Multiple fractures and impaired bone metabolism in Wolfram syndrome: a case report

Antonino Catalano¹
Federica Bellone¹
Giuseppe Cicilia²
Annalisa Giandalia¹
Nunziata Morabito¹
Domenico Cucinotta¹
Giuseppina Tiziana Russo¹

¹ Department of Clinical and Experimental Medicine, University Hospital of Messina, Italy
² Orthopaedics and Traumatology Unit, University Hospital of Messina, Italy

Address for correspondence:
Antonino Catalano, M.D., Ph.D
Department of Clinical and Experimental Medicine
University Hospital “G. Martino”
Via C. Valeria
98125 Messina, Italy
Phone: +39 090 2213946; Fax: +39 090 2217176
E-mail: catalanoa@unime.it

Summary
Wolfram Syndrome (WS) is a rare and lethal disease characterized by optic atrophy, diabetes mellitus, diabetes insipidus, and hearing loss. To date, osteoporotic related fractures have not been reported in affected patients. Here, we describe the case of a man affected by WS complicated by several bone fragility fractures.

Case presentation
A 50-year-old Caucasian man was hospitalized because of a fracture of the right leg due to fall occurred at home. At admission, he had asthenia, without any neurological focal sign. A brain CT showed a reduction of the attenuation values of the periventricular white matter bilaterally and ample subarachnoid spaces and ventricular system above and below tентorial, the brain stem, the middle cerebellar peduncles and the worms have less volume than normal. Previously undiagnosed multiple rib fractures were also detected.

To the best of our knowledge, this is the first report of osteoporotic related fractures in a patient affected by WS. Although no effective treatments are currently available to delay the progression of the disease, this case report suggests to evaluate fracture risk in the diagnostic work-up of WS.

KEY WORDS: Wolfram syndrome; diabetes; bone; osteoporosis; fractures.

Introduction
Wolfram syndrome (WS) is a rare autosomal recessive genetic disorder. It is also known as DIDMOAD syndrome, an acronym for diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA), and sensorineural deafness (D) (1). Wolfram and Wagener, who found four of eight siblings with juvenile diabetes mellitus and optic nerve atrophy, first described the syndrome in 1938 (2). The diagnosis is delayed by the progressive occurrence of the different clinical features over time, with most of WS patients presenting with non-immune, insulin-deficient diabetes mellitus followed by optic atrophy in the first decade, central diabetes insipidus and sensorineural deafness in the second decade, delayed renal outflow tracts in the third decade, and multiple neurological abnormalities early in the fourth decade (1, 3). Although there have been over 200 WS cases reported to date, the prognosis is still fatal, as most patients prematurely die because of severe neurological disabilities, such as bulbar dysfunction and organic brain syndrome (3).

Two different genetic deficits are responsible for clinical variants of WS (type 1 and type 2 WS), with gastric or intestinal strictures, that were noted during hospitalization in spite of a satisfactory surgical osteosynthesis by internal fixation. Because of polyuria and excessive thirst, that were noted during hospitalization in spite of a metabolic unit of our University Hospital because of tibia and fibula fractures. After surgery, at day 7 he was admitted in our Metabolic Unit of our University Hospital because of a fracture of the right leg due to fall occurred at home. The patient underwent satisfactory surgical osteosynthesis by internal fixation. At day 5 he underwent surgical osteosynthesis by internal fixation. After surgery, at day 7 he was admitted in our Metabolic Unit of our University Hospital because of tibia and fibula fractures. After surgery, at day 7 he was admitted in our Metabolic Unit of our University Hospital because of tibia and fibula fractures. After surgery, at day 7 he was admitted in our Metabolic Unit of our University Hospital because of tibia and fibula fractures.

