Arthrophathic Presentation of Wilson’s Disease

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Abstract
A patient is described who presented with polyarthritis involving small and large joints of limbs with later onset of tremors affecting all four extremities. Investigations including genetic study confirmed the diagnosis of Wilson’s disease (WD). The case highlights the importance of considering the possibility of WD in young patient presenting with repetitive unexplained joint symptoms with or without tremor.

INTRODUCTION
Wilson’s disease (WD) is an autosomal recessive disorder of biliary copper excretion due to mutation in the ATP7B gene on chromosome 13, with an estimated prevalence of 1 in 30,000. Since the publication of Wilson’s classic article (Wilson 1912) the illness, which has come to bear his name, has generally been considered to be a neurologic disease. Of late years, however there has been an increasing awareness that WD is a genetically determined metabolic disorder involving liver and many other systems. Symptomatic joint disease, which occurs in 25-50% of patients,1,2 usually presents late in course of the disease, frequently after 20 years of age; although occasionally osteoarthritis may be the initial manifestation. There was no Kayser Fleischer (KF) ring on naked eye examination. Motor system examination showed mild rigidity and bradykinesia involving all four limbs. He had normal power, generalized brisk deep tendon reflexes, and bilateral flexor plantar response. There was no evidence of dystonia. Sensation was normal and there was no cerebellar sign. Examination of musculoskeletal system showed flexion deformities of fingers and toes. Over the past two years he noticed intermittent tremulousness of all four limbs both at rest and in posture, but not on intention. He denied history of morning stiffness, joint swelling, skin rash, and fever. He had no history of behavioural disturbance, cognitive decline, weakness of any limb, stiffness of extremities, sensory impairment, sphincteric disturbances, convulsion, unsteadiness of gait, dimness of vision, deafness, and symptoms suggestive of lower cranial nerve dysfunction.

There was no history of jaundice, upper and lower gastrointestinal bleeding. He denied any history of consanguinity. He has four brothers and three sisters. He reported that one of his sisters died of jaundice at 15 years of age. His academic career is up to class VI.

Physical examination on admission revealed mild pallor, lack of jaundice and skin pigmentation, with a pulse rate of 76/min, BP of 120/80 mm of Hg, respiration 18/min. Neurological survey disclosed that he was right handed individual with normal higher mental function (MMSE score being 28). Fundus oculi and cranial nerve examination were normal. There was no Kayser Fleischer (KF) ring on naked eye examination. Motor system examination showed mild rigidity and bradykinesia involving all four limbs. He had normal power, generalized brisk deep tendon reflexes, and bilateral flexor plantar response. There was coarse tremor in distal part of upper and lower limbs, present both at rest and in posture, with no terminal accentuation during action. There was no evidence of dystonia. Sensation was normal and there was no cerebellar sign. Examination of musculoskeletal system showed flexion deformity of proximal and distal interphalangeal joints of both hands and feet with mild tenderness. There was painful restriction of movements of both hip and knee joints with palpable joint crepitus in both the knees. Gastrointestinal examination showed only mild nontender firm splenomegaly.

