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Review

WINCHESTER SYNDROME: A SHORT REVIEW

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ABSTRACT

Winchester syndrome (WS) comprises dwarfism, coarsening of facial features, corneal opacities, leathery complexion, and hypertrichosis. It is an inherited osteolysis syndrome and is considered a bone syndrome. WS is inherited autosomally recessively, and pathological characteristics include time-worsened cutaneous, ocular, and bony-articular changes, multiple bony articular abnormalities, and cataracts. Although clinical symptoms vary, carpal and tarsal bone disintegration, generalized osteoporosis, increasing joint contractures, low height, peripheral corneal opacities, and coarse facial characteristics are prevalent. Skin characteristics include hypertrichosis, gingival enlargement, leathery skin in an annular or linear distribution, subcutaneous nodules, and extensive progressive multilayered symmetrical limited banding. Mucopolysaccharidosis with enzymatic abnormalities is suspected to be the cause of this disease. WS is now recognized as a homozygous missense mutation (E404K) in matrix metalloproteinase-2. Specialists, including paediatricians, orthopedists, radiologists, ophthalmologists, rheumatologists, neurologists, stomatologists, dermatologists, and psychologists, evaluate patients with symptoms suggesting this pathologic syndrome to make a diagnosis and arrange treatment.

KEYWORDS: *Winchester syndrome, vanishing bone, skeletal-articular system, mucopolysaccharidosis*

INTRODUCTION

Winchester syndrome (WS) includes dwarfism (caused by problems with the skeletal-articular system), coarsening of facial features, corneal opacities, leathery complexion, and hypertrichosis. It is one of the inherited "vanishing bone" syndromes, or osteolysis (1). WS is a genetic condition that runs in the family and is inherited in an autosomal recessive manner. The pathologic alterations' underlying molecular causes are not fully known. The aberrant activity of the fibroblasts, which contributes to some of the pathologic alterations in this condition, was investigated (2, 3). Winchester et al. (4) initially identified pathologic alterations in two sisters, ages 3.5 and 12, who were first cousins, in 1969. These

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sisters were said to have "a novel acid mucopolysaccharidosis" and rheumatoid arthritis-like skeletal abnormalities. Later, Brown and Kuwabara (5) obtained a corneal biopsy; the outcomes were typical of the mucopolysaccharidoses. Three occurrences of this disease were reported in Mexico by consanguineous relatives in 1974 (2). The WS was the name that authors gave to the collection of observations. They specifically identified skin alterations in the extremities and trunk that Winchester et al. (4) did not address. A 3-month-old Iranian was the sixth patient described in 1977 (6), while a 4-year-old in Bombay, India, was diagnosed with a similar instance in 1978 (7). The parents were first cousins in both situations. Dunger et al. (8) reported 2 more occurrences in 1987, while Lambert et al. (9) discussed two examples involving siblings in France, a 13-month-old girl and a 12-year-old girl.

CLINICAL PRESENTATION

One of the hereditary osteolysis syndromes, this rare genetic illness is characterized by the breakdown and resorption of afflicted bones, leading to skeletal abnormalities and functional disability (10). Although the clinical symptoms differ, it is common to notice the dissolution of the carpal and tarsal bones, generalized osteoporosis, progressive joint contractures, low stature, peripheral corneal opacities, and coarse facial features. Hypertrichosis, areas of hyperpigmented, gingival enlargement, hypertrichosis leathery skin in an annular or linear distribution, subcutaneous nodules, and extensive progressive multilayered symmetrical restricted banding of the skin are examples of cutaneous characteristics. The patient's first year of life is often when the first pathologic alterations occur (1, 4, 6). Inflammatory disorders with painful joints and restricted mobility first occur, which is suggestive of rheumatoid arthritis. These inflammatory alterations frequently affect the interphalangeal, metacarpophalangeal, and carpal joints. Both bilaterally and symmetrically were altered. Large joints like the knee and spinal joints may also undergo alterations simultaneously (10).

Winchester reported findings in the second instance involving a 3.5-year-old child with joint abnormalities resulting in rigidity of the spinal column and limbs (4). The patient had this stiffness before turning 20 months old. Permanent flexion contractures in the tiny joints of the hands and feet and in the knee, hip, elbow, and shoulder joints are caused by the disease's gradual course, which may endure for many years. The spinal column may experience similar alterations. Failure of motion could be the outcome of inflammatory changes in the joints. Patients with peripheral corneal opacities develop them between 2 and 5 years, or they are discovered later. The child's eyesight declined over time. Cataracts are not discovered in 5 documented cases involving children 3 months, 13 months, 4 years, 12 years, and 16 years of age (9, 10).

Prognosis and diagnosis

The condition progresses, causing worsening cutaneous, ophthalmic, and bony-articular alterations. In these people, managing anaesthesia can be difficult (11). Destructive changes occur in the joints of the hands, wrists, tarsus, and foot due to intensified osteoporosis, including osteolysis of the carpal and tarsal bones. Backbone compression fractures can result from severe osteoporosis of the vertebral bodies. Strong contractures in the knee and hip joints can make movement difficult (3). Multiple bony articular alterations may result in lifelong impairment. As a result of exacerbated cataracts, visual loss may ensue. Skin and gum biopsy samples should be obtained for histological and ultrastructural analysis to confirm the diagnosis of WS (11).

