**Case Report**

**Osteopetrosis complicated by schizophrenia results from mutations on Chromosome 16**

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**Abstract:** Objective: To investigate the genetic pathogenesis and diagnosis of osteopetrosis, and its relationship with schizophrenia. Methods: Conducting extensive review of literature related to osteopetrosis patients with schizophrenia, summing common disease genes and diagnosis of osteopetrosis in association with schizophrenia. Results and Conclusion: Osteopetrosis is a rare inherited metabolic bone disease, with 12 kinds of common disease genes. In particular, mutations at 16p13.3 are closely related to schizophrenia. In recent years, molecular studies have identified three genes on chromosome 16 closely associated with schizophrenia, located at 16p13.3, 16p11.2, 16p13.11. Thus osteopetrosis and schizophrenia may not be two independent diseases, and understanding their relationship may help to identify schizophrenia at an earlier stage in osteopetrosis patients with mutations of chromosome 16. Conversely, patients with a family history of schizophrenia may be at increased risk for developing osteopetrosis.

**Keywords:** Osteopetrosis, schizophrenia, pathogenic gene, diagnosis

**Introduction**

Osteopetrosis is an extremely rare hereditary metabolic bone disease characterized by a decrease in number or functionality of osteoclasts, resulting in defective bone resorption. Typical clinical manifestations include increased bone density, skeletal deformities, and various associated complications. Osteopetrosis is also known as marble bone disease or Albers-Schönberg disease. Schizophrenia is a group of diseases with a complex etiology comprising hereditary, neurodevelopmental, neurochemical and socio-environmental factors. The clinical syndrome of schizophrenia is characterized by dysfunction of reasoning, emotions, insight and other aspects of thought and behavior. Patients generally have intact consciousness, acceptable intellectual capacity, although during the course of their disease they may have episodes of disturbed cognitive function. At first glance, there seems to be no discernable connection between osteopetrosis and schizophrenia, the former being a metabolic bone disease, and the latter being a neuropsychiatric disorder. However, we seek to explore the possibility of such an association in the present case study of a patient diagnosed with both disorders and possessing common identified genetic mutations. In this study, the patient was given a written informed consent.

**Case report and results**

The patient is a 25 year old female, presenting with a 2 year history of continuous, low-intensity lower back pain that initiated as a result of an accidental fall (landing on her lower back). She experienced no limitations of activities and thus did not seek medical attention. 3 months ago, following the pass away of her brother, she reports an increase in intensity of her pain, with a sensation of rigidity located in her lumbar spine, and activity limitation. The symptoms improved with rest and were exacerbated with emotional stress. During this time, she also reports oligomenorrhea (once per 2-3 months, low flow volume), as well as gradual onset of depressed mood, auditory hallucinations, thoughts of self-harm and suicide. She was subsequently admitted to our hospital for evaluation of lower back pain and psychiatric symp-
A case report of osteopetrosis

Table 1. Auxiliary examinations: bone density of lumbar vertebrae

<table>
<thead>
<tr>
<th></th>
<th>L1</th>
<th>L2</th>
<th>L3</th>
<th>L4</th>
<th>Average L1-4</th>
</tr>
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<tbody>
<tr>
<td>T-score</td>
<td>3.4</td>
<td>2.9</td>
<td>3.3</td>
<td>2.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Z-score</td>
<td>3.5</td>
<td>3.0</td>
<td>3.4</td>
<td>2.8</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Symptoms. A preliminary diagnosis of schizophrenia was made based on positive family history, as well as the suicide-death of her brother 3 months prior.

Physical examination

The patient had stable vital signs on admission, clear consciousness, psychomotor excitement, normal cardiopulmonary and abdominal examination, and without notable trunk and limb deformities.

Biochemical markers of bone turnover

Serum calcium (Ca) 2.19 mmol/L, serum inorganic phosphorus (P) 1.49 mmol/L, bone alkaline phosphatase (B-ALP) 14.81 µg/L, C-terminal telopeptide of type I collagen (CTX-1) 0.605 ng/mL, N-MID osteocalcin (NMID) 31.3 ng/mL, parathyroid hormone (PTH) 6.51 pmol/L, thyroid hormone (TSH) 6.14 mU/L, thyroid peroxidase antibody (TPOAb) 131.1 IU/mL. Her bone mass density was detected as below (Table 1).

