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Review

LARGE FOR GESTATIONAL AGE, MACROSOMIA, OVERGROWTH: AN UPDATE ON DEFINITIONS AND DETERMINANTS

Ettore Piro, Gregorio Serra, Ingrid Anne Mandy Schierz,Vincenzo Antona, Mario Giuffrè, Giovanni Corsello

Department of Health Promotion, Maternal and Infant Care, Internal Medicine and Medical Specialties "G. D'Alessandro". University Hospital "P.Giaccone", University of Palermo,

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ABSTRACT

Human growth and development, starting from conception, are characterized by a progressive increase in body and organ dimensions, as well as specific functional maturity, under the influence of genetic as well as environmental and epigenetic determinants. Beyond a possible normal familial trait, increased fetal growth resulting in a large for gestational age newborn, isolated macrosomia or that associated with congenital malformation, can be attributable to both maternal metabolic and genetic pathology. Overgrowth syndromes are a heterogeneous group of diseases characterized by excessive tissue development often concomitant to neurodevelopmental involvement. Recently, an increased risk of fetal overgrowth with Assisted Reproductive Technology has been reported. Thus, in pediatric practice, it is fundamental to monitor any patient who presents with increased growth parameters, variable malformations, neurodevelopmental delay, and distinctive features from birth, aiming to ensure as adequate a medical management as possible, and for some of the disorders, strict tumor monitoring is also necessary.

1. Introduction

Conventionally gestation is the period of time between conception and birth when a baby grows and develops inside the mother's womb. Since, apart from selected cases as in Assisted Reproductive Technology (ART), it is impossible to know exactly when conception occurs, gestational age is measured in weeks from the first day of the mother's last menstrual cycle to the current date. Thus, although a normal pregnancy lasts for about 280 days or 40 weeks, the corresponding period of real embryofetal development lasts 266 days or 38 weeks. A preterm or premature baby is delivered before 37 weeks of pregnancy. Extremely preterm infants are born from 23 to 28 weeks of gestation. Moderately preterm infants are born between 29 and 33 weeks, and late preterm from 34 to 36+6 weeks. Thus, to monitor both anthropometric and functional neurodevelopment a corrected age for prematurity must be considered for at least the first two years of life. During all three trimesters of pregnancy normal fetal growth is a critical component of a healthy pregnancy and influences the long-term outcomes of the offspring (1). To monitor intrauterine growth, charts derived from anthropometric studies conducted on the reference population only should be adopted (2,3).

Using a statistical approach, any neonate weighing >90th percentile for gestational age is considered large for gestational age (LGA). Nevertheless, to better identify the more at-risk conditions some researchers prefer to use the two standard deviations from the mean accounting for about 95.4% of the population. To define the most severely affected subjects, similarly to other anthropometric-clinical correlations, three standard deviations, accounting for about 99.7% of the population, are generally used (4).

A strict postnatal clinical and instrumental follow-up should be planned in case of overgrowth, especially oriented towards early identification of concomitant neurosensorial involvement. Nowadays, hearing screening using the Otoacoustic Emissions Test (OAEs), and the examination of the red reflex of the eyes are routinely performed in every newborn, relying on developmental surveillance for early impairment identification. Nevertheless, is important to consider that, apart from the cardiac localized overgrowth of fibrous and elastic tissues (endocardial fibroelastosis), present in 3-Methylglutaconic aciduria type 2 (Barth Syndrome, MIM# 302060), the generalized overgrowth syndromes are not identified through expanded neonatal metabolic screening (5).

* *Corresponding author*: Ettore Piro, *ettore.piro@unipa.it*
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2. Large for gestational age and macrosomia

The term Large for gestational age (LGA) defines a newborn whose birthweight is over the 90th percentile, referring to growth charts built on the reference population. Thus, around 9.9% of newborns are expected to be LGA. The term macrosomia is used to define a term neonate birthweight > 4,000 g, or > 4,500 irrespective of gestational age (6). Nevertheless, it might be more appropriate to define macrosomia as a value 2 standard deviations (SD) above the mean adopting the reference population growth charts.

It is important to differentiate a generalized overgrowth from macrosomia. Infants with generalized overgrowth are frequently described as "long and thin" with relatively increased weight secondary to their presentation of increased birth length.

The most frequent pathology responsible for LGA and macrosomia is maternal diabetes.

In pregnancy two types of diabetes can occur; a pregestational diabetes related to women who already have insulin-dependent diabetes and become pregnant, and gestational diabetes affecting a mother who does not have diabetes before becoming pregnant, but develops a resistance to insulin because of the hormones of pregnancy (estrogen, cortisol, human placental lactogen). The great majority of investigators find a two- to threefold increase in malformations in infants of insulin-dependent diabetic mothers compared to infants of gestational diabetics. When diabetes is controlled by diet or oral hypoglycemic agents, the increased risk of malformation is not reported.

