Follow-up nationwide survey on predictive genetic testing for late-onset hereditary neurological diseases in Japan

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Running title: Predictive test for neurological diseases in Japan

Abstract

A follow-up nationwide survey on predictive genetic testing for late-onset neurological diseases in Japan was conducted. A questionnaire was sent to 89 institutional members of the Japan's National Liaison Council for Clinical Sections of Medical Genetics, and was returned by 60 (67.4%). A total of 301 clients with an interest in predictive testing were accumulated from April 2006 to March 2011. The greatest interest was shown for spinocerebellar degeneration (SCD, *n*=110), followed by myotonic dystrophy type 1 (DM1, *n*=69), Huntington's disease (HD, *n*=52), and familial amyloid polyneuropathy (FAP, *n*=35). The ratios of clients who actually underwent predictive testing were: SCD, 21.8%; DM1, 39.1%; HD, 26.9%; and FAP, 74.3%, indicating that predictive testing was conducted very cautiously for untreatable neurological diseases in Japan. Clinical geneticists were predominantly involved in genetic counseling, whereas the participation of non-medical doctor (non-MD) staff, including nurses, clinical psychologists, and genetic counselors, was not common. Lack of non-MD counseling staff was one of the most serious issues in conducting predictive testing, which has not been improved since the previous survey performed in 2006. Institutional arrangements, such as revision of medical insurance system regarding genetic testing and counseling, might be necessary to resolve this issue.

Key words: clinical geneticist / clinical psychologist / genetic counseling / genetic counselor / hereditary neurological diseases / predictive genetic testing

Introduction

In recent years, clinical sections of medical genetics and genetic counseling have been set up all over Japan. At present, there are 99 institutions, including all 80 university hospitals, with genetic counseling departments that have become members of the Japan's National Liaison Council for Clinical Sections of Medical Genetics (JNLCCSMG). The JNLCCSMG was established in 2003 for the purpose of cooperation between clinical sections of medical genetics in university hospitals and other core medical institutions (http://www.idenshiiryoubumon.org).

Predictive genetic testing is a matter of great concern for at-risk relatives of patients with late-onset hereditary neurological diseases, and is one of the most controversial topics in clinical genetics. In 2006, we performed the first nationwide survey on this issue in Japan[1]; however, little is known about the global situations and problems regarding predictive testing after 2006. Here, we report the results of a follow-up nationwide survey on predictive genetic testing for late-onset hereditary neurological diseases in Japan.

Materials and Methods

A questionnaire was sent to 89 institutional members of the JNLCCSMG (all institutional members of the JNLCCSMG on August 15, 2011). The questionnaire contained 7 questions as shown in Table 1. The chief person responsible for the genetic counseling department in each hospital was asked to fill out the questionnaire. This study was approved by the Ethical Committee of Shinshu University School of Medicine.

Results

The questionnaire was returned by 67.4% (n = 60) of the hospitals surveyed. Of the 60 hospitals, 41 (68.3%) had clients with an interest in predictive testing for late-onset neurological diseases during the period from April 2006 to March 2011 (Table 1, Q1). Attitudes toward predictive testing for neurological diseases in each hospital were as follows: 22 (36.7%) hospitals provide both genetic counseling and testing, 30 (50%) hospitals provide genetic counseling only, and 8 (13.3%) hospitals do not provide genetic counseling or testing (Table 1, Q2) .

In total, 301 clients from 257 families were reported from the 41 hospitals during the study period. The greatest interest was shown with regard to spinocerebellar degeneration (SCD, 97 families, 110 clients), followed by myotonic dystrophy type 1 (DM1, 59 families, 69 clients), Huntington's disease (HD, 46 families, 52 clients), and familial amyloid polyneuropathy (FAP, 24 families, 35 clients). The remaining clients interested in amyotrophic lateral sclerosis (ALS), spinal and bulbar muscular atrophy (SBMA), Alzheimer's disease (AD), facioscapulohumeral muscular dystrophy (FSHD), Parkinson's disease (PD), adrenoleukodystrophy (ALD), and frontotemporal dementia and parkinsonism (FTDP). The numbers of clients who actually underwent predictive genetic testing were as follows: SCD, 24 (21.8%); DM1, 27 (39.1%); HD, 14 (26.9%); FAP, 26 (74.3%); AD, 1 (25%); and ALD, 1 (100%). No clients interested in ALS, SBMA, FSHD, PD, and FTDP underwent predictive genetic testing (Table 1, Q3).

