

McCune-Albright Syndrome Division

The McCune-Albright Syndrome is named for the two physicians who described it over 50 years ago. They reported a group of children, most of them girls, with an unusual pattern of associated abnormalities: bone disease, with fractures, asymmetry and deformity of the legs, arms and skull; endocrine disease, including early puberty with menstrual bleeding, development of breasts and pubic hair and an increased rate of growth; and skin changes, with areas of increased pigment distributed in an asymmetric and irregular pattern. Today, we use the term "McCune-Albright Syndrome" to describe patients who have some or all of these bone, endocrine, and skin abnormalities. In the years since it was first identified, however, we have studied many additional patients, and have learned that the condition has a broad spectrum of severity. Sometimes, children are diagnosed in early infancy with obvious bone disease and markedly increased endocrine secretions from several glands; a very few of these severely affected children have died. At the opposite end of the spectrum, many children are entirely healthy and have a normal life expectancy. They have little or no outward evidence of bone or endocrine involvement, may enter puberty close to normal age, and have no unusual skin pigment at all. Because of this marked variability among some patients, the various components of this complicated syndrome are treated separately in the following sections.

ENDOCRINE ABNORMALITIES

Precocious Puberty

When the signs of puberty (development of breasts, testes, pubic and underarm hair, body odor, menstrual bleeding and increased growth rate) appear before the age of 8 years in a girl and 9 1/2 years in a boy, it is termed 'precocious puberty'. In the most common form of precocious puberty, there is early activation of the regions in the brain which control the maturation of the gonads (ovaries in a girl and testes in a boy). One brain center, the hypothalamus, secretes a substance called gonadotropin-releasing-hormone or GnRH. This acts, in turn, on another part of the brain, the pituitary gland, to cause increased secretion of hormones called gonadotropins (LH and FSH) that travel through the bloodstream, and act on the ovaries or testes to stimulate secretion of estrogen or testosterone. Endocrinologists find out whether a child with precocious puberty has early activation of the hypothalamus and pituitary (gonadotropin-dependent precocious puberty) by measuring the levels of LH and FSH in the blood after an injection of a synthetic preparation of GnRH.

After studying many girls with McCune-Albright syndrome, however, we have learned that most do not appear to have early activation of the hypothalamus and pituitary, because their levels of LH and FSH are usually low, or similar to those of prepubertal children. The precocious puberty in McCune-Albright girls is caused by estrogens which are secreted into the bloodstream by ovarian cysts, which enlarge, and then decrease in size over periods of weeks to days. The cysts can be visualized and measured by ultrasonography, in which sound waves are used to outline the dimensions of the

ovaries. The cysts may become quite big, occasionally over 50 cc in volume (about the size of a golf ball). Frequently, menstrual bleeding and breast enlargement accompany the growth of a cyst. In fact, menstrual bleeding under 2 years of age has been the first symptom of McCune-Albright syndrome in 85% of patients. Although ovarian cysts and irregular menstrual bleeding may continue into adolescence and adulthood, many adult women with McCune-Albright syndrome are fertile, and can bear normal children.

The precocious puberty in McCune-Albright syndrome has been difficult to treat. After surgical removal of the cyst or of the entire affected ovary, cysts usually recur in the remaining ovary. A progesterone-like hormone called Provera can be given to suppress the menstrual bleeding, but does not appear to slow the rapid rates of growth and bone development, and may have unwanted effects on adrenal functioning. The biosynthetic forms of GnRH (Deslorelin, Histerelin, and Lupron) which suppress LH and FSH, and are used to treat the common, gonadotropin-dependent, form of precocious puberty, are not effective in most girls with McCune-Albright syndrome. An investigational form of treatment, using oral medications which block estrogen synthesis, (testolactone and fadrozole) is now being tested in girls with McCune-Albright syndrome, and has been beneficial in many patients.

Thyroid Function

Almost 50% of patients with McCune-Albright syndrome have thyroid gland abnormalities; these include generalized enlargement called goiter, and irregular masses such as nodules and cysts. Some patients have subtle structural changes detected only by ultrasonography. Pituitary thyroid-stimulating-hormone (TSH) levels are low in these patients, and thyroid hormone levels may be normal or elevated. Therapy with drugs which block thyroid hormone synthesis (Propylthiouracil or Methimazole), can be given if thyroid hormone levels are excessively high.

