Case Report

Identification of Sandhoff Disease in a Thai Family: Clinical and Biochemical Characterization

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Sandhoff disease is a GM2 gangliosidosis that is rare in Thailand. The authors report a Thai family with two children known to have infantile form of Sandhoff disease. The index case exhibited mitral valve prolapse with mitral regurgitation as an early sign, which is a rare presentation in Sandhoff disease. Thereafter, the patient had developmental regression, startle reaction, and cherry red spots. The diagnosis was confirmed by biochemical analysis.

Keywords: Infantile sandhoff disease, Cherry red spot, Mitral valve prolapse

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Gangliosides are components of plasma membranes, which comprise sphingosine, fatty acids, hexose, hexosamine, and neuraminic acid. Gangliosides degraded in cellular lysosomal compartment(1). Normally, the hydrolysis of gangliosides is accomplished by the action of two structurally related lysosomal enzymes, hexosaminidase A (Hex A) and hexosaminidase B (Hex B), and the GM2 activator protein(2). Hex A is composed of two subunits, α and β (αβ), whereas Hex B has only β subunits (ββ). In the degradation of GM2 gangliosides mediated by Hex A, GM2 activator protein is crucial for the phenomenon. The subunits of hexosaminidase, α and β are encoded by two main genes, HEXA (15q23-q24) and HEXB (5q13) respectively(2-4). Particularly, mutation of any one of these genes can result in autosomal recessive GM2 gangliosidosis which then results in intralysosomal accumulation of GM2 gangliosides and a few related glycolipids in neurons of the brain, and to a much lesser extent in other organs(2). Theoretically, there are three diseases sharing similar clinical phenotypes, i.e., Tay-Sachs (α-defects), Sandhoff (β-defects), the AB-variant (activator defects), most of them cannot be distinguished by clinical manifestations(3).

Sandhoff disease has three subtypes, which are infantile, juvenile, and adult onset(4,5). The infantile form is characterized by early onset of symptoms, which usually occur in the first 6 to 18 months of life. An abnormal acoustico-motor reaction, psychomotor deterioration, together with axial hypotonia and bilateral pyramidal signs, and cortical blindness with macular cherry red spots are clinical hallmarks of this disease. This form usually presents as a stereotypical progression of disease, leading to death before the age of 4(4,5).

In the present report, the authors present a Thai family with two children affected by Sandhoff disease and a healthy carrier child. Relevant physical findings and biochemical analysis of hexosaminidase assay are described.
Case Report

A 1-year-5-month Thai boy, previously diagnosed with cerebral palsy, was hospitalized due to uncontrolled generalized tonic clonic and myoclonic seizures aggravated by loud noises. He was born full-term by vaginal delivery with normal birth weight. At 9 months of age, he was incidentally found to have asymptomatic heart murmur from which echocardiogram revealed mitral valve prolapse with moderate mitral regurgitation of unclear etiology. Coincidentally, at that time, his mother also mentioned a developmental regression of her child as being unable to sit without support. Thereafter, the generalized tonic clonic and myoclonic seizures following the exposure to loud noise began to develop most notably from 15 months of age. Neurologic examination revealed generalized hypotonia with hyperreflexia, while other physical findings appeared to be normal. Brain ultrasound at 10 months showed no significant abnormalities. Brain CT/MRI was not performed.

The patient was the third child of a healthy, non-consanguineous couple who came from the same district in Northeastern Thailand. As for the other two sons, the oldest died at 3 years of age and was described to have similar progressive neurological disorder as the patient, while the second child, now 6 years old, has normal development.

Physical examination at 1 year and 5 months of age showed that he could not follow objects and had neither visual attention nor eye contact. Ophthalmological examination revealed inability to fixate his eyes on objects and not follow moving targets. Pale optic discs and cherry red spots in the macula were detected (Fig. 1).

As a result, Tay-Sachs disease was suspected and peripheral blood samples were taken from the patient and his living brother for biochemical analysis at Genetic Laboratory, Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University. Plasma hexosaminidase A and B activity was assayed by using spectrophotometric method and 4-methylumbelliferyl-2-acetamido-2-deoxy-β-D-glucopyranoside as tested substrate. The analysis showed a marked reduction of both total Hex A and B (5-6% of normal control), and Hex B (9% of normal control) activities in the patient’s specimen, whereas Hex A activity was normal (70% of normal control). These results were consistent with Sandhoff disease (Table 1). In his brother’s specimen, the result showed moderately reduced activities of total Hex A and B, and Hex B, suggesting carrier status of the disease. Genetic counseling was provided to the parents. Due to the lack of effective treatment for Sandhoff disease, the patient’s condition deteriorated and eventually died of respiratory complication at 2 years of age.