Investigations revealed Hb-11.5 gm/dl, with normal total and differential WBC counts, ESR 20 mm in the 1st hour, reticulocyte count 2%, and platelet count 1,50,000/cu mm. Routine urinalysis was normal. Blood biochemistry including Blood sugar, urea and creatinine was normal. The serum calcium was 8.9 mg/dl and serum phosphate was 4 mg/dl. Liver function test revealed serum albumin 3.5 gm/dl, globulin 4.9 gm/dl, total serum bilirubin 0.5 mg/dl, SGOT 46 IU/ml, SGPT 44 IU/ml, and serum alkaline phosphatase 137 IU/l. The ELISA for HBsAg was negative. His prothrombin time was 19 secs (control being 14 secs). The serum ceruloplasmin was 3 mg/dl (normal 0.2-4.5 gm/l). The slit lamp examination
demonstrated the presence of clear KF ring. Collagen vascular profile including C-reactive protein, Rheumatoid factor, and anti-nuclear factor was negative. The Coomb’s test was negative. 24 hours urinary copper excretion was 120 micrograms (normal<40(gm/24 hrs.). Upper GI endoscopy showed grade II oesophageal varices. USG of abdomen revealed heterogeneous echotexture of liver parenchyma, portal venous diameter having 13 mm, and splenomegaly. CT scan of brain showed prominent sulci suggesting generalized cortical atrophy and hypodensity in the right basal ganglia region. Liver biopsy could not be performed because of altered prothrombin time. MRI could not be arranged for financial constraints. Skeletal survey - X-ray of both hands showed osteoporotic changes with sclerosis of joint margins, bony fragmentation and fringed margins of interphalangeal joints (Fig. 1); X-ray of knee joints showed degenerative changes including osteophytes, marginal sclerosis, osteopenia and subchondral paint brush appearance (Fig. 2); X-ray of hip joints showed typical degenerative changes including osteophytes, sclerosis and diffuse osteoporosis (Fig. 3). Haplotype analysis was performed using three microsatellite markers for the ATP7B gene namely, D13S 316, D13S 133, and D13S 314. For all of them, we used the same polymerase chain reaction (PCR) conditions: 33 cycles of 94°C for 20 seconds, 62°C for 30 seconds, and 72°C for 25 seconds. For each marker we used one fluorescently labeled primer in the PCR. To define the exact site of the fragment detected by the respective marker, an ABI Prism 310 Genetic analyzer and Genescan software were used. For comparison with the numbering of haplotypes according to convention, we have received and haplotype

**DISCUSSION**

Our patient presented with small and large joint polyarthritis as revealed by mildly tender, deformed distal and proximal interphalangeal joints of both hands and feet with painful restriction of both hip and knee joints. Besides, he had extrapyramidal system involvement as judged by the
presence of resting tremor affecting all four limbs, rigidity and bradykinesia. From the above features we considered three possibilities. It included connective tissue disorder in the form of rheumatoid arthritis with secondary CNS vasculitis affecting the basal ganglia, hypoparathyroidism having hypocalcemic joint involvement with basal ganglia dysfunction, and WD presenting with premature osteoarthritis affecting small and large joints and basal ganglia involvements. Slit lamp examination revealed prominent KF rings in both eyes. This narrowed down our diagnostic possibility to WD. Besides this, a low serum ceruloplasmin level, an increased 24 hours urinary copper excretion, and genetic study showing mutation of ATP&B gene were consistent with the diagnosis of WD. Clinical and radiological features suggested small and large joint arthropathy affecting interphalangeal, metacarpophalangeal, wrist, hip, and knee joints.

The general radiographic features of Wilson’s Disease consists of osteopenia and arthropathy. The arthropathy of WD observed on radiographic evaluation in 3/4th of all patients is a degenerative process that resembles premature osteoarthritis. The arthropathy generally involve the spine, large appendicular joints such as wrist, elbow, shoulder, hip, knee, and metacarpophalangeal joints, associated with periarticular osteopenia. Radiologic studies reveal typical degenerative changes including osteophytes, sclerosis, subchondral pseudocysts, and bone fragmentation. Our patient had osteoarthritic involvement of large and small appendicular joints including interphalangeal, metacarpophalangeal, wrist, hip, and knee joints.

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The prognosis of arthritis in Wilson’s disease is not known. It may be that by the time arthritis develops in WD, most of them become neurologically disabled and it has not been studied in that way. Moreover, whether a particular type of mutation in ATP7B Gene is associated with early arthopathic presentation of WD is not known.

**CONCLUSION**

With varied clinical manifestations of Wilson’s disease being encountered, a heightened awareness among the clinicians that premature osteoarthritis may be a presenting feature will help in early diagnosis and initiation of early therapy in this group of patients.

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**References**