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good glycemic control and the absence of glycosuria, plasma and urine osmolality were measured (315 and 287 mOsm/KgH2O, respectively), confirming the suspicion of diabetes insipidus (6). The estimated glomerular filtration rate (eGFR) according to the CKD-EPI equation was 45 ml/min. Due to the clinical features including early onset of diabetes mellitus, loss of vision due to optic atrophy and sensorineural hearing loss, but also sign of diabetes insipidus, the diagnosis of WS type 1 was hypothesized and then confirmed by the identification of a mutation in gene WFS1 encoding wolframin at DNA analysis (1, 4). Because of multiple fractures, the patient also underwent a complete workout for osteoporosis. Bedside quantitative ultrasound (QUS) at the proximal phalangeal metaphysis of the last four fingers of the non-dominant hand (using a DBM Sonic Bone Profiler, Igea, Carpi, Italy) measured several parameters: Amplitude Dependent Speed of Sound (AD-SoS), Bone Transmission Time (BTT), Fast Wave Amplitude (FWA), Signal Dynamic (SDy), and, finally, Ultrasound Bone Profile Index (UBPI) was automatically calculated \[ UBPI = 0.018 x SDy - 0.0560 x FWA 0.0560 - 1.1467 x BTT + 3.0300 \], which are presented in Table 1. Serum levels of surrogate markers of bone remodeling were determined, revealing a high bone turnover, with elevated levels of the bone resorption marker C-telopeptide of type 1 collagen (CTX) and the bone formation marker osteocalcin (BGP) (Table 1); moreover, a secondary hyperparathyroidism resulting from the combination of vitamin D deficit and incipient renal failure (eGFR: 45 ml/min) in addition to referred low dietary calcium intake was also observed (Table 1). All these exams indicated a reduced bone density and impaired bone metabolism consistent with severe osteoporosis with elevated bone turnover. Medical treatment for osteoporosis was then started with high dose of cholecalciferol (25000 UI/weekly) and calcium carbonate (500 mg/day), and programming the i.v. administration of zoledronic acid (5 mg/yearly) after the correction of secondary hyperparathyroidism. Treatment of diabetes insipidus with desmopressin nasal spray administration (5 µg twice a day) was also introduced during hospitalization. At day 16, after full recovery of consciousness and amelioration of clinical and laboratory parameters, the patient was then discharged. An insulin MDI regimen with insulin lispro and insulin glargine (40 UI/die) for the management of type 1 diabetes mellitus and valsartan 160 mg/die for the treatment of high blood pressure were confirmed at discharge.

Our work has been performed in accordance with ethical standards laid down in the 1964 Declaration of Helsinki. Informed consent was acquired from the patient for the use of his clinical data.

Discussion

WS is a very rare monogenic disease resulting from the combination of several medical disorders including diabetes mellitus, diabetes insipidus, optic atrophy, and hearing loss (1).
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Table 1 - Phalangeal quantitative ultrasound (A), glucometabolic indices (B), bone metabolic parameters (C), and other laboratory data (D) of a patient affected by Wolfram syndrome with multiple fragility fractures.

<table>
<thead>
<tr>
<th>A. Phalangeal quantitative ultrasound</th>
<th>B. Glucometabolic indices</th>
<th>C. Bone metabolism</th>
<th>D. Other laboratory tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD-SoS (m/sec)</td>
<td>Fasting glucose (normal values 60-110 mg/dl)</td>
<td>Calcium (normal values: 8.2-10.4 mg/dl)</td>
<td>Hemoglobin (normal values: 14.4-18 g%)</td>
</tr>
<tr>
<td>UbPI (U)</td>
<td>HbA1c (normal values: 4-6 %)</td>
<td>Phosphorus (normal values: 3.2-4.2mg/dl)</td>
<td>Creatinine (normal values: 0.5-1.2 mg/dl)</td>
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<tr>
<td>BTT (µsec)</td>
<td>Glycosuria (normal values: absent)</td>
<td>Alkaline phosphatase (normal values: 0-130 U/l)</td>
<td>Total protein (normal values: 6-8.2 gr/dl)</td>
</tr>
<tr>
<td>T-Score (SD)</td>
<td>Chetonuria (normal values: absent)</td>
<td>Osteocalcin (normal values: 5-35 ng/ml)</td>
<td>Sodium (normal values: 130-149 mmol/L)</td>
</tr>
<tr>
<td>Z-Score (SD)</td>
<td></td>
<td>25(OH)D (normal values: &gt;30 ng/ml)</td>
<td>Potassium (normal values: 3.5-5.2 mmol/l)</td>
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<td></td>
<td></td>
<td>PTH (normal values: 8-76 pg/ml)</td>
<td>Serum osmolality (normal values: 275-295 mOsm/KgH2O)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum CTX-1 (normal values: 0.11-0.74 μg/l)</td>
<td>Urine osmolality (normal values: mOsm/KgH2O)</td>
</tr>
</tbody>
</table>

| AD-SoS (m/sec) | 1634 | Fasting glucose (normal values 60-110 mg/dl) | 132 |
| UbPI (U) | 0.05 | HbA1c (normal values: 4-6 %) | 7.8 |
| BTT (µsec) | 0.68 | Glycosuria (normal values: absent) | Absent |
| T-Score (SD) | -7 | Chetonuria (normal values: absent) | Absent |
| Z-Score (SD) | -6.39 | | |