Although both types of diabetes can lead to LGA and macrosomia conditions, pregestational diabetes can exert toxic effects on the embryo, through hyperglycemia-induced teratogenesis affecting the development of several organsbefore the seventh gestational week. The most frequent malformations reported include; central nervous system (CNS) (anencephaly, spina bifida, holoprosencephaly, microcephaly), cardiovascular system (single umbilical artery, transposition of the great vessels, ventricular septal defects, atrial septal defects, coarctation of the aorta), gastrointestinal system (duodenal atresia, small left colon syndrome, anorectal atresia,), renal system (renal agenesis, ureteric abnormalities), skeletal system (limb defects, caudal regression syndrome/syrenomelia, isolated sacral agenesis) (7,8).

Macrosomia is associated with increased risks of intra-uterine death and stillbirth.At birth, maternal complications have been reported as prolonged labor, and with vaginal delivery uterine rupture, perineal trauma and postpartum hemorrhage. Newborns with macrosomia show a higher risk of shoulder dystocia, clavicle fracture and brachial plexus palsy. Admission to neonatal intensive care unit (NICU) can be related to cardiorespiratory, maladaptation or asphyxia, and polycythemia along with prolonged hypoglycemia that can lead to severe neurological consequences, when not identified early and treated (9,10).

Frozen embryo transfer, one of the newest types of ART, in relation to a reduced risk of ovarian hyperstimulation syndrome, multiple pregnancy, and low birth weight in singleton has become a technique of choice versus fresh embryo transfer. Nevertheless, the frozen versus the fresh type has been correlated with an increased risk of LGA (11).

A long term effect of being LGA is an increased risk of obesity and/or insulin-resistance (12,13).

Nevertheless, a recent study showed that the associations between birth weight and overweight/obesity at 15–20 years of age were modest, whereas the influence of body mass index (BMI) at 2–4 and 5–7 years on overweight/obesity at 15–20 years was moderate to strong (14).

3. Overgrowth

Samples Somatic growth is dependent on an increase in cell size, cell number or both. Overgrowth can be generalized, involving the whole body and accompanied by other clinical signs, defining a syndrome, or segmental, e.g. hemimegaloencephaly. It is important to distinguish at birth between a syndrome of generalized overgrowth from macrosomia "sensu strictu", as previously defined.

Nowadays we are seeing a continuous expansion in the genes responsible for clinical conditions characterized by overgrowth, and the two terms are not always well distinguished. Thus, searching for "overgrowth" in Online Mendelian in Men (OMIM), we obtained 221 entries, and searching for "macrosomia" 44 entries (15). Some chromosomal conditions, often associated with generalized overgrowth, have been diagnosed by chromosome microarray (16,17).

Overgrowth syndromes comprise a heterogeneous group of diseases that are characterized by excessive tissue development, share several clinical signs and are associated with various degrees of developmental delay/intellectual disabilities as well as neurobehavioral disorders (Table 1).

Underlying mechanisms responsible for overgrowth have been recently defined.

Some of these syndromes may be associated with dysfunction in the receptor tyrosine kinase (RTK)/PI3K/AKT pathway, which results in an increased expression of the insulin receptor.

Other reported mechanisms are; epigenetic regulator genes, transcription factors, mutations of the gene encoding the endoribonuclease, channelopathies and disruption of extracellular signaling (16). Interestingly, growth pattern can be characterized in Cantu, Costello, Pallister Killian, and Perlman syndromes by a postnatal slowing (18).

In Costello syndrome a postnatal failure to thrive and growth deficiency are often reported too (19).

In Pallister Killian only up to 40% of patients maintain increased growth parameters, thus most of them show a postnatal progressive reduction to the lower centiles (20).

Neurofibromatosis type 1 (NF1) is characterized by growth retardation and short stature. Nevertheless, overgrowth is part of the phenotypic spectrum in patients with the common 1.4/1.2 Mb NF1 microdeletions. Thus, the chromosomal region comprised by the microdeletions should contain a gene whose haploinsufficiency causes overgrowth which is most evident in preschool children aged 2-6 years (21,22).

Overgrowth syndromes are frequently associated with an increased risk of cancer, specifically embryonic tumors in childhood and carcinomas in adulthood. An increased risk of neoplasia is present in Beckwith Wiedemann, Neurofibromatosis Type 1 (NF1), Sotos, Proteus, Perlman, BW syndrome (BWS), Costello, Simpson-Golabi-Behmel, Weaver and PTEN hamartoma tumor syndromes (23).

Embryonic types of cancer due to the overexpressing of IGF2, have been well described in BWS withup to 10% of children developing a cancer; Wilms tumor, adrenocortical carcinomas, carcinomas, hepatoblastomas. neuroblastoma and rhabdomyosarcoma. The individual risk is related to the genetic basis and is higher, up to 26%, in the hypermethylation group, in comparison to KCNQ1OT1:TSS-DMR (IC2) subgroup (2.6%) (24).

In NF1, the most frequent tumors are neurofibromas with plexiform type occurring in about 50% of patients.

