Female Siblings with Pendred’s Syndrome

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Female siblings with Pendred’s syndrome were admitted to our clinic. The abnormality of the acoustic structure was examined by MRI. Bilateral enlargement of the vestibular aqueduct and a prominently marked endolymphatic sac were found on MRI. These findings seemed likely to represent a Mondini deformity. Acoustic structure in Pendred’s syndrome was examined here by MRI for the first time. We examined their HLA-DR locus as a genetic marker using the affected sib-pair method preliminary. HLA typing might be a diagnostic criteria of Pendred’s syndrome, although the present siblings possessed 2 HLA genes in common.

(Key words: MRI, affected sib-pair method)

Introduction

Pendred’s syndrome, first reported by Pendred (1) in 1896, consists of congenital sensorineural hearing loss and goiter based on a congenital defect in iodine organification (2-6). Genetically this syndrome probably represents pleiotropism of an autosomal recessive gene (2, 4). Many problems remain to be resolved concerning the pleiotropy of the gene mutation of the thyroid gland and inner ear. The incidence of this syndrome is estimated to be 1.14 per 100,000 population in Japan. Recently, MRI (magnetic resonance imaging) has been widely used for diagnosis of the cranial nerve lesions, but the acoustic structure in Pendred’s syndrome had not been previously examined by MRI. Here, we report female siblings with Pendred’s syndrome; the abnormalities of acoustic structure were examined by MRI for the first time.

Case Report

A 16-year-old female was admitted to our clinic for a thorough examination of goiter. Her family history revealed the absence of the disease in her eldest sister, but the presence of congenital sensorineural hearing loss and goiter (estimated weight 40 g) in another elder sister. No similar symptoms were manifested in her parents or grandparents. There had been no consanguineous marriages (Fig. 1). She was born by normal delivery. Hearing loss was found at 8 months of age by audiometry. Since then, she has used a hearing aid. When the goiter appeared at 14 years of age, she consulted a nearby hospital and was suspected of having Pendred’s syndrome. She was subsequently admitted to our clinic. A soft, diffuse goiter (estimated weight 60 g) was palpable, but neither tubercles nor lymph node swelling was detected. No abnormal finding was observed by routine tests. A roentogenogram of the chest revealed tracheal compression from right to left. She was totally deaf in the right ear and had severe sensorineural hearing loss in the left ear revealed by audiograms. ENG (electronystagmogram) was within normal range. Aspiration cytodiagnosis of the thyroid gland revealed class II; neither malignant cells nor lymphocyte

![Fig. 1. The pedigree of the patient’s family.](image)

72y.o Healthy 8y.o HT 67y.o Heart failure 64y.o Healthy 42y.o Healthy 19y.o Healthy 18y.o 16y.o

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infiltration were found. The serum concentration of TSH, T₃ and Free T₄ was 5.5 μU/ml (normal range: 0.5–4.6 μU/ml), 1.7 ng/ml (0.8–1.8 ng/ml) and 1.4 ng/dl (0.8–2.0 ng/dl), respectively. Thus, her thyroid function was subclinically in the hypothyroid state. The thyrotropin releasing hormone test (TRH-test) revealed a normal response of TSH (Fig. 2).

A perchlorate discharge test (7) yielded an ¹³¹I uptake of 17.1% after administration of ¹³¹I of 25 μCi, and 8.3%, 30-min after administration of 1g of KClO₄. Thus, the release rate was 50.9%, and the presence of an iodine organification defect was suspected. Based on the above findings, she was diagnosed to have Pendred’s syndrome. She is being treated with 50 μg of levothyroxin, and on an iodine-restricted diet to induce the regression of the goiter. Computed tomography (CT) revealed bilateral cochlea hypoplasia which corresponded to findings usually observed in a Mondini type deformity (Fig. 3) (8, 9). MRI revealed bilateral enlargement of the vestibular aqueduct and a prominently marked endolymphatic sac, compatible with a Mondini deformity (Fig. 4). Abnormalities in the acoustic structure in Pendred’s syndrome were confirmed by MRI for the first time. We examined the DR locus of the human leukocyte antigens (HLA) of the patients parents and siblings, to identify the genes causing Pendred’s syndrome (Fig. 5). The present siblings possessed 2 HLA genes in common. These combinations may also have been a chance occurrence in this family.