Growth Hormone

Excessive secretion of pituitary growth hormone has been seen in a few patients with McCune-Albright syndrome. Most of these have been diagnosed as young adults, when they developed the coarsening of facial features, enlargement of hands and feet, and arthritis characteristic of the condition termed acromegaly. Therapy has included surgical removal of the area of the pituitary which is secreting the hormone, and the use of new, synthetic analogs of the hormone somatostatin, which suppress growth hormone secretion.

Other Endocrine Abnormalities

Rarely, adrenal enlargement, and excessive secretion of the adrenal hormone cortisol is seen in McCune-Albright syndrome. This may cause obesity of the face and trunk, weight gain, skin fragility and cessation of growth in childhood. These symptoms are called Cushing's Syndrome. Treatment is removal of the affected adrenal glands, or use of drugs which block cortisol synthesis.

Some children with McCune-Albright syndrome have very low levels of phosphorus in the blood due to excessive losses of phosphate in the urine. This may cause bone weakening and the condition called rickets. It may be treated with oral phosphates and supplemental vitamin D.

BONE DISEASE; POLYOSTOTIC FIBROUS DYSPLASIA

The term polyostotic fibrous dysplasia means "abnormal fibrous tissue growth in many bones". In affected areas, normal bone is replaced by irregular masses of fibroblast cells. When this occurs in weight-bearing bones, such as the femur (upper leg bone), limping, deformity and fractures may result. In many children, the arms and/or legs are of unequal length, even in the absence of actual fracture. Regions of fibrous dysplasia are also very common in the bones that form the skull and upper jaw. If these areas begin to expand, skull and facial asymmetry may result. Polyostotic fibrous dysplasia can often be seen in a plain X-ray picture of the skeleton. A more sensitive method of finding lesions is a bone scan, in which a small amount of radioactivity (an isotope of technetium) is injected into a vein, taken up by the abnormal tissues, and detected by a scanner.

The severity of bone disease in McCune-Albright syndrome is quite variable. Some children may be minimally affected, with no asymmetry, deformity or fracture, and lesions detected only by bone scan. In a few children, lesions are only found in the base of the skull. By repeating bone scans at intervals of one to two years, we have seen that in some children, the bone disease may become more extensive over time. Unfortunately, severe bone disease can have permanent effects upon physical appearance and mobility.

There is no known hormonal or medical treatment that has been proven to be effective in controlling progressive polyostotic fibrous dysplasia. Surgical procedures to correct fracture and deformity include grafting, pinning and casting. Skull and jaw changes are often corrected surgically, with great improvement in appearance.

SKIN ABNORMALITIES

The irregular, flat areas of increased skin pigment in McCune-Albright syndrome are called cafe-au-lait spots because, in children with light complexions, they are the color of coffee with milk. In dark-skinned individuals, these spots may be difficult to see. Most children have the pigment from birth, and it almost never becomes more extensive. The pattern of the pigment distribution is unique, often starting or ending abruptly at the midline on the abdomen in front or at the spine in back. Some children have no cafe-au-lait pigment at all; in a few, it is confined to small areas, such as the nape of the neck or crease of the buttocks.

There are seldom any medical problems associated with the areas of cafe-au-lait pigment. Some adolescent children may want to use makeup to obscure areas of dark pigment on the face.

RECENT RESEARCH

So far, we have not found a cure for the bone and endocrine disease in McCune-Albright syndrome. It cannot yet be diagnosed before birth and we cannot accurately predict how severe the disease may become in an affected child. There are no reported cases of any parent being affected, and the children of women with McCune-Albright syndrome are normal. All races appear to be affected equally. Thus, we are not yet certain of the genetic origin of the defect. It is believed, however, that it may be the result of a mutation occurring early in the development of the embryo.

Recently, researchers have discovered abnormal mutations in DNA obtained from the affected ovaries, adrenals and liver of several patients with the McCune-Albright syndrome. The DNA contained the genetic code for one component, called a G protein, of a signalling system which is present in many cells, and which is known to be involved in endocrine cell growth and secretion. The presence of this mutation could result in uncontrolled cell function or hormone secretion. This research is continuing, and it may soon enable us to plan better methods of treatment for patients with the McCune-Albright syndrome.

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The MAGIC Foundation is a national nonprofit organization created to provide support services for the families of children afflicted with a wide variety of chronic and/or critical disorders, syndromes and diseases that affect a child's growth. Some of the diagnoses are quite common while others are very rare.

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