During the period of the survey, clinical geneticists were predominantly involved in genetic counseling, as they participated in ≥ 50% of the total counseling sessions in 38 of the 48 hospitals (79.2%). Neurologists participated to a certain degree in counseling sessions in 32 hospitals (66.7%).

The contribution of psychiatrists was much smaller, as they participated in counseling sessions only in 8 hospitals (16.7%). The participation of non-medical doctor (non-MD) staff was not common, as nurses, clinical psychologists, and genetic counselors were involved in 20 (41.6%), 16 (33.3%), and 16 (33.3%) hospitals, respectively (Table 1, Q4).

Insufficiency of genetic counseling system, especially the lack of non-MD counseling staff, was the most serious obstacle to genetic counseling and/or testing in most hospitals (Table 1, Q5-7).

Discussion

In a previous nationwide survey in Japan[1], 322 clients (excluding FAP) visited hospitals with an interest in predictive testing for late-onset neurological diseases between April 2004 and May 2006 (161 clients/year). Surprisingly, the number of clients excluding FAP substantially decreased between April 2006 and March 2011, as only 266 clients visited the genetic counseling department (53 clients/year). A possible explanation for the decrease is that a large number of university hospitals and other core medical institutions had opened clinical sections of medical genetics in the early 2000s and clients who had been seeking predictive testing visited hospitals between 2004 and 2006.

In the present study, the ratio of predictive genetic test usage was surveyed for the first time in Japan. Attitude toward predictive testing varies among counties[2-12] due to culture, nationality, religion, and availability of genetic counseling and testing systems. In addition, decision-making by clients in predictive genetic testing is largely influenced by their counselors[7]. In Japan, the ratios of predictive test usage in HD (26.9%) and SCD (21.8%) were much lower than those in other

countries (36% – 88% for HD[2-11] and 48% – 87% for SCD[2, 6, 11, 12]), indicating that Japanese counselors and clients took a cautious approach toward predictive testing in untreatable neurological diseases. In addition to the Japanese culture and nationality, an insufficient psychological support system after predictive testing is considered to be an important reason for the low ratio of predictive test usage in Japan. In contrast to HD and SCD, most (74.3%) clients interested in FAP actually underwent predictive testing in Japan, suggesting that the availability of disease-modifying therapy promoted the usage of testing[13-15].

The present study showed that the respondents felt lack of non-MD counseling staff was one of the most serious issues in providing predictive testing for neurological diseases in Japan. This issue was also noted in the previous survey[1]; however, the situation has not improved since then. Institutional arrangements, such as revision of the medical insurance system regarding genetic counseling and testing, might be necessary to resolve this issue.

There are two limitations that need to be acknowledged regarding the present study. The first limitation concerns the attitude to predictive testing. Both counselor's and client's attitude to predictive testing are influenced by various factors, such as age, sex, family composition, educational background, disease type, and religion. However, we did not survey such factors in this study. The second limitation is that we did not survey actual hereditary risk in each client. These issues need to be analyzed in future follow-up studies.

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Table 1. Questionnaire and results regarding predictive genetic testing for hereditary late-onset neurological diseases

Q1 Have you had clients who visited your hospital with an interest in or requesting predictive genetic testing for late-onset neurological diseases during the period from April 2006 to March 2011? (total responding = 60)

Yes;	41
No;	19

Q2 Does your hospital provide genetic counseling and/or testing for late-onset neurological diseases? (total responding = 60)

Provides both genetic counseling and testing.	22
Provides genetic counseling only.	30
Does not provide genetic counseling or testing.	8

Q3 What kinds of diseases were your clients interested in? Please indicate the numbers of families, clients, predictive tests performed, and positive for disease-causing mutations for each disease. (total responding = 41)