Fig. 2. TRH-test. The thyrotropin releasing hormone test revealed a normal response of TSH.

Fig. 3. Temporal bone, brain CT shows bilateral cochlea hypoplasia that was not found in the apical turn but in the basal and middle turns (arrows).

Fig. 4. Axial and coronal T₂-weighted MR image of brain. MRI shows bilateral enlargement of the vestibular aqueduct and a prominently marked endolymphatic sac (arrows). (1.5 T, TR 3000 msec, TE 90 msec)
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![Diagram](image)

**Fig. 5.** The DR locus of the HLA of the patient’s parents and siblings (A). The number in (B) represents DR locus that was shared in siblings.

**Discussion**

Pendred’s syndrome consists of congenital sensorineural hearing loss, goiter and a positive perchlorate discharge test. The syndrome is genetically inherited in an autosomal recessive manner.

In the examination of inner ear anomalies of the present patient with Pendred’s syndrome, MRI revealed bilateral enlargement of the vestibular aqueduct and a prominently marked endolymphatic sac.

In 1968, Hvidberg-Hansen and Jorgensen (10) reported that enlargements of the vestibular aqueduct and endolymphatic sac are pathologically demonstrated in Pendred’s syndrome. Thereafter, Johnsen et al (11), also examined 5 cases of Pendred’s syndrome histologically. They found that hypoplasia of the cochlea was present in all cases and enlargement of the endolymphatic sac was detected in three cases. These abnormalities were the same as those reported by Mondini (12). Thus, inner ear anomalies in Pendred’s syndrome appear to be due to a Mondini deformity. In 1973, Illum et al (13) clinically examined 15 cases of Pendred’s syndrome by temporal bone polytomography. They detected Mondini deformities in 8 out of 15 cases. In 1988, Johnsen et al (8) examined 5 adult patients with Pendred’s syndrome using CT. They detected a typical Mondini cochlea in all cases. In the present case, a prominently marked endolymphatic sac was demonstrated in addition to the bilateral cochlea hypoplasia and bilateral enlargement of the vestibular aqueduct revealed by CT. These findings suggest that the inner ear anomaly was due to Mondini deformity, and that MRI is more useful in the detection of inner ear anomalies of Pendred’s syndrome than CT.

Wouwe et al (14) reported a case of Pendred’s syndrome and dup (10p) syndrome. Chromosome studies of that case showed a der (8) chromosome with dup (10p) and a deficiency for a small distal segment of 8q. Their report suggests that both goiter and deafness in Pendred’s syndrome are caused by chromosome anomalies.

In this report, we used the affected sib-pair method (15) the other tool to identify the genes causing Pendred’s syndrome as an attempt. HLA have many alleles used as gene markers. The relationship between Pendred’s syndrome and HLA has not been fully examined in Japan. Figure 5 show the DR locus of the HLA of the patient’s parents and siblings. This patient’s parents had heterozygous DR alleles. There are 4 possible combinations of DR alleles in their children, i.e., the sisters, and therefore, 16 DR combinations (4x4) in 2 of them. If the siblings had the same DR alleles, there would be 4 combinations, i.e., 4/16, or 25%. If the siblings had only one DR in common, the result would be 8/16, or 50%. If there were some linkage between the pathologic genes and HLA, a bias would occur in their probable distribution, and the tendency for affected siblings to possess a common HLA gene would increase. The present siblings possessed 2 HLA genes in common. These combinations may also have been a chance occurrence in this family. We will investigate the familial occurrence of Pendred’s syndrome in 7 patients in 5 families who have undergone HLA typing in our department (16), and examine whether there is any linkage between the genes responsible and HLA genes in Pendred’s syndrome, using the affected sib-pair method.

**References**