札幌医学雑誌　**93**（1 － 6）65 ～ 78（2024）　doi：10.15114 / smj.93.65

ORIGINAL

Psychological impact and genetic counseling in patients with multiple endocrine neoplasia type 1 (MEN1): addressing quality of life concerns

Sachiko Miyazaki[1)], Kentaro Suda[1)], Masanori Ito[2)], Masanori Yamazaki[3)], Shinya Uchino[4)], Akihiro Sakurai[1)*]

[1)] Department of Medical Genetics and Genomics, Sapporo Medical University School of Medicine
[2)] Enterprise Insights and Digital Solutions（EIDS）, Digital, Analytics and Technology, Astellas Pharma Inc.
[3)] Department of Diabetes, Endocrinology and Metabolism, Division of Internal Medicine, Shinshu University School of Medicine
[4)] Department of Surgery, Noguchi Thyroid Clinic and Hospital Foundation

*Corresponding author：Akihiro Sakurai, M.D., Ph.D, Department of Medical Genetics and Genomics, Sapporo Medical University School of Medicine, S-1 W-17 Chuo-ku, Sapporo 060-8556, Japan
Tel：+81-11-611-2111, Fax：+81-11-688-5354
E-mail：sakurai.akihiro@sapmed.ac.jp

ABSTRACT

Multiple endocrine neoplasia type 1（MEN1）is an autosomal dominantly inherited disease that causes tumors in various endocrine and non-endocrine organs and requires cross-sectional and long-term healthcare management. In patients with MEN1, anxiety affects quality of life（QOL）, not only because of concerns about health care, but also due to the hereditary nature of the disease. In this study, we examined the psychological impact of MEN1 on patients and the influence of genetic counseling（GC）. After conducting a preliminary survey, a questionnaire battery was sent to MEN1 patients recruited from 3 medical institutions and a patient association in Japan. Responses from 76 patients were analyzed（response rate 54%）. High correlation coefficients were found between the Mental health subscale of the 36-Item Short Form Health Survey version 2 as a standardized QOL scale and two anxiety scales, the Hospital Anxiety and Depression Scale and State-Trait Anxiety Inventory. The highest component of anxiety concerned "transmission to children and grandchildren", which was significantly higher in the group that received GC. Low QOL has been reported in patients with MEN1. Although GC provides psychological support, the information provided additional to genetic information may increase anxiety. Thus, while the usefulness of GC in hereditary diseases is widely recognized, to ensure its value for individuals, it is necessary to consider each person's background and emotional state and bear in mind its possible risks.

（Accepted January 9, 2024）

Key words: Multiple endocrine neoplasia type 1, quality of life, anxiety, genetic counseling

Introduction

Multiple endocrine neoplasia type 1（MEN1）is an autosomal dominantly inherited endocrine tumor syndrome characterized by tumor development in various endocrine organs, such as the parathyroid, endocrine pancreas, and anterior pituitary. In particular, primary hyperparathyroidism is the most commonly associated condition, affecting almost 100% of patients with MEN1, and it is usually the initial manifestation. Pancreatic neuroendocrine neoplasm（P-NEN）and anterior pituitary tumor occur in approximately 60% and 50% of MEN1 patients, respectively. Other tumors related to MEN1 include thymic and bronchial neuroendocrine tumors, adrenocortical tumors, and skin tumors[1, 2)]. MEN1 is clinically diagnosed by confirming neoplastic disease in at least two of the commonly affected organs（parathyroid, endocrine pancreas, and/or

anterior pituitary), in one of three endocrine tumors (parathyroid, anterior pituitary, or well-differentiated neuroendocrine tumors of the gastroenteropancreatic tract), and in a first-degree relative with MEN1, or in a combination of one of the three lesions and a confirmed pathogenic variant in the responsible gene, *MEN1*[3]. Sequence analysis of *MEN1* detects pathogenic variants in 80%-90% of familial cases and in 65% of isolated cases, while targeted deletion/duplication analysis detects 1%-4% of germline pathological variants[4].

