QUESTIONS AND ANSWERS

ABOUT

FIBROUS DYSPLASIA

A PUBLICATION OF

THE PAGET FOUNDATION
FOR PAGET'S DISEASE OF BONE AND RELATED DISORDERS

1. Q. What is fibrous dysplasia and which bones are most commonly affected?

A. Fibrous dysplasia is a chronic disorder of the skeleton characterized by one or more expansile areas in which normal bone is replaced by abnormal bone and fibrous tissue. Fibrous dysplasia can cause uneven bone growth, brittleness and deformity in affected bones.

Any bone can be affected. In some patients, only one bone is affected (monostotic fibrous dysplasia), whereas in other patients numerous bones are affected (polyostotic fibrous dysplasia). The most common sites are the femur (thigh bone), tibia (shin bone), ribs, skull, facial bones, humerus (upper arm), and pelvis. The vertebrae (of the spine) are commonly affected. Fibrous dysplasia in the spine is associated with scoliosis, which can be progressive. If scoliosis is present, it should be monitored for progression. Although many bones can be affected at once, fibrous dysplasia does not spread across joints from one bone to another. However, the bones that make up the skull and pelvis are not separated by joints. Thus, fibrous dysplasia can spread through the skull and pelvis as though they were single bones. Often, multiple affected bones are found on one side of the body.

2. Q. How common is fibrous dysplasia and who is affected?

A. Fibrous dysplasia is a very rare disorder; the exact incidence is not known. It usually affects children and young adults and persists throughout life. If the disease affects more than one bone, it is more likely to produce problems before the age of 10 years. The disease is found equally in males and females and the incidence does not seem to vary among different races.

3. Q. What causes fibrous dysplasia?

A. Cells contain “switches” that are able to recognize stimulating chemicals released by other cells. Fibrous dysplasia is caused by an abnormal chemical “switch” (called the Gs-alpha protein) in the affected cells, which results in their constant over-stimulation. The chemical abnormality occurs because of a mutation (change) in the structure of the gene which produces the protein. The abnormality occurs after conception in the early stages of development, and only affects cells that develop from the original affected cell. Thus, fibrous dysplasia is a congenital disorder, meaning that it is present from birth, although it may not be apparent until much later.

4. Q. Is fibrous dysplasia inherited?

A. No. fibrous dysplasia is not inherited and does not occur in multiple family members.

5. Q. What are the symptoms of fibrous dysplasia?

A. The most common symptoms are bone pain, bone deformity and fractures.

Bone Pain - Bone pain may be present as a result of the expanding fibrous tissue in the bone. The onset of pain in bone that has been sufficiently weakened by the

expansion of fibrous tissue may signal an impending fracture. A fracture may cause a sudden increase in severe pain. Less commonly, abnormal bone could produce pain by pressing on an adjacent nerve. Patients who have considerable deformity of the weight-bearing long bones (thighs and shins) can develop arthritis in the hips and knees.

Bone Deformity **-** Bone deformity can occur anywhere in the skeleton. However, bone deformity caused by fibrous dysplasia is often very apparent when it occurs in the skull and facial bones. Fibrous dysplasia of the skull may cause loss of vision and/or hearing.

Fractures **-** When a bone is affected by fibrous dysplasia, the fibrous tissue expands by invading the surrounding normal bone. As a result, although the fibrous tissue is thick, it is soft and when the surrounding normal bone becomes thin and fragile, fractures can occur, particularly in the long bones of the legs.

6. Q. How is fibrous dysplasia usually diagnosed?

A. The bones affected by fibrous dysplasia usually have a characteristic appearance on x-ray. When there is a doubt about the diagnosis, a physician may obtain a small bone specimen for examination by a pathologist. In some patients, there is an elevation of the enzyme serum alkaline phosphatase (SAP). However, elevated SAP does not always mean that a person has fibrous dysplasia, and affected individuals may have normal laboratory tests, including the SAP levels.

