A Familial Case of Insulin Dependent or Non-insulin Dependent Diabetes Mellitus Associated with Hearing Loss

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Aggregation of diabetes and hearing loss in a family is observed in some hereditary disease. All members of the present family are affected with sensory hearing loss and diabetes mellitus. Diabetes types observed were insulin dependent diabetes mellitus (IDDM) in the proposita and the sister, non-insulin dependent diabetes mellitus (NIDDM) in the brother, and impaired glucose tolerance in the mother. The combination of hearing loss and diabetes and the concordant expression of IDDM or NIDDM in the siblings have not hitherto been described in any hereditary syndrome. This family may exhibit a new hereditary syndrome which is characterized by diabetes and hearing loss.

Key words: Hearing loss, IDDM, NIDDM and hereditary disease

Diabetes mellitus aggregation in a family has been reported in several hereditary diseases, such as mild familial diabetes mellitus with dominant inheritance1), DIDMOAD syndrome composed of diabetes insipidus, diabetes mellitus, optic atrophy and deafness2,3), and Alström syndrome involving nerve deafness, obesity retinitis pigmentosa and diabetes mellitus4). Recently, diabetes mellitus has been classified into two categories. One is non-insulin dependent diabetes mellitus (NIDDM) and the other is insulin dependent diabetes mellitus (IDDM)5). NIDDM is observed in mild familial diabetes mellitus with dominant inheritance and Alström syndrome, whereas IDDM is found in DIDMOAD syndrome. It has not hitherto been reported that both of IDDM and NIDDM are expressed in a family through hereditary disease. We encountered an uncommon family in which all sibs are IDDM or NIDDM, with accompanying hearing loss.

CASE REPORT

The family pedigree is shown in Fig. 1. The three sibs (III-1, III-2, III-3) and one parents (II-7) are all diabetic. The father (II-6) died of congestive heart failure at age of 67 and his hearing seemed almost normal in his daily life. It is not clear whether or not he was diabetic. The mother (II-7) and all sibs have loss in hearing to various degrees. No consanguine marriage is known in the family pedigree. I-1, I-2 and II-1 survived until 82, 80 and 81 years of age respectively without particular disease. II-2, II-3 and II-4 were killed in the second world war. II-5 died of cervical cancer at the age of 60. I-3 and I-4 died suddenly of unknown disease at age 40 and 50, respectively. II-9 and II-10 died in childhood. II-8, III-4, and IV-2 are all well without any obvious disease. Other than the four affected with diabetes, no member of this family is known to have hearing loss or diabetes mellitus.

A. Case-1 (III-1)

A 33 year old man who is the proposita, was admitted to a nearby hospital due to a deteriorating level of consciousness. Hyperglycemia (780 mg/dl) and ketouria (+++) provided a diagno-
Fig. 1. Family pedigree. Symbols are □; male, ♂; female, ♀; diabetes mellitus, □▼; □♂; upper left number is number in generation, lower number is present age, D is age at death, and △; proposita.

sis of diabetic ketoacidosis, and immediately fluid transfusion and insulin administration were started. He was transferred to our University hospital after one week for control of his diabetes, following an improvement in his consciousness. At the time of admission to the University hospital, the patient was lean and his consciousness was clear. Height was 169 cm, body weight 49 kg (79% of ideal body weight), blood pressure 135/88 mmHg and pulse 102/min. Examination of the breast, heart and lung was normal, but slight hepatomegaly was observed in the right hypochondrium. Neurologically, his achilles tendon reflex was diminished. Results of clinical laboratory tests are summarized in Table 1. The pattern of glucose level in a 75 g oral glucose tolerance test revealed the diabetic pattern accompanied with a low response of C-peptide. The circulating islet cell antibody was positive. Haematologically, hypochromic microcytic anemia was observed. The erythrocyte sedimentation rate was 1h-50 mm and CRP was 3+. No definite inflammatory lesion was recognized in his chest X-ray, bile duct or urinary tract. Thyroid hormone levels were normal, including negative for the microsome test. No diabetic complication was noticed in his eye, kidney or peripheral nerves. Neither optic nerve atrophy nor retinitis pigmentosa was noticed. For differential diagnosis for diabetes insipidus, an 18 hour dehydration test was performed. The ratio of urine versus plasma osmolality increased normally to 3.2. A daily injection of lente insulin 30 U resulted in fasting blood sugar 90–140 mg/dl, postprandial blood sugar 165–249 mg/dl, 24h-urine sugar 5 g and Hb Al 14.6% (normal range 5.5–8.0%).