Patients with MEN1 require cross-sectional and long-term medical care, including surgery, medication, and regular surveillance of at-risk organs. Periodic surveillance is also recommended for asymptomatic subjects with *MEN1* pathogenic variants for the early detection and treatment of related lesions because disease onset can be detected up to 10 years before clinical symptoms appear[5].

In patients with MEN1, anxiety about healthcare, such as fear of disease occurrence (FDO) and of its hereditary traits, as well as FDO in relatives, can affect quality of life (QOL)[6]. American adults with MEN1 have been reported to have worse health-related QOL than the general US population[7]. Thus, FDO and QOL should be emphasized in the management of MEN1 in clinical practice[8].

Anxiety and QOL in patients with MEN1 have been reported in countries with various cultural and ethnic backgrounds[6–15], but such studies have not been conducted in Japan. Thus, the aim of this study was to clarify the psychosocial burden and the relationship between anxiety and QOL in Japanese patients with MEN1 and to determine how to improve their QOL. In addition, because there are no reports on the relationship between genetic counseling (GC) and QOL in patients with MEN1, we aimed to identify how healthcare professionals providing GC should approach working with them.

Methods

Study design

Patients with MEN1 were recruited from three medical facilities—Sapporo Medical University Hospital, Noguchi Thyroid Clinic and Hospital Foundation, and Shinshu University Hospital—and the patient association Mukuroji. The patients were sent a questionnaire battery to complete by mail. This prospective multicenter observational study was approved by the Sapporo Medical University Ethics Committee (approval number, 4-1-4) and the Institutional Review Board (IRB) of Sapporo Medical University Hospital (approval number, 342-3502). The study was conducted between April 2021 and October 2022.

Prior to this study, a pilot study was conducted with six patients to select relevant questionnaires, which included the 36-Item Short Form Health Survey version 2 (SF-36v2) as a standardized QOL scale, the Hospital Anxiety and Depression Scale (HADS) as a depression and anxiety scale, and the State-Trait Anxiety Inventory (STAI) as an anxiety scale. The Japanese version of the World Health Organization Quality of Life Instrument–26 items (WHOQOL-26) developed by Tazaki and Nakane[16] and the Beck Depression Inventory-Second Edition (BDI- II) were also administered. In the pilot study, we evaluated these questionnaires based on time required, fatigue level, number of questions and ease of answering, and effect on mood (i.e., if participants felt upset when answering the questions). Based on the responses from participants, we selected the SF-36v2, HADS, and STAI as the questionnaires for this main study.

In addition to these assessments, we developed a questionnaire to assess the nature of MEN1-specific concerns and GC. This questionnaire was also evaluated in the pilot study and the questionnaire used in this main study is shown in Appendix 1.

In the main study, the abovementioned questionnaires were sent to the patients by the participating medical facilities and patient association.

SF-36v2

The SF-36 is a scientific, reliable, and valid scale for measuring health-related QOL. The SF-36 was created in the United States and has been extensively used internationally. It is a comprehensive QOL scale that does not limit targets and measures health status via 36 items. It comprises 8 subscales: Physical functioning, Role physical, Bodily pain, Social functioning, General health (GH), Vitality, Role emotional, and Mental health (MH).

The higher the total score (0–100), the higher the QOL. The national standard determined using normal based scoring in 2017 for the Japanese population is 50 points and its standard deviation is 10 points[17].

HADS

The HADS is a 14-item scale consisting of seven depression and seven anxiety items measuring depression and anxiety in patients with physical illness. Each item is scored on a scale of 0–3. The subscales depression and anxiety are calculated as the sum of the item scores, with higher scores indicating worse health: a score of 0–7 is considered normal, 8–10 mild, 11–14 moderate, and 15–21 severe.