Disease	Number of hospitals	Number of families	Number of clients	Predictive tests performed	Positive for disease-causing mutations
Spinocerebellar degeneration	29	97	110	24 (21.8%)	8
Myotonic dystrophy type 1	21	59	69	27 (39.1%)	15
Huntington's disease	22	46	52	14 (26.9%)	6
Familial amyloid polyneuropathy	7	24	35	26 (74.3%)	10
Amyotrophic lateral sclerosis	7	10	12	0 (0%)	0
Spinal and bulbar muscular atrophy	6	9	9	0 (0%)	0
Alzheimer's disease	3	4	4	1 (25%)	1
Facioscapulohumeral muscular dystrophy	2	4	4	0 (0%)	0
Parkinson's disease	1	1	3	0 (0%)	0
Adrenoleukodystrophy	1	1	1	1 (100%)	0
Frontotemporal dementia and parkinsonism	1	1	1	0 (0%)	0
Unknown	1	1	1	0 (0%)	0

Q4 How much did the following professions contribute to the counseling sessions of such clients? Please select the most appropriate percentage among the following: a: 0%, b: 0% – 25%, c: 25% – 50%, d: 50% – 75%, and e: 75% – 100% ("0%" indicates no participation and "100%" indicates full-time participation in the counseling sessions). (total responding = 48)

	0%	0% – 25%	25% – 50%	50% – 75%	75% – 100%
*Clinical geneticist	2	4	4	9	29
Neurologist	16	14	5	4	9
Psychiatrist	40	8	0	0	0
Nurse	28	9	3	2	6
Clinical psychologist	32	6	3	2	5
**Genetic counselor	44	2	0	0	2

Q5 What is the reason for being unable to provide genetic counseling and/or testing? (multiple answers allowed) (total responding = 35)

Insufficiency of genetic counseling system in the hospital (go to Q6)	28
No clients interested in or requesting predictive genetic testing for neurological diseases (go to Q7)	12
Taking an opposing position on predictive genetic testing for late-onset, neurological diseases (go to Q7)	3
Not enough experience to provide genetic counseling and/or testing (go to Q7)	2

Q6	What kind of genetic counseling system is insufficient in your hospital? (multiple answers allowed) (total responding = 28)	
	Genetic counseling staff	20
	[**Genetic counselor]	[17]
	[Clinical psychologist]	[13]
	[Nurse]	[9]
	[*Clinical geneticist]	[8]
	[Psychiatrist]	[6]
	[Neurologist]	[5]
	[Medical social worker]	[1]
	Time for clinical practice of genetic counseling	7
	Genetic testing system	5

Q7 What do you think are the most important requirements for maintaining genetic counseling for such clients? Please select the three most important requirements from the following and rank them in the order of their importance, (1st) being most important. (total responding =60)

	1st	2nd	3rd	Rank unknown
Genetic counseling staff	28	9	8	6
Understanding and recognition of clinical genetics by the general	10	5	9	3
Genetic testing system	6	10	11	1
Administrative support for genetic counseling	4	8	5	3
Time and space for clinical practice of genetic counseling	2	14	12	4
Cooperation with the other hospitals	2	4	2	4
Others	1	2	2	0

*Clinical geneticist indicates a medical doctor who has the “Japanese Board of Medical Genetics, Clinical Geneticist” certification. **Genetic counselor indicates a non-medical doctor who has the “Japanese Board of Medical Genetics, Certified Genetic Counselor” certification. The certificates are given by the Japan Society of Human Genetics and the Japanese Society for Genetic Counseling.

Table 2. Comparison of the ratio of predictive genetic test usage among countries

Disease	Italy [Ref 2–4]	France [Ref 5,6]	Germany [Ref 7]	Netherlands [Ref 8]	Canada [Ref 9]	Mexico [Ref 10]	Cuba [Ref 12]	Brazil [Ref 11]	Japan (present study)
HD	36-57%	47-57%	52%	73%	75%	88%		45%	21.8%
SCD	66%	63%					87%	48%	39.1%
DM1									26.9%
FAP								38%	74.3%

Abbreviations: HD, Huntington's disease; SCD, Spinocerebellar degeneration; DM1, Myotonic dystrophy type 1, FAP, Familial amyloid polyneuropathy