GROWTH
Genetics & Hormones
Vol. 10 No. 1 March 1994

# Overgrowth Syndromes and Disorders: Definition, Classification, and Discussion

**David D. Weaver, MS, MD**
*Professor of Medical and Molecular Genetics*
*Indiana University School of Medicine*
*Indianapolis, Indiana*

A recent review of the literature made it apparent that a confusing group of disorders with excessive growth and/or development exists. These have been labeled *overgrowth syndromes*. The confusion exists partly because there is no accepted definitive definition or classification of these disorders. The purpose of this article is to present definitions of, and a classification system for, the known types of overgrowth syndromes and disorders.

## PROBLEMS WITH DEFINITION AND CLASSIFICATION

Problems with definition and classification of overgrowth conditions are illustrated best by a few examples. One classic overgrowth syndrome is the Beckwith-Wiedemann syndrome. Most children with this condition have excessive prenatal and postnatal growth involving both height and weight, and have macroglossia, visceromegaly, and advanced skeletal maturation. The condition is a classic overgrowth syndrome since there is excessive growth in most growth parameters. Interestingly, however, the head size and presumably the brain size in children with Beckwith-Wiedemann syndrome are normal.

The Marshall-Smith syndrome is another example of the confusion associated with overgrowth conditions. This condition is characterized by a prominent calvarium, forehead, and eyes, a low nasal bridge, an upturned nose, micrognathia, widened middle and distal phalanges, best appreciated on radiographs, markedly advanced skeletal maturation, respiratory distress, frequent pneumonias, failure to thrive, and often death during infancy.[1] Even though the Marshall-Smith syndrome is associated usually

### Letter From the Editor

Human growth hormone (hGH) has been used in humans for 35 years (1958-1993). The benefits to growth hormone deficient (GHD) children is well known to all of us. For the first 27 years (1958-1985), we were impressed with the safety of the hormone when it was used in physiologic amounts. In 1985, 2 cases of Creutzfeldt-Jakob disease were described in patients who received hGH many years previously. Subsequently, due to various conjectural reports, concern developed whether hGH produces leukemia, tumor recurrence in the CNS, immunologic deficiency, atherosclerosis, other cardiovascular disease, and/or an increased incidence of diabetes mellitus.

In response to these suspicions, the European Society of Paediatric Endocrinology (ESPE) established a committee of renowned pediatric endocrinologists to review all available data regarding these suspicions and to publish in the official journal of ESPE, *Hormone Research*, a statement concerning the safety and/or toxicity of hGH therapy. This has been accomplished and an official statement from ESPE was published in *Horm Res* 1993;39:92-110. The Lawson Wilkins Pediatric Endocrine Society approved the report.

Continued on page 5

### In This Issue

with a normal birth weight and failure to thrive, the condition has been classified in the past as an overgrowth syndrome.[2] This occurred since normally a dramatic increase in the overall bone age is found with the carpal bone maturation being even more advanced.

The Patterson-David syndrome also illustrates the problem in classifying overgrowth conditions. This relatively unknown syndrome has been confused with leprechaunism (Donohue syndrome).[3,4] Patients with the Patterson-David syndrome present with redundant, loose folds of skin of the hands, large ears, hands, and feet, phallic enlargement in males, generalized bronzed hyperpigmentation, hirsutism, severe mental retardation, and characteristic skeletal changes. In this syndrome the birth weight and length are usually at the 97th percentile; the postnatal length is in the high normal range but the weight typically drops below the 3rd percentile (which probably accounts for the confusion with Donahue's syndrome). Since birth weight and length are increased and since there is redundancy of the skin, large ears, large penis, and large hands and feet, one can make a case that this condition truly is an overgrowth syndrome, despite the postnatal weight deficiency.

A final example includes the localized overgrowth disorders such as isolated macrodactyly. Should these disorders be considered under the umbrella of "overgrowth syndromes"? Perhaps not, but they clearly do represent overgrowth in localized tissues or organs and clearly constitute overgrowth disorders.

## DEFINITION AND CLASSIFICATION

Keeping in mind the above examples, I propose that an overgrowth syndrome or disorder simply be defined as a condition in which there is either localized or generalized excessive growth and/or development for the age and sex of the individual. Under this definition, most overgrowth syndromes or disorders can be classified into 1 of the following 3 general categories:

1. Generalized overgrowth syndromes
2. Regional overgrowth disorders
3. Parameter-specific overgrowth disorders

Generalized overgrowth syndromes which include the classic overgrowth conditions are those in which all or most parameters of growth and physical development are in excess of 2 standard deviations (SD) above the mean for the person's age and sex. The relatively few conditions that fall into this category are listed in Table 1. The regional overgrowth disorders include those in which excessive growth is confined to one or a few regions of the body. An example is benign familial macrocephaly, an autosomal dominant condition associated with a large dolichocephalic head and normal intelligence. Some of the conditions classified as regional overgrowth disorders are listed in Table 2. Finally, there are parameter-specific overgrowth disorders in which a single or, at most, several growth parameters are in excess of normal. Familial idiopathic obesity and Prader-Willi syndrome are examples that belong to this category. Others are listed in Table 3.