On the high-scoring side of the options, "healthy" and "unhealthy" were placed as appropriate for each item to eliminate any bias related to the response set. Participants are unlikely to be fatigued or burdened by completing the HADS. Item content relates to the cognitive component of depression and anxiety and is unlikely to be moderated by physical symptoms. The HADS has been translated into various languages, and reliability and validity studies have been conducted[18].

STAI

The STAI is an anxiety measurement test based on the state-trait anxiety theory of Spielberger et al.[19, 20]. The questionnaire separately measures ever-changing anxiety states and anxiety-prone personality traits. It is believed to be able to simultaneously assess state anxiety (A-State), which represents reactions to transient situations, and trait anxiety (A-Trait), which is characteristic of relatively stable people. The Japanese version of the STAI was translated and developed by Nakazato and Mizuguchi, and its reliability and validity have been examined[21]. The response form is divided into A-State and A-Trait, and the degree of anxiety in these two areas is calculated from each of the 20 responses. Items are scored on a 4-point Likert scale ranging from 1 (not at all) to 4 (very much so). The total score ranges from 20 to 80, with higher scores indicating higher levels of anxiety symptoms. The rating scale criteria vary by sex and A-State and A-Trait, with five levels ranging from very low (I) to very high (V).

MEN1-specific questionnaire

The MEN1 questionnaire was developed for this study and is specific to those with a MEN1 diagnosis. The questionnaire items comprise the following: age; sex; presence or absence of partners, children, grandchildren, and siblings; diagnosis and number of years since diagnosis; basis for diagnosis; presence or absence and continuity of allogeneic members of the family; presence or absence and continuity of those diagnosed before onset; most severely affected members of the family and symptoms; presence or absence and timing of GC; presence of a companion during GC; usefulness of GC; presence of a genetic test; number of years since the genetic test was performed; presence of a companion during disclosure of the test results; feelings immediately after disclosure of the test results; anxiety immediately after disclosure of the test results; current anxiety; availability of a place to discuss concerns about the condition; and an item for free description (Appendix 1).

Statistical analysis

Summary statistics for continuous variables and frequency tabulations for categorical data were obtained for patient demographics, family history, GC details, genetic testing, disclosure of results, current anxiety, and SF-36v2, STAI, HADS, and MEN1 questionnaire scores. Summary statistics were also calculated for A-State and A-Trait on the STAI. For the HADS total score, the frequencies were tabulated as normal for 0–7, mild for 8-10, moderate for 11–14, and as severe for 15–21 for the HADS-D (depression) and HADS-A (anxiety). The SF36v2 scores of MEN1 patients were compared with the national standard value of 50[17] by calculating the mean of the 8 subscales using a one-sample t-test. Correlation coefficients of SF-36v2 scores with the HADS-D, HADS-A, A-State, and A-Trait scores were calculated to evaluate the relationship among these variables. Frequency tabulations were performed on the items of the MEN1 questionnaire (current anxiety). Subgroup analyses were also conducted by GC status. In addition, tabulations were performed for the SF-36 domain scores in subgroups by anxiety status (very anxious and anxious were defined as "anxious";

other results were defined as "no anxiety"). Kruskal Wallis test and Wilcoxon signed-rank sum test were also conducted to examine the relationship of anxiety about the next generation with genetic testing and GC. Python 3.8 and JMP were used for all of the statistical analyses, and Microsoft Excel (Microsoft, Redmond, WA, USA) was used for creating all figures in this research.

Results

The questionnaires were mailed to 141 patients, 76 (54%) of whom responded (29 men [38.2%], 46 women [60.5%], 1 unknown [1.3%]) and were included in the analysis. Their general background is given in Table 1. Of these patients, 74 answered they had been diagnosed with MEN1 and the most common time of diagnosis was within the last 5 years (22.4%). Summary statistics for the STAI are shown in Table 2. The instructions for the Japanese version of the STAI indicate that scores decrease as age increases: the respective scores for A-State and A-Trait in normal adults were found to be 36.6 ± 8.98 and 38.8 ± 9.68[22], which were lower than those of our MEN1 patients, at 42.80 ± 10.60 and 45.28 ± 12.82. The values were also higher in our female patients than male patients.