The optic nerve gliomas affect about 10-15% of patients, and women with NF1 have a 3.5-fold increased risk of developing breast cancer (25,26).
In Perlman syndrome there is an increased risk of developing a Wilms tumor which has been documented in 64% of patients (27).
In Simpson-Golabi-Behmel, a lower, in comparison to previous reports, prevalence of Wilms tumor and leukemia has been reported (28).
In Costello syndrome a significant increased risk, up to 15%, of developing a neuroblastoma, transitional cell carcinoma of the bladder and rhabdomyosarcoma is described (29)
Sotos syndrome, in comparison to other overgrowth syndromes shows a lower risk of tumor, at around 3%, however, it is still present, and includes neuroblastoma, retinoblastoma, small cell lung cancer, sacrococcygeal teratoma and presacral ganglioma.
It is important to remember that is not unusual for children with a milder form of Sotos syndrome to eventually be given a diagnosis after several years of investigations for a variable degree of developmental delay (30).

Overgrowth syndrome	MIM #	Inheritance	Gene (Location)
Beckwith- Wiedemann	1300650	AD	11p15.4 (CDKN1C) - 11p15.5 (H19, ICR1,KCNQ1OT1/LIT1)
Sotos	117550	AD	NSD1 (5q35.3)
Perlman	267000	AR	DIS3L2 (2q37.1)
Costello	218040	AD	HRAS (11p15.5)
Simpson-Golabi-Behmel type1	312870	XLR	GPC3 (Xq26.2)
Weaver	277590	AD	EZH2 (7q36.1
Pallister-Killian	601803	Somatic mosaicism	Extra isochromosome 12p
Proteus	176920	Postzygotic mutation event resulting in mosaicism	AKT1(14q32.33)
Cantu	239850	AD	ABCC9 (12p12.1)

Table 1. Main overgrowth syndromes

4. Epigenetic determinants

Genomic imprinting is an epigenetic phenomenon, involving around 4100 imprinted genes in humans, that leads to parent-specific differential expression of a subset of mammalian genes.
The expression of every imprinting domain, formed from most imprinted genes, is regulated by imprinting control regions (ICRs). ICRs are identical to differentially methylated regions (DMRs), which are characterized by DNA methylation on one of the two parental alleles, either maternally methylated DMRs or paternally methylated DMRs. There are two classes of imprinted DMRs, gametic DMRs and somatic DMRs.
Gametic DMRs acquire DNA methylation during gametogenesis, and the methylation is maintained from zygote to somatic cells during all developmental stages. Most gametic DMRs are identical to ICRs. Methylations of somatic DMRs are established during early embryogenesis after fertilization under the control of nearby ICRs.
Epigenetic abnormalities responsible for an aberrant expression of imprinted genes mostly include histone modification, chromatin modelling and aberrant hypomethylation or hypermethylation at ICRs.
Epigenetic regulator genes have been identified for Sotos, Weaver, Cohen-Gibson and Perlman syndromes (16).
In embryos conceived by ART, especially through in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), an increased risk of imprinting disorders, such as BWS and Angelman syndrome, has been reported. The causative alteration for most of ART-related BWS is loss of methylation (LOM) at KvDMR1 (KvDMR1-LOM).
Thus, a closer follow-up is necessary in case of ART for early identification of developmental anomalies (31, 32).

5. Practical clinical and diagnostic considerations

Early clinical identification of the specific overgrowth syndrome can be difficult for the clinician since phenotypes often overlap with patients exhibiting similar facial findings. In the first months of life, suspected developmental delay, generally associated with a generalized hypotonia of central origin, does not always allow for the identification of a developing cognitive impairment or the presence of autistic features. Thus, from 6-8 months of age (corrected age for prematurity), applying standardized instruments for developmental assessment, the clinician should define the patient's developmental quotient (mental age/chronological age). A normal development can orientate the diagnosis towards a familial type or endocrine conditions (hyperthyroidism, growth hormone-secreting adenoma, congenital adrenal hyperplasia, familial glucocorticoid deficiency, aromatase deficiency) (32).
As a general rule, a clinician approaching an infant with suspected overgrowth syndrome should first rely on his own clinical acumen using the so-called "diagnostic handles" to identify a recognizable facial gestalt or specific pattern of malformations. Thus, an accurate clinical and instrumental diagnosis, including brain imaging and neurophysiological investigations, can allow the clinician to limit the number of genes to be analyzed in gene panels, reducing the number of results including variants of uncertain significance (VUS). The widespread adoption of exome sequencing and gene panels (16) has made it possible to significantly increase the diagnosis rate of overgrowth syndromes, which was around 50%, 10 years ago (33).

6. Conclusions

Clinicians should attempt to define the diagnosis in a child with an overgrowth syndrome as early as possible. A multidisciplinary diagnostic and therapeutic team with pediatric leadership and including clinician geneticist, molecular biologist, pediatric neurologist, neurodevelopmental pediatrician, child neuropsychiatrist, ophthalmologist, audiologist and rehabilitation staff, should develop an individualized plan of developmental surveillance, rapid interventions in case of complications and strict monitoring in relation to the frequently increased tumor risk (34).

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