Table 1
**Generalized Overgrowth Syndromes***

- Bannayan-Riley-Ruvalcaba syndrome (Bannayan-Zonana syndrome, Ruvalcaba-Myhre syndrome, or Riley-Smith syndrome)†
- Beckwith-Wiedemann syndrome†
- Diabetic embryopathy (infants of diabetic mothers)†
- Elejalde syndrome†
- Familial rapid maturation
- Familial tall stature
- Fragile X syndrome
- Gigantism/acromegaly
- Hyperthyroidism, congenital
- Hyperthyroidism, infancy and childhood
- Klinefelter syndrome
- Marfan syndrome
- Nevo syndrome†
- Perlman syndrome†
- Precocious puberty (precocious adolescence)
  - Precocious gonadotropin-induced adolescence
  - Congenital adrenal hyperplasia, untreated
  - Hormone-secreting tumors
    - Interstitial cell tumor with androgen production in males
    - Granulosa cell tumor with inappropriate estrogen production in females
- Simpson-Golabi-Behmel syndrome (Golabi-Rosen syndrome)†
- Sotos syndrome (cerebral gigantism)†
- Teebi-type overgrowth syndrome†
- Trisomy 8 mosaicism (Warkany syndrome)†
- Weaver syndrome†

* List is not all-inclusive.
† Excessive growth and/or weight is usually present at birth in this condition.

The above classification scheme is a modification of the one used by Beighton[5] who divided overgrowth conditions into generalized overgrowth, obesity, localized overgrowth, and digital overgrowth syndromes. Cohen[6] also has categorized overgrowth conditions according to whether the condition is a normal variant of growth, such as familial tall stature, or whether the overgrowth is of prenatal onset as in Sotos syndrome, or whether the overgrowth is of postnatal onset as that occurring with early and excessive production of sex hormones.

## GENERAL CHARACTERISTICS

Because of the marked diversity of features associated with the various overgrowth syndromes and disorders, no general statements can be made about common characteristics in these conditions. The exception is that they are associated with excessive growth or development of one type or another. However, the conditions in the generalized overgrowth category that have excessive growth at birth (denoted by † in Table 1) share a few common characteristics. These characteristics include the following.[6]

1. Weight is generally increased as much as length.
2. The condition is usually associated with various other anomalies.
3. Mental deficiency often is present.
4. Neoplasias occur at a higher than expected frequency.

## INCIDENCE AND NUMBER OF OVERGROWTH SYNDROMES AND DISORDERS

The incidence of each overgrowth syndrome or disorder varies tremendously, being as common as 1 in 1,000 to 1,500 as occurs with the fragile X syndrome, to less than 1 in 1,000,000 births in Elejalde syndrome and others. Elejalde syndrome is a striking prenatal overgrowth syndrome that has been reported in only 3 siblings.[7]

If one accepts the classification system presented above, the number of currently recognized overgrowth conditions is dramatically large. A number of growth parameters and the corresponding number of recognized conditions associated with each of these features is presented in Table 4. These data were generated from 2 syndrome data bases, Pictures of Standard Syndromes and Undiagnosed Malformations or POSSUM and the London Dysmorphology Data Base or LDDB, and clearly indicate the number and complexity of syndromes that can be classified as overgrowth syndromes or disorders.

Table 2
**Conditions Classified as Regional Overgrowth Disorders***

- Cutis marmorata telangiectatica congenita
- Familial macrocephaly
- Hemifacial microsomia-macrodactyly syndrome
- Hemihyperplasia (hemihypertrophy)
- Klippel-Trenaunay-Weber syndrome
- Macrodactyly
- Maffucci syndrome
- Neurofibromatosis
- Ollier syndrome
- Patterson-David syndrome
- Proteus syndrome

* List is not all-inclusive.

## ETIOLOGY AND PATHOPHYSIOLOGY

A whole gamut of genetic etiologies is associated with overgrowth syndromes and disorders. For instance, an autosomal dominant gene mutation (FBN1) is the cause of Marfan syndrome. The Perlman syndrome is produced by an autosomal recessive mode of inheritance. The Simpson-Golabi-Behmel syndrome is inherited in an X-linked recessive fashion, and familial tall stature is polygenetic in etiology. Genomic imprinting is the usual cause of Prader-Willi syndrome, since

Table 3
**Conditions Classified as Parameter-Specific Overgrowth Disorders***

- Berardinelli lipodystrophy or Seip-Berardinelli syndrome (tall stature and advanced skeletal maturation)
- Börjeson-Forssman-Lehmann syndrome (obesity)
- Cohen syndrome (obesity)
- Congenital contractual arachnodactyly or Beals syndrome (tall stature)
- Familial idiopathic obesity
- Marshall-Smith syndrome (accelerated skeletal maturation)
- Michelin tire baby syndrome (subcutaneous lipomatous nevus)
- Prader-Willi syndrome (obesity)
- Teebi macrosomia-microphthalmia-cleft palate syndrome (obesity)

* List is not all-inclusive.

the disorder usually is associated with either an interstitial deletion (q11 to q13) of the paternally derived chromosome 15 or maternal uniparental disomy of chromosome 15. In many other overgrowth syndromes and disorders, eg, Proteus syndrome, all reported cases have been sporadic and the etiologies of the conditions are unknown.

