order to identify problems that require specific clinical and surgical approaches, intensive care and prolonged hospitalization in high risk settings. These newborns are exposed to health care associated infections, particularly by multidrug resistant organisms (such as Methicillin Resistant Staphylococcus Aureus, ESBL producing Gram negative bacteria and carbapenemase producing Klebsiella pneumoniae), which determine further increase of morbidity and mortality (11-13). A rapid correct identification of the underlying genetic condition makes the difference in terms of survival and comorbidity, but it is based on a diffused basic genetic knowledge among healthcare pediatric professionals.

Despite the developing of prenatal and postnatal diagnosis, the largest part of genetic diseases is diagnosed during childhood or infancy. Apart from the aforementioned situations in which clinical signs are precociously detectable, there is a huge group of genetic disorders that become clinically evident during growth or adolescence or, rarely, adulthood.

Pathologic growth and/or neuromotor and language developmental delays are usually the reason why parents or general practitioners refer to genetic consultants.

Genetic disorders of growth are numerous and include defects of the central nervous system, hypothalamus-pituitary axis, thyroid, skeleton and other glands, tissues or organs. These disorders have a genetic makeup which interferes at different levels on the hypothalamus-pituitary axis and other synthetic pathways that are necessary for growth. Also included in this group are: achondroplasia, hypochondroplasia, Fanconi anemia, Di George syndrome, rasopathies, Turner syndrome and others with collateral or absent involvement of the hypothalamus-pituitary axis. Numerous poly-malformative syndromes, such as Sotos syndrome, Marfan, Marshall-Smith, Weaver, Simpson-Golabi, are also characterized by pathologic overgrowth, and their molecular bases have been recently found (14).

Among the prominent health problems in pediatric healthcare, neurodevelopmental disorders (NDDs) likely involve over 3% of the general population. The spread of these disorders increases in people with poor socioeconomic status and in developing countries. NDDs are a heterogeneous group of conditions with or without dysmorphisms or multiple congenital anomalies (15). Newly developed techniques for genetic diagnosis recently showed a significant role of sub-telomeric anomalies in people with autism and neurodevelopmental delays without malformations. Autism spectrum disorders represent a range of neurodevelopmental disorders that seem to have a strong genetic component. Microarray-based comparative genomic hybridization and other molecular cytogenetic techniques are revealing an increasing number of copy number variations in individuals with autism spectrum disorders (16).

The analysis of clinical features and natural history (auxological, neurological, developmental characteristics) of the most common genetic syndromes can help pediatricians and neonatologists to infer hypothesis, through a “gestalt process”, in order to confirm the diagnosis with specific genetic tests (“analytic process”). Gestalt identification is a method to organize clinical suspects, based on visual experience and pathways, into specific diagnoses, which can ultimately be confirmed with appropriate diagnostic tests and clinical history (17). This technique is frequently performed in clinical genetics, as the facial dysmorphic features are often the most specific clinical criteria of a syndrome (18). Moreover, it can also be applied in cases of specific auxological and neurological evolution, in Prader-Willi syndrome for example, which shows a distinctive alternation of hypotonia, poor growth and feeding during the first month of life, and hyperphagia, obesity, and neurological and developmental delays later on. A specific behavioral phenotype with sleep disturbance, stereotypes and oppositional behavior can suggest Smith-Magenis syndrome, as well as an outgoing personality, excessive interaction with strangers, associated to an “elfin face”, hypertension and cardiac defect (supravalvular aortic stenosis) could underpin the William’s syndrome phenotype.

Patients with suspected pediatric genetic conditions greatly contribute to high healthcare costs, according to various studies.

Studying these patients' healthcare utilization pointed out that they use disproportionate resources and showed potential for earlier molecular diagnosis to relieve some of the economic burden by reducing iterative diagnostic processes and improving targeted interventions. Researchers found that children with suspected genetic disorders were more likely to recur surgical procedures, had longer hospitalization, and had higher mortality rates than the rest of the pediatric patient population (19). This relates to higher healthcare costs and charges. Improving physicians' awareness, earlier diagnosis, and using comprehensive genetic testing approaches could significantly reduce costs associated with the diagnostic odyssey and decisively improve the quality of life of patients and their families.

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