Discussion

In the present report, a Thai boy who suffered from the infantile form of Sandhoff disease is described. The important clues pointing to the diagnosis in the present case are degenerative brain disorder, startle reaction, and macula cherry red spots. With all clinical evidences, GM2 gangliosidosis, i.e. Sandhoff and Tay-Sachs disease was suspected. Nevertheless, these two disorders cannot be distinguished by clinical phenotypes alone since both share almost identical clinical pictures. Only a few evidences are helpful in clinical diagnosis; organomegaly and occasional bone

<table>
<thead>
<tr>
<th>Individual</th>
<th>Total Hex A and B activity (nmol/ml/hr)</th>
<th>Hex B activity (nmol/ml/hr)</th>
<th>Hex A activity (% total activity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>1,038.72</td>
<td>343.74</td>
<td>57.92</td>
</tr>
<tr>
<td>Normal control</td>
<td>1,190.64</td>
<td>327.84</td>
<td>71.90</td>
</tr>
<tr>
<td>Living brother</td>
<td>735.36</td>
<td>118.02</td>
<td>51.45</td>
</tr>
<tr>
<td>Patient</td>
<td>57.96</td>
<td>31.92</td>
<td>44.93</td>
</tr>
</tbody>
</table>
deformity can be found in some Sandhoff-affected individuals, but not in Tay-Sachs disease\(^{(3,4,7)}\). The present patient did not have organomegaly or bone involvement but showed cardiac abnormality. It follows therefore that the laboratory analysis of Hex profiles are necessary for definite diagnosis\(^{(7)}\).

A lysosomal enzyme assay from peripheral blood of the presented patient showed a marked reduction of both total Hex A and B isoenzymes in the serum, being a hallmark for Sandhoff disease\(^{(8)}\). The relatively higher percentage of Hex A activity compared to that of Hex B activity in Sandhoff disease can be explained by the excess $\alpha$ subunits due to the fact that fewer $\beta$ subunits are produced\(^{(3,5)}\). The patient’s brother had moderate reduction of total Hex A and B, and Hex B isoenzymes, which characterized him as a carrier of Sandhoff disease\(^{(5,7-9)}\). Unfortunately, parental specimens were not available for biochemical analysis.

In general, Tay-Sachs disease is rare, but with a higher prevalence than Sandhoff disease. The prevalence of Tay-Sachs disease is estimated 1 in 201,000 live births, while Sandhoff disease is described at 1 in 384,000 live births\(^{(4)}\). Tay-Sachs disease is more prevalent in Jewish populations with an incidence of 1 in 3,900 live births, whereas the incidence of Sandhoff disease is 1 in 1,000,000\(^{(1,7)}\). The Tay-Sachs carrier frequency is much higher in the Ashkenazi Jews (1 in 30) and eastern Quebec French Canadian (1 in 14) populations compared to that in the general population (1 in 300)\(^{(4,7)}\). The Sandhoff carrier frequency in non-Jewish populations (36 in 10,000) is slightly higher than Jewish populations (20 in 10,000)\(^{(10)}\). In Thailand, only one single case of Sandhoff disease (infantile form) was previously reported\(^{(11)}\). The case was confirmed by enzyme analysis in skin fibroblast culture\(^{(11)}\).

Macular cherry-red spot is an ophthalmic sign of lysosomal storage disease and can be used as a diagnostic clue even though it is not pathognomonic\(^{(12)}\). This fundus appearance also accompanies other neuronal lipid-storage disorders including Sandhoff disease (GM2 type II), gangliosidosis GM2 type III and GM1 type I, Niemann-Pick disease, sialidosis types I and II, Farber disease, mucolipidosis III, and metachromatic leukodystrophy\(^{(13,14)}\). The cherry red spot in the macula is due to the accumulation of sphingolipid in retinal ganglion cells. As the disease progresses, optic atrophy can be present\(^{(12)}\).

Mitral valve prolapse (MVP) has been documented to be more prevalent in patients with Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta and other collagen related disorders\(^{(18)}\). The patient described had MVP with moderate mitral regurgitation, which in fact, could represent an extremely rare manifestation of Sandhoff disease. Similar cardiac findings have been previously reported in a single patient with infantile Sandhoff disease\(^{(19)}\). To the authors knowledge, there is no correlation of MVP and hexosaminidase, thus MVP may be an incidental finding.

Treatment for Sandhoff disease generally involves symptomatic and supportive care, i.e. management of the seizures and interventional programs for motor and mental retardation. Genetic counseling and prenatal diagnosis for future pregnancy should be offered to the affected families.

In conclusion, the authors described a patient with classic infantile form of Sandhoff disease who had a rare cardiac manifestation as an early sign. Although uncommon association, this is an important sign to recognize. Further studies are needed to determine the correlation between hexosaminidase and MVP.

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References
Sandhoff disease รายงานผู้ป่วยในครอบครัวไทย: อาการแสดงทางคลินิก และผลปฏิบัติการทางชีวเคมี

กุลเสฏฐ ศักดิ์พิชัยสกุล, ไพริตน์ เคนาวิทย์, อัจฉรา นิธิภัณษาสกุล, ทศพร ศรีโชคกิตติ

Sandhoff disease เป็นโรคในกลุ่ม GM2 gangliosidosis ซึ่งพบน้อยมากในประเทศไทย ผู้นิพนธ์ รายงานผู้ป่วย 2 รายเป็นพี่น้องกันเป็นโรค Sandhoff disease ที่มีอาการแรกเริ่ม ในช่วงทารก ผู้ป่วย 1 ราย มาพบแพทย์ด้วยอาการทางหัวใจ ได้แก่ mitral value prolapse และ mitral regurgitation โดยเป็นอาการนำที่พบน้อยมากใน Sandhoff disease หลังจากนั้นผู้ป่วยเรื่มมีพัฒนาการถดถอย รวมกับ startle reaction และตรวจพบ cherry red spots การวินิจฉัยดูแลผู้ป่วยนี้ยังยืนยันโดยผลปฏิบัติการทางชีวเคมี