Because of the diverse genetic mechanisms causing overgrowth syndromes, and because of the varied manifestations of excessive growth found in individuals with overgrowth conditions, there must be a multitude of mechanisms producing excessive growth. It is indeed intriguing to consider the vast knowledge about human growth and the regulation of cell division and growth that we will have when we come to understand all of the mechanisms producing overgrowth and its associated syndromes and disorders.

Most overgrowth conditions result from either hyperplasia, hypertrophy, an increase in the interstitium, or some combination of these 3 factors.[6] With the exception of certain hormone disorders such as untreated congenital adrenal hyperplasia, acromegaly, and diabetic embryopathy, the causes for these changes are unknown. Perhaps abnormal states of insulin-like growth factors (IGFs), their cell-surface receptors, insulin-like growth factor-binding proteins, epidermal growth factors, human placental lactogen (chorionic somatomammotropin), and the regulators of these factors cause many of these disorders.[8,9] In addition, perhaps partial or complete disruption of the normal function of proto-oncogenes or tumor-suppressor genes results in regional overgrowth disorders in some cases, although none is recognized to do so at the present time.

An abnormal accumulation of body fluid, as seen in hydrops fetalis or anasarca, can cause an increase in the size and weight of a fetus or individual. However, these categories of disorders have not been included in the classification scheme presented here since the accumulation of fluid does not truly represent *excessive* growth in the normal sense of the word.

## EVALUATION, COUNSELING, AND FOLLOW-UP

The evaluation of a child with an unrecognized overgrowth condition should be individualized, and based on the type of overgrowth condition present and the presence of other abnormalities. Such an evaluation might normally include: (1) a careful patient history, family history and physical examination; (2) appropriate physical measurements; (3) complete skeletal survey, including bone age; (4) chromosomal analysis that might include specialized testing for specific conditions, eg, fragile X syndrome; (5) urine analysis for metabolic disorders; and (6) endocrine studies, including serum IGF-1 and thyroid function studies. Other studies would be dictated by the patient's history and examination. In many situations it is appropriate to evaluate the parents and siblings of the affected child. It is also necessary to run serial glucose levels on all neonates with generalized overgrowth to detect hypoglycemia. Children with either the Beckwith-Wiedemann syndrome, hemihyperplasia, or the Simpson-Golabi-Behmel syndrome need to be evaluated on a regular basis for intra-abdominal tumors. Finally, appropriate genetic counseling and long-term follow-up care should be provided to both the family and the child with an overgrowth condition.

Table 4
**Overgrowth Parameters and the Number of Syndromes and Disorders Listed in 2 Syndrome Data Bases**

| FEATURE | Number of Disorders POSSUM* | LDDB† |
|---|---|---|
| Macrocephaly | 166 | 137 |
| Macrodactyly | 8 | 10 |
| Tall stature | 49 | 44 |
| Asymmetry of the body with hemihypertrophy/ hemiatrophy | 36 | 16 |
| Truncal and generalized obesity | 49 | 80 |
| Excessive birth weight | 20 | 23 |
| Advanced osseous maturation | 36 | 43 |
| Hepatomegaly | 91 | 99 |
| Long and/or large ears | 133 | 77 |
| Large phallus | 22 | 13 |
| Macrotestes | 13 | 8 |
| Large hands | 47 | 23 |

* Pictures of Standard Syndromes and Undiagnosed Malformations, Version 3.0, 1991
† London Dysmorphology Data Base, 1991

Extensive summaries of overgrowth conditions, in addition to specific information about these conditions, are found in articles and chapters by Beighton,[5] Cohen,[6] and Gorlin and associates.[2] The reader will find these references of benefit in evaluating the child with overgrowth.

### REFERENCES


1. Johnson JP, et al. *Pediatrics* 1983;71:219-223.
2. Gorlin RJ, et al. *Syndromes of the Head and Neck*. 3rd ed. New York, NY: Oxford University Press; 1990:323-352.
3. Patterson JH. *Birth Defects* 1969;5(4):117-121.
4. David TJ, et al. *J Med Genet* 1981;18:294-298.
5. Beighton P. *Inherited Disorders of the Skeleton*. New York, NY: Churchill Livingstone; 1988:454-473.
6. Cohen MM Jr. *Adv Hum Genet* 1989;18:181-303.
7. Elejalde BR, et al. *Birth Defects* 1977;13(3B):53-67.
8. D'Ercole AJ. *Growth Genet Horm* 1992;8:1-5.
9. Warshaw JB. *Growth Genet Horm* 1992;8:5.