Pathophysiology

It appears that WS is inherited autosomally recessively (4). The abnormalities that take place in this syndrome are thought to be the result of problems with glycosaminoglycan metabolism. In the urine of two WS patients, Dunger et al. (8) discovered an aberrant oligosaccharide composed of one fucose and two galactose molecules. Hollister et al. (2) and Cohen et al. (3) studies did not find morphological proof of lysosomal storage. These authors contend that uronic acid is also found in 27% of healthy individuals, making metachromasia of the fibroblasts and a 2-fold increase in the uronic acid content in these fibroblasts insufficient evidence for the diagnosis of mucopolysaccharidosis.

The authors contend that WS should not be considered an acid mucopolysaccharidosis but rather a nonlysosomal connective-tissue disorder. Their findings imply that this spectrum of pathologic alterations is mainly mediated by fibroblasts. Anomalous fibroblast functions are likely to manifest as contractures, leathery skin, aberrant collagen in the dermis, and

corneal opacities. The authors advise additional research to understand the pathophysiology of this autosomal recessive illness. A 21-year-old woman with a severe case of osteolysis who was diagnosed with WS had a homozygous missense mutation (E404K) in the active region of matrix metalloproteinase 2 (MMP2) (12). In addition, an MMP2 homozygous new mutation was found in a WS family. Allelic disorders include WS, nodulosis-arthropathy-osteolysis, and Torg syndrome (13). MMP2 deficiency and MMP 2 gene mutations are linked to these two disorders (14, 15). In 13 people with multicentric osteolysis nodulosis and arthropathy, five unique MMP2 mutations were found in India (16). One patient had homozygous mutations in membrane type-1 metalloproteinase (MT1-MMP or MMP14), an inactivating homoallelic mutation that decreased MT1-MMP membrane localization and impaired pro-MMP2 activation as a result of the hydrophobic-region signal-peptide substitution (p.Thr17Arg) (1). The MMP2 gene has a homozygous frameshift variation that has been described (17). The WS phenotype appears to be determined mainly by MMP14 catalytic activity (18).

The following test results and distinctive symptoms of the pathologic alterations should be taken into consideration when diagnosing WS is hypothesized:

the recessive autosomal inheritance pattern in a case history involving siblings and cousins;

arthritic changes that start when the patient is around a year old, along with symptoms resembling rheumatoid arthritis;

joint abnormalities and chronic damage in older individuals, together with short height;

an actual absence of the carpal and tarsal bones is one of the skeleton's distinctive radiologic alterations of multifocal osteoporosis;

the opacity of the cornea's periphery;

the agglomeration of facial characteristics.

With leathery skin, hyperpigmentation, and hypertrichosis, there may be focal or diffuse thickenings. Winter proposed WS diagnostic standards in 1989. These consist of the skeletal radiologic features mentioned above and at least two traits: short stature and progressive articular contractures, corneal opacities, thickened hyperpigmentations or hirsutism of the skin, hypertrophy of the gums, and coarsened facial features (10).

Both small and big joints, as well as the spinal column, experience pathologic alterations. The fundamental characteristic of this pathological syndrome is the involvement of these joints and the spinal column. Changes in the bones that make up the joints and oedema of the periarticular tissues may result in deformities. The joints of the hands and feet, the toes, the wrists, and the metatarsals all show these modifications. Similar changes can affect the backbone, knee, elbow, shoulder, and hip joints (18).

Management

Patients exhibiting signs suggestive of this pathologic illness should be examined by numerous specialists to determine the definitive diagnosis of WS. Pamidronate does not reduce peripheral osteolysis in nodular arthropathy and multicentric osteolysis brought on by matrix metalloproteinase 2 gene mutations (19).

Patients with findings suggestive of this pathologic syndrome involve evaluations by specialists, including paediatricians, orthopedists, radiologists, ophthalmologists, rheumatologists, neurologists, stomatologists, dermatologists, and psychologists, in order to determine the precise diagnosis and plan further medical care. In addition, for appropriate genetic counselling and consultations, families with this syndrome should be referred (20).

The pathologic changes in the spine and limb joints impair the patient's ability to be active. Therefore, exercise as a treatment is suggested. Orthopaedic devices are necessary for some WS patients. However, future therapies are needed for a long-term treatment plan (21).

CONCLUSION

WS includes hypertrichosis, corneal opacities, leathery skin, and coarsening of the facial features. It is an inherited bone syndrome called osteolysis syndrome. The homozygous missense mutation (E404K) in the active site of MMP2 currently causes WS. MT1-MMP and MMP14 also cause this condition. Families with this syndrome should be referred for proper genetic counselling and consultations. It is advised to exercise as a treatment. Some patients with WS need orthopaedic equipment. For a long-term treatment strategy, nevertheless, further therapies are required.

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