7. Q. What is McCune-Albright syndrome?

A. If the Gs-alpha mutation occurs at a sufficiently early stage in development, tissues other than bone may also be affected. The most typical additional tissues are hormone-secreting glands and pigment-containing skin cells. Drs. Donovan McCune and Fuller Albright separately published classical descriptions of the syndrome in which fibrous dysplasia of bone is seen along with patches of pigmented skin ("cafe-au-lait spots") and hormonal disturbances, particularly "precocious puberty." It has also been shown that the same Gs-alpha mutation can affect other organs, including the heart. In current usage, the term "McCune-Albright Syndrome" describes the finding of fibrous dysplasia together with one or more of the other features.

a. Symptoms of hormonal disturbance:

Early or "precocious" puberty **-** Appearance of secondary sexual characteristics at a very early age appears to be the most common hormonal problem among children with McCune-Albright syndrome. It is much more common in girls than in boys. It is usually caused by estrogen-producing cysts in the ovaries. In McCune-Albright syndrome, this can result in the appearance of pubic hair, breast development and uterine bleeding as early as one year of age or less.

Hyperthyroidism **-** The thyroid gland, a hormone-secreting gland at the lower portion of the front of the neck, regulates metabolism and is essential for normal

mental and physical development. When this gland is overactive, a person suffers from hyperthyroidism. Signs of hyperthyroidism include anxiety, excessive sweating and weight loss. In McCune-Albright syndrome, the problem is usually caused by an overactive nodule within the thyroid gland.

Overactivity of the adrenal glands - The adrenal glands, two hormone-secreting glands located directly above the kidneys, help regulate the body's use of carbohydrates, fat, sugar and protein and also control the body's response to stress. Signs of overactivity of adrenal glands include weight gain, red face, muscle weakness and high blood sugar. Adrenal gland overactivity only occurs within the first year of life in McCune-Albright syndrome.

Oversecretion of pituitary hormones - The pituitary gland, located at the base of the skull beneath the section of the brain called the hypothalamus, is the most important hormone-secreting gland in the body. It not only controls other hormone-secreting glands like the thyroid and the adrenal glands, but is also essential for many normal bodily functions. Signs of oversecretion of pituitary hormones could include:

- Milk production in the breasts of women who have not recently been pregnant. This would indicate overproduction of the pituitary hormone prolactin.
- Gigantism (extreme height). This condition results from overproduction of growth hormone, beginning before puberty.
- Acromegaly (overgrowth of soft tissue or extreme fleshiness). This condition also indicates overproduction of growth hormone. Acromegaly begins after puberty.

High blood calcium (hypercalcemia) due to overactive parathyroid glands - The parathyroid glands, located adjacent to the thyroid gland, control the metabolism of calcium in the body. Signs of high blood calcium caused by excessive production of parathyroid hormone may include nausea, vomiting, constipation and impaired mental function.

Rickets - In this condition, the bones are too soft because not enough calcium and phosphate are deposited to the bone. The soft bones tend to bend under body weight. In rare instances, children with fibrous dysplasia may experience impaired growth and develop skeletal deformities due to rickets. When this happens, it is related to excessive loss of phosphate in the urine due to overproduction of a hormone called FGF-23. Inadequate vitamin D may produce a similar condition.

b. Skin Pigmentation

Patients with McCune-Albright syndrome may have one or more skin lesions. These skin lesions consist of patches of skin that are more darkly pigmented than the patient's normal skin. They are often referred to as "birthmarks" and are usually very irregular in shape.

8. *Q. Why do some patients with fibrous dysplasia also develop hormonal problems while others do not?*

A. It has been demonstrated that the same chemical abnormality of the Gs-alpha protein that is found in bones affected by fibrous dysplasia is present in the affected glands of patients who develop the hormonal disorders. This results in the excessive release of hormones by the affected gland or glands. For example, if the chemical abnormality occurs in the thyroid gland, hyperthyroidism will result.

