

Wilson's disease: An endocrine revelation

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ABSTRACT

Wilson's disease is an inherited disorder of copper metabolism. The affected patients, who otherwise have a near normal life span, may often suffer from some potentially treatable and under recognized endocrine disorders that may hinder their quality of life. We explored previously published literature on the various endocrine aspects of this disease with their probable underlying mechanisms, highlighting the universal need of research in this area.

Key words: Bone mineral density, hypothyroidism, hepatic osteodystrophy, renal tubular acidosis, Wilson's disease

INTRODUCTION

Wilson's disease is an inherited disorder of copper metabolism, which is characterized by an accumulation of copper that occurs predominantly in the liver and the brain. Although it is a rare autosomal recessive disease, it appears to have gained significant recognition in countries like India and a state like Tamil Nadu wherein the frequency of consanguineous marriages amounts to 20% thereby having a significant impact in increasing the prevalence.^[1,2]

Although the accumulation of copper begins at birth, symptoms of this disorder appear later, generally between second and fourth decade of life. In a majority of patients with the disorder, early recognition and appropriately treatment generally result in resolution of symptoms and an improved quality of life.^[3] Liver transplantation is a definitive form of treatment which subsequently corrects the expression of the underlying genetic defect and may not be an option in many developing countries in view of limited resources.

Patients with Wilson's disease, who otherwise have a near normal life span with the current treatment options, often may have some potentially treatable and frequently under recognized endocrine disorders that may hinder their quality of life.^[3,4]

The endocrine manifestations of Wilson's disease may include disorders of growth and puberty, hypothyroidism, hypoparathyroidism, and metabolic bone disease. However, there appears to be a paucity of medical literature with regards to the prevalence and magnitude of these endocrine manifestations in Wilson's disease.^[5-7]

ENDOCRINE MANIFESTATIONS OF WILSON'S DISEASE

Growth and puberty may be significantly affected in patients with Wilson's disease, secondary to the presence of a long standing chronic illness. However, literature pertaining to this appears to be inadequate in connection with the magnitude of this problem. There are a few case reports which might suggest that infertility, anovulation, amenorrhea, and short stature do occur in patients with Wilson's disease.^[5]

The current pathophysiology for short stature in patients with Wilson's disease is still not completely understood. However, apart from the traditional risk factors for short stature in any patient with chronic liver disease such as poor nutritional intake, fat malabsorption, trace element deficiency, and a relative state of growth

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hormone resistance due to a poor hepatic insulin like growth factor-1 (IGF-1) synthesizing capacity,^[8] there is also an additional contribution by a high prevalence of renal tubular acidosis in patients with Wilson's disease.^[9] Therefore the growth stunting seen in these individuals seems to be multifactorial.

Hypogonadotropic hypogonadism secondary to chronic liver disease is the most common cause of gonadal dysfunction in patients with Wilson's disease. Several other factors like excessive sex hormone binding globulin production, elevated prolactin levels, and direct suppression of leydig cell function also contribute to gonadal dysfunction in these patients.^[10]

In addition, ovarian follicular aromatase dysfunction has also been documented in subjects with Wilson's disease. Kaushansky *et al.* has demonstrated a disturbed ovarian function in a series of patients with Wilson's disease, as evidenced by low estradiol, high total testosterone (T) levels along with a normal free T and elevated androstenedione. An interference of ovarian follicular aromatase activity, possibly due to copper intoxication could explain these findings as the cause of the ovulatory disturbances of Wilson's disease.^[11]

The metabolic bone disease that is associated with Wilson's disease includes rickets, osteomalacia, osteoporosis, and renal tubular acidosis (RTA).

Both proximal and distal RTA have been reported in patients with Wilson's disease.^[7] The clinical presentation of RTA in Wilson's disease includes a number of facets which may involve hypercalcuria, nephrocalcinosis, urolithiasis, hypokalemic periodic paralysis, and a low bone mass.^[12] Surprisingly, urolithiasis has been reported in about one sixth of patients with Wilson's disease and at times, renal colic may be the sole presenting feature.^[13] Indeed, undiagnosed nephrocalcinosis may progress to end stage renal disease.^[14] An acute presentation with hypokalemic periodic paralysis has been described.^[15] The development of renal tubular acidosis appears to be dependent on the duration of untreated copper overload.^[16]

Although there does not appear to be much data on the impact of Wilson's disease on Bone Mineral Density (BMD), several mechanisms have been described as to how liver disease may affect bone strength.

Bony deformities have been reported in as many as 33% of patients of Wilson's disease in a publication from our institute around 25 years ago.^[17] About 50% of patients with

this disorder were found to have a low bone mass which had no correlation with vitamin D status.^[18]

Low BMD is the predominant component of hepatic osteodystrophy and has been reported in about 20-50% of these patients, based on Dual energy X-ray Absorptiometry (DXA).^[19,20] Osteomalacia, which may be due to the presence of concomitant vitamin D deficiency and calcium malabsorption was traditionally considered to be the major metabolic bone disorder in patients with chronic liver disease, but is now observed in only a minority of patients.^[21]

A reduced BMD in patients with hepatic disease, tends to largely affect the trabecular bone and has been characterized by low bone turnover with reduced osteoblast function and low serum osteocalcin levels. However, the exact pathogenesis of hepatic osteodystrophy is still largely unknown and there appears to be much controversy with regard to the risk factors in relation to osteoporosis in CLD and in Wilson's disease.^[22]

Diabetes has occasionally been described in patients with Wilson's disease. Excessive fat deposition in liver and nuclear glycogen deposition contributing to hepatic insulin resistance has been postulated in these individuals.^[23]

Penicillamine, Zinc, and Trientine are the therapeutic agents that have been conventionally utilized in the management of Wilson's disease. The effect of these drugs on bone mineral metabolism has not been well characterized. The study of these drugs on bone mineral metabolism has yielded conflicting results.^[24] Chelating agent such as Penicillamine, that have been used for the treatment of Wilson's disease have been reported to reduce the severity of renal tubular disease.^[25]

CONCLUSION

Indeed there appears to be a universal need for research in this area. It is therefore vital that medical institutions of this country, who treat large volume of these patients, investigate in detail the various endocrinopathies that are associated with Wilson's disease. This article emphasizes the need for further studies in this area to add on to add to the existing literature. This will not only help patients of Wilson's Disease who are suffering from endocrine disorders but will also enable us to formulate guidelines for appropriate screening and management of these individuals. Addressing these issues would further improve the quality of life of these patients who appear to be currently effectively managed for their primary manifestations.

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