Audiometry revealed moderate bilateral sensorial hearing loss at high tones (Fig. 2).

B. Case-2 (III-2)

A 36 year old woman was first referred to the internist for evaluation of glycosuria and proteinuria eight years ago. A 50 g oral glucose tolerance test revealed fasting blood sugar 262 mg/dl and 2 h blood sugar 320 mg/dl. She was diagnosed as having diabetes mellitus, and injections of lente insulin 22 u/day were started. Her diabetic condition has been hardly controlled despite several trials employing different kinds of insulin and multi-injections. Her present diabetic control is poor, as for example fasting blood sugar (299–300
Diabetes Mellitus and Hearing Loss

Fig. 2. Audiograms of three siblings (III-1, III-2, III-3) and their mother (II-7) showing bilateral sensorineural hearing losses.

mg/dl) and Hb Al 9.6% under 36 U of semilente insulin injection. Mild proteinuria has been persisting, whereas she is free from diabetic retinopathy. No optic atrophy is found. Her audiometry test revealed a mild bilateral sensorial hearing loss at high tones, at an equivalent level to that of III-1 (Fig. 2).

C. Case-3 (III-3)

A 38 year old man who noticed hearing loss at age 7. His hearing loss progressed gradually and his audiometry performed recently showed severe bilateral sensorial hearing loss, worse for high frequencies, as shown in Fig. 2. At age 31, glycosuria was found and diet treatment was undertaken for the following 2 years. However his diabetes deteriorated and a 50 g oral glucose tolerance test performed at age 33 revealed fasting blood sugar 281 mg/dl and IRI 6.4 μIU/ml, and 1h-blood sugar 492 mg/dl and IRI 6.6 μIU/ml, respectively. Insulin treatment was started with lente insulin at 12 U/day and has been maintained at 8 U/day. His present fasting sugar and Hb Al level are 80–140 mg/dl and 9.6–10.3%, respectively. Neither diabetic nephropathy nor retinopathy has been found yet.

D. Case-4 (II-7)

A 64 year old widow and the mother of the three affected sibs, was asked to co-operate for the family study. Her medical history is unremarkably except for an appendectomy at age 43. Her blood sugar and insulin in a 75 g oral glucose tolerance test showed 123 mg/dl and 7 μIU/ml at 0 min, 230 mg/dl and 29 μIU/ml at 60 min and 195 mg/dl and 28 μIU/ml at 120 min, respectively and she was diagnosed as having impaired glucose tolerance. Her audiometry test also showed sensory hearing loss characterized by flat patterns (Fig. 2). She and the proposita live together in a quiet area, and their two sibs had lived together with them until they married.

E. Study for HLA haplotypes

The study for HLA haplotypes was carried out for the 4 members (II-7, III-1, III-2 and III-3) in the family (Fig. 3). III-3 affected with IDDM and III-2 were determined to share the B and C haplotype. The C haplotype that was inherited from the mother has the antigens HLA A26, B35, CW3 and DRW9. The B haplotype having HLA A31, B51, CW3 and DR5 was the common type in II-2 and III-3 but not in II-7 and III-1. Other members except III-2 and III-3 in this family had different combinations of haplotype, which were A and B for the father, C and D for mother and A and D for III-1. These haplotypes were determined to be (A) HLA A2, B51, CW- and DR-; and (D) HLA A24, BW52, CW- and DR2.