9. Q. How is fibrous dysplasia treated?

A. ***Surgery***

Surgery is recommended to relieve intractable bone pain, to improve mobility that may be impaired due to skeletal deformity, to facilitate fracture healing, to relieve pressure on the spinal cord, spinal nerves or brain and to treat the unusual complication of bone sarcoma. Some surgical procedures that are commonly used are:

- Removal of affected bone followed by bone grafting in patients with persistent bone pain.
- Removal of a wedge of bone with placement of nails or pins and bone grafts to correct a deformity

Medical treatment

A group of drugs called bisphosphonates, which includes pamidronate (Aredia®), zoledronic acid (Reclast®, Aclasta® and Zometa®)***, alendronate (Fosamax®), and others are drugs that control the breakdown of bone by cells called osteoclasts. They are approved by the US Food and Drug Administration (FDA) for use in patients who suffer from certain tumors that invade bone (breast cancer, prostate cancer and myeloma), for treatment of high blood calcium levels due to cancer and for treatment of Paget's disease of bone and osteoporosis. Results from studies at several medical centers suggest that a regular schedule of treatment with pamidronate (Aredia®) can decrease pain associated with fibrous dysplasia. Some studies suggest that these treatments may slow the progress of fibrous dysplasia to adjacent normal bone whereas other treatments have not done so.

Because of the rarity of fibrous dysplasia, it is unlikely that drug manufacturers will seek specific approval of their products for treatment of fibrous dysplasia. Thus, all such treatment is "off label."

10. Q. Which types of physicians are specialists in the diagnosis and treatment of fibrous dysplasia?

A. Usually fibrous dysplasia patients are evaluated and treated by orthopaedic surgeons since most symptomatic patients have bone pain and/or skeletal deformity. Craniofacial or plastic surgeons are needed for the correction of facial deformities; neurosurgeons are needed for the treatment of brain or spinal complications. Bone tumors should be treated

by orthopaedic surgeons who have been specially trained in bone tumor surgery. Patients with hormonal problems are best treated by endocrinologists. Physicians who specialize in treating bone and mineral disorders will be most experienced with the medical aspects of treating fibrous dysplasia, such as the use of bisphosphonates.

11. Q. What is the prognosis for patients with fibrous dysplasia?

A. The prognosis for patients with fibrous dysplasia varies greatly, depending on the extent of the disease. Young patients who have fibrous dysplasia in many bones may experience more complications than other patients. Patients with one or few lesions may have mild or no symptoms. Hormonal abnormalities are usually treated successfully once the problem is diagnosed. Fibrous dysplasia has seldom been thought to cause death. A very small percentage of patients develop a malignant tumor in an affected bone. The vast majority of skeletal complications occur before the age of 15, with very few fractures occurring after that age. While the nerves of vision and hearing in the skull are frequently surrounded by fibrous dysplasia, vision and hearing loss is distinctly uncommon. For this reason, surgery to free these nerves from fibrous dysplasia is usually not indicated

12. Q. Why is exercise important for fibrous dysplasia patients?

A. Exercise is very important in maintaining skeletal health and is helpful in avoiding weight gain and in maintaining mobility of the joints. Although exercise is recommended for fibrous dysplasia patients, an exercise program should be carefully designed under physician supervision to minimize the risk of fracture.

13. Q. Why are calcium and vitamin D important for fibrous dysplasia patients?

A. Calcium and vitamin D are important for maintaining bone health for everyone including fibrous dysplasia patients. For adults, 1000-1500 mg of calcium and 1000 units of vitamin D (preferably D_3) are considered appropriate doses. However, calcium should be reduced by patients who have calcium kidney stones. For children, doses of 1000 mg of calcium and 400 units of vitamin D are appropriate. The calcium is usually obtained by consuming dairy products.

Calcium and vitamin D intake are particularly important when patients are being treated with a bisphosphonate drug. Also, children who are vitamin D deficient can develop rickets.

**** Zoledronic acid (Zometa®) is used for certain cancer indications. Zoledronic acid, Reclast® - the name of the drug in the U.S. - and Aclasta® - the name of the drug in all countries other than the U.S. - is used to treat osteoporosis and Paget's disease.

The Paget Foundation for Paget's Disease of Bone and Related Disorders provides information and programs for consumers and health professionals on several bone disorders including Paget's disease of bone, primary hyperparathyroidism, fibrous dysplasia, osteopetrosis, and the complications of certain cancers on the skeleton.

Foundation programs and services include:
Patient Education and Assistance, Professional Education, Public Education,
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A copy of the Foundation's annual report is available by writing to the Foundation office or the Office of the Attorney General, Charities Bureau, 120 Broadway, New York, NY 10271.

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