We reported the case of a man suffering from WS who incurred into multiple fractures because of a trivial fall. In order to explore bone health status, phalangeal QUS and several bone turnover markers, as well hormonal regulators of bone metabolism have been measured. In particular, phalangeal QUS measurements were previously associated with fractures and showed good association with DXA data (7); moreover phalangeal QUS may serve to evaluate bone quality that is, independently from DXA measurements, a determinant of bone strength (8, 9). QUS evaluation as well as clinical and laboratory data all indicated a reduced bone density and impaired bone metabolism consistent with severe osteoporosis with elevated bone turnover in this patient. Higher fracture rate was not previously reported in WF patients but, as WFS1 negatively regulates the ER stress response, and WFS1 deficiency in mice increases ER stress and triggers apoptosis, it may be speculated that apoptosis of bone cells could mediate bone fragility in WS (1, 10). WS clinical features progressively develop overtime, and the increased fracture risk may be a late manifestation of this rare syndrome. Thus, our patient was aged 50 years, and it has been described that WS patients usually die prematurely at the median age of 30 years (range 25-49 years) (3, 11), which could explain the lack of previous reports in the literature.

The alternate hypothesis is that fractures are related to the presence of type 1 diabetes mellitus per sé. The association of bone abnormalities with diabetes has been increasingly recognized (12-15) and, irrespectively of age, subjects with type 1 diabetes show decreased value of bone mineral density (BMD) and increased fracture risk when compared with healthy age-matched controls (13, 14). Impairment of bone health is linked to insulin deficiency that has detrimental effects on bone biomechanical properties, leading to decreased strength and mineralized surface area, and also decreased osteoid surface (16, 17). Chronic hyperglycemia may increase PPARγ2 expression, thus suppressing osteoblast differentiation and promoting an adipocyte-like phenotype (18, 19); moreover it encourages non-enzymatic glycosylation of key proteins in bone, such as collagen type 1, and animals with high content of pentosidine, a glycation-involving cross-link of collagen type 1, showed higher fracture risk, despite normal BMD (19, 20). Due to the early age of its onset, type 1 diabetes can result in failure to reach an adequate peak of bone mass, as possibly in the case of our patients, and impaired bone metabolism related to diabetes could maintain a lower BMD in comparison to healthy age- and sex- matched subjects (18). The role of some adipokines, as leptin, ghrelin and adiponectin, may also exert additional detrimental effects on bone in diabetic subjects (21, 22).

Also diabetes insipidus may contribute to the pathogenesis of impaired bone strength in WS. Thus, arginine vasopressin (AVP) was shown to stimulate renal production of PGE2 and PGF2α may be involved both in bone formation and bone resorption (23), and a reduced urinary excretion of PGs was reported in subjects with diabetes insipidus (24); moreover, hyperactivation of the hypothalamus-pituitary-adrenal axis may increase cortisol secretion with consequent corticosteroid-related bone impairment (25).

Finally, the high risk of fall, due to vision deficit and neurological alterations observed in affected subjects (9, 13, 26), also boosts the possibility of fractures in WS. The high bone turn-over rate observed in our patient, as resulted from high levels of BGP and serum CTX was consistent with the recent osteoporotic fractures, and possibly with prolonged immobilization (27). The low vitamin D levels and the decreased kidney function may also have contributed to the hyperparathyroidism with further perturbation of bone homeostasis and demineralization (28).

In conclusion, to the best of our knowledge, this is the first report of osteoporosis and fragility fractures in a patient af-
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affected by WS. Although no specific treatment of WS is currently available for this rare disease, screening for osteoporosis and fracture prevention should be required in order to improve quality of life in affected subjects.

References