Serology

Immunoglobulin G (IgG) 20.1 g/L, Immunoglobulin A (IgA) < 66.7 mg/L, Immunoglobulin M (IgM) 2350 mg/L, antinuclear antibody (ANA) weakly positive, anti-neutrophil cytoplasmic antibody (ANCA) negative, erythrocyte sedimentation rate (ESR) 20 mm/h, C-reactive protein (CRP) 4.24 mg/L, urinary light chains normal, rheumatoid factor (RF) < 20.00 IU/mL

Radiography

The three images displayed as bellow. Figure 1A shows normal appearance of heart and lungs, increased density of superior and inferior aspects of vertebral bodies, with sandwich sign. Figure 1B presents sandwich-like change of vertebral bodies, increased bone density. From Figure 1C, we can see heterogeneous increase in density of bilateral femoral head, acetabulum and right sacroiliac joint, growth rings appearance.

Genetic analysis

CLCN7 mutation, locus 16p13.3.

Discussion

Osteopetrosis is a generic disease composed of a group of rare bone disorders characterized by increase of bone mass due to defective osteoclast function. It is divided into ARO (autosomal recessive osteopetrosis) and ADO (autosomal dominant osteopetrosis) types. Further divisions are as follows [1-4]: Autosomal Recessive Osteopetrosis (ARO): 1. Intermediate subtype: thickening of calvarium, stunted growth, osteomyelitis, mild anemia; 2. Severe subtype: earlier age of onset, including within postnatal months. Sick children can have recurrent infections and frequent bleeding secondary to medullary hyperplasia. They can also have blindness and deafness caused by compressions of cranial nerves. Autosomal Dominant Osteopetrosis (ADO): 1. ADO subtype I: mild diffuse generalized osteosclerosis; 2. ADO subtype II: thickening of superior and inferior aspects of vertebral bodies, high rate of long bone fractures, classic sandwich-like change of vertebral bodies (rugger-jersey sign), growth rings appearance, significant increase in serum ALP and creatine kinase BB (CK-BB); 3. ADO subtype III: “eccentric osteopetrosis” with osteosclerosis mainly involving distal extremities and skull. Our patient’s radiographic findings of sandwich-like change of vertebral bodies, increased bone density and heterogeneous increase in density of bilateral femoral head, acetabulum and right sacroiliac joint conform to manifestations of ADO subtype II, which is also called benign osteoptrosis. Current research lists 12 common genetic mutations for osteopetrosis, as follows (Table 2) [3, 5-14]:

Our patient has an identified mutation of CLCN7 at 16p13.3, which allows for a genetic diagnosis of chromosome 16 (CLCN7) mutation induced ADO subtype II. Concurrent diagnosis of schizophrenia with positive family history as well as exacerbation of her back pain with emotional stress leads us to speculate on a connection between osteopetrosis and schizophrenia. After searching our nationwide and international database, mutations in 3 etiologic genes for schizophrenia are identified on chromosome 16, specifically at 16p11.2, 16p13.11, 16p13.3 [15-24], note the proximity of the 3 loci. Our
A case report of osteopetrosis

Table 2. Twelve genetic mutations for osteopetrosis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
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<tbody>
<tr>
<td>CAII</td>
<td>8q22</td>
</tr>
<tr>
<td>TCIRG1</td>
<td>11q13.2</td>
</tr>
<tr>
<td>CLCN7</td>
<td>16p13.3</td>
</tr>
<tr>
<td>OSTM1</td>
<td>6q21</td>
</tr>
<tr>
<td>RANKL</td>
<td>13q17</td>
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<tr>
<td>PLEKHM1</td>
<td>17q21.3</td>
</tr>
<tr>
<td>Kindlin-3</td>
<td>11q13.1</td>
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<tr>
<td>RANK</td>
<td>18q22.1</td>
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<tr>
<td>CalDAG-GEFI</td>
<td>11q13.1</td>
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<tr>
<td>NEMO</td>
<td>Xq28</td>
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<td>LRP5</td>
<td>11q13.4</td>
</tr>
<tr>
<td>SNX10</td>
<td>7p15.2</td>
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</table>

Figure 1. Radiography Imagines. A. Increased density of superior and inferior aspects of vertebral bodies, with sandwich sign; B. Sandwich-like change of vertebral bodies, increased bone density; C. Heterogeneous increase in density of bilateral femoral head, acetabulum and right sacroiliac joint, growth rings appearance.

patient has an identified mutation at 16p13.3. Therefore, we boldly speculate that this mutation on chromosome 16 may be responsible for the pathogenesis of both osteopetrosis and schizophrenia, and that the 2 diseases may not be entirely independent, but rather share a common genetic basis. Furthermore, we propose to increase screening of schizophrenia in osteopetrosis patients with identified mutations of chromosome 16, as well as performing related prevention for osteopetrosis in applicable schizophrenic patients, all in the effort to decrease co-morbidity with a second disease.

Disclosure of conflict of interest

None.

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A case report of osteopetrosis


A case report of osteopetrosis