![Fig. 3. HLA types of a family having four individuals with diabetes mellitus and hearing loss.](image-url)
DISCUSSION

All the members of this family case were affected with hearing loss of various levels accompanied with diabetes mellitus.

Several factors are known to affect hearing, such as a noisy environment and diabetic microangiopathy. However, the hearing loss in this family seems to be hereditary for three reasons. Firstly they live in a quiet area, secondly hearing loss in the brother of the proposita was noticed in his childhood prior to the onset of diabetes, and thirdly all sibs are affected.

The combination of hearing loss and diabetes has been known in patients with Alström syndrome and Wolfram syndrome. Alström syndrome is an unlikely diagnosis for this family since neither obesity nor retinitis pigmentosa, which characterize the syndrome besides deafness and NIDDM type diabetes, were observed.

Wolfram syndrome was originally reported in 1938 as juvenile onset diabetes mellitus accompanied with slowly progressive atrophy of the optic nerve in siblings. In 1976, Gunn et al. pointed out that this syndrome can be associated with sensory nerve deafness and diabetes insipidus. Dreyer et al. reviewed 98 cases of DIDMOAD syndrome in 1982 and reported juvenile onset diabetes is the most frequent and commonly the first symptom and the average onset age is 7 years. They have also reported that the decrease in visual activity remains undetected for some time, though 98% of patients are able to detect it before the age of 22. In this family case, the lack of optic atrophy and the relatively late onset of the diabetes makes it difficult to confirm DIDMOAD syndrome. Thus, the hearing loss of this family is different from any hereditary syndrome described previously.

Recently, diabetes mellitus has been classified into two group (IDDM vs. NIDDM) on the base of clinical and immunological characteristics. The characteristic properties of IDDM are juvenile onset (under 30 year old), lean body weight, ketosis prone, positive circulating islet antibody and necessary insulin treatment. In contrast, maturity onset, obesity, rare incidence of ketosis, negative circulatory islet cell antibody and no requirement for insulin treatment are the characteristics of NIDDM. The type of diabetes mellitus of the proposita is IDDM since ketoacidosis was the onset of his diabetes and his circulating islet cell antibody was positive. There is a conflict in the identification of the diabetes type of his elder sister (III-2). Clinical characteristics suggest that she is likely to be NIDDM, except for the requirement of insulin treatment from the onset; however her HLA haplotype being identical with that of the IDDM proposita strongly suggests that she is genetically IDDM. It is well known that HLA association is as high as 50% in IDDM. In caucasian IDDM, a significantly increased frequency of HLA antigens B8, BW15, DW3 and DW4 has been observed. Kobayashi et al. have compared HLA antigen frequencies between IDDM and control and reported that the correlation with IDDM was positive in BW54, DR4/DRW9 and negative in BW52 and DR2. It is interesting that the HLA study of this family showed the DRW9 positive in the proposita and sister who are considered to be IDDM and positive for both BW52 and DR2 in the brother and mother who are not IDDM.

With regard to the diabetes aggregation in family, Tattersall et al. have reported three families as having mild familial diabetes with dominant inheritance. The features of the syndrome are direct parent to child inheritance through at least three generations, 1:1 ratio of affected: unaffected children of diabetic parents and mild diabetes which is capable of control without insulin treatment. The present family seems to be a different case from mild familial diabetes with dominant inheritance since two of the members are affected with IDDM and one with NIDDM. Kuzuya and Matsuda have examined the family history of IDDM in relatively large numbers and have reported that the prevalence of diabetes in first degree relatives of IDDM is low, such as 8/104, 5/195 and 1/57 in parents, siblings and children, respectively. Therefore, the evidence that all siblings are affected with IDDM or NIDDM in this family is very uncommon, and may be a new syndrome accompanied with hearing loss. It is interesting that the brother with the most severe hearing loss among the siblings was NIDDM, in other words he had the mildest diabetes. It is not clear
how diabetes mellitus is linked with hearing loss in the family in this study. Careful observation of the course of the diabetes in all members, including the children of the brother, should be carried out.

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