The results of the frequency tally for the HADS are shown in Table 3. Overall, 8.3% and 4.1% of the participants had a "moderate" score on the HADS-A and HADS-D, respectively, with none of the patients having a "severe" score. The SF-36v2 results are shown in Figure 1. General health (GH) was significantly lower compared with the national reference value of 50 ($P < 0.05$). Correlation coefficients of SF-36v2 scores with the HADS-D, HADS-A, A-State, and A-Trait scores are shown in Figure 2. A trend for a negative correlation was observed between SF-36 MH and A-State and A-Trait. In addition, SF-36v2 MH was highly correlated with HADS-D, HADS-A, A-State, and A-Trait scores. In particular, A-State had a high value. Frequency totals for the items of the MEN1 questionnaire (current anxiety) are shown in Table 4. Most patients were "very anxious" or "anxious" about their health, the possibility of disease recurrence, transmission to their children and grandchildren, and medical costs, with 46 patients (60.5%) "very anxious" about passing the disease to their children and grandchildren.

Table 1. Demographics and background characteristics of patients with multiple endocrine neoplasia type 1 (n = 76).

	n	%
Sex		
Male	29	38.2
Female	46	60.5
NA	1	1.3
Age (years)		
0-19	1	1.3
20-29	5	6.6
30-39	7	9.2
40-49	20	26.3
50-59	23	30.3
60-69	12	15.8
70-	8	10.5
Married		
Yes	51	67.1
No	25	32.9
Children		
Yes	54	71.1
No	22	28.9
Grandchildren		
Yes	21	27.6
No	52	68.4
NA	3	3.9
Diagnosis of MEN1		
Yes	74	97.4
No	1	1.3
NA	1	1.3
Time of diagnosis (years earlier)		
0 - 4	17	22.4
5 - 9	9	11.8
10 - 14	15	19.7
15 - 19	7	9.2
10 - 14	6	7.9
25 - 29	2	2.6
30 -	1	1.3
NA	19	25

Table 2. Summary statistics for A-State and A-Trait in patients with multiple endocrine neoplasia type 1

		STAI	
	n	A-State	A-Trait
MEN1	74		
mean		42.80	45.28
SD		10.60	12.82
Male	28		
mean		38.18	40.54
SD		7.6	11.4
Female	45		
mean		45.60	48.04
SD		11.4	13.0

SD: Standard deviation; STAI: State-Trait Anxiety Inventory; A-State: state anxiety; A-Trait: trait anxiety

Table 3. Summary of participants' HADS scores according to severity

	HADS-A	HADS-D
	n (%)	n (%)
Normal	55 (76.4)	58 (79.5)
Mild	13 (18.1)	13 (17.8)
Moderate	6 (8.3)	3 (4.1)
Severe	0 (0)	0 (0)

HADS: Hospital Anxiety and Depression Scale; HADS-A: Anxiety scale; HADS-D: Depression scale

Table 4. Item and degree of current anxiety determined using the MEN1-specific questionnaire

	Very anxious	Anxious	A little anxious	Not very anxious	Not at all anxious	Missing
My health	21 (27.6%)	27 (35.5%)	20 (26.3%)	5 (6.6%)	2 (2.6%)	1 (1.3%)
My life	22 (28.9%)	17 (22.4%)	23 (30.3%)	9 (11.8%)	3 (3.9%)	2 (2.6%)
Future treatment	21 (27.6%)	16 (21.1%)	26 (34.2%)	8 (10.5%)	3 (3.9%)	2 (2.6%)
Possible recurrence	23 (30.3%)	23 (30.3%)	18 (23.7%)	8 (10.5%)	2 (2.6%)	2 (2.6%)
Communication with healthcare providers	6 (7.9%)	9 (11.8%)	20 (26.3%)	24 (31.6%)	15 (19.7%)	2 (2.6%)
Relationship with partner	3 (3.9%)	4 (5.3%)	14 (18.4%)	16 (21.1%)	29 (38.2%)	10 (13.2%)
Impact on family	29 (38.2%)	12 (15.8%)	19 (25.0%)	8 (10.5%)	4 (5.3%)	4 (5.3%)
My marriage	4 (5.3%)	4 (5.3%)	6 (7.9%)	9 (11.8%)	31 (40.8%)	22 (28.9%)
Passing on to children and grandchildren	46 (60.5%)	8 (10.5%)	8 (10.5%)	2 (2.6%)	8 (10.5%)	4 (530.0%)
Impact on work	12 (15.8%)	16 (21.1%)	16 (21.1%)	11 (14.5%)	15 (19.7%)	6 (7.9%)
Medical costs	30 (39.5%)	16 (21.1%)	20 (26.3%)	3 (3.9%)	5 (6.6%)	2 (2.6%)
Vague anxiety	20 (26.3%)	11 (14.5%)	20 (26.3%)	6 (7.9%)	7 (9.2%)	12 (15.8%)
About others 1	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
About others 2	0(0%)	1 (1.3%)	0(0%)	0(0%)	0(0%)	75 (98.7%)
About others 3	1 (1.3%)	0(0%)	0(0%)	0(0%)	0(0%)	75 (98.7%)

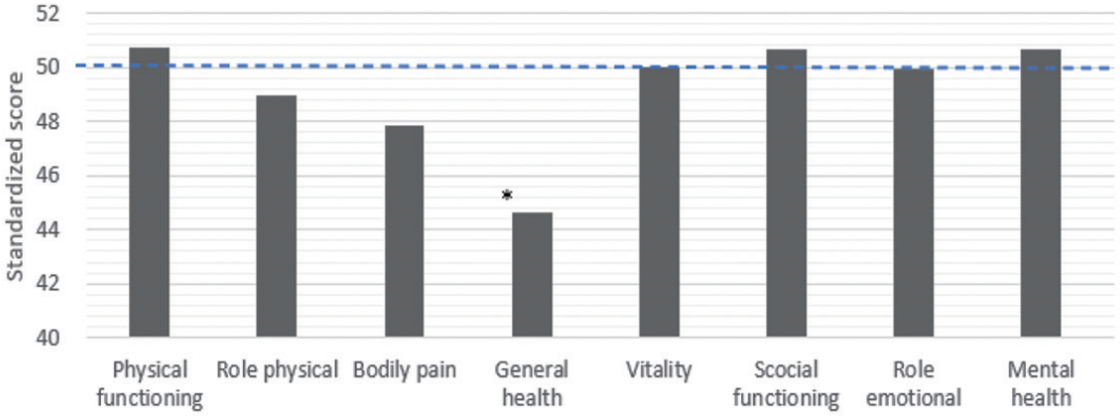

Figure 1. SF-36v2 scores in patients with multiple endocrine neoplasia type 1
Domain scores are standardized to have mean of 50 and standard deviation of 10.
SF-36v2: 36-Item Short Form Health Survey version 2.
Note that the baseline of the vertical axis starts at 40.
*: One-sample t-test. (P value<0.05) against the general Japanese population

	PF	RP	BP	GH	VT	SF	RE	MH	HADS-D	HADS-A	A-State	A-Trait
PF	1.00	0.70	0.57	0.55	0.55	0.65	0.67	0.51	-0.37	-0.32	-0.36	-0.34
RP	0.70	1.00	0.59	0.43	0.46	0.68	0.77	0.45	-0.30	-0.18	-0.26	-0.16
BP	0.57	0.59	1.00	0.40	0.48	0.50	0.55	0.37	-0.16	-0.24	-0.22	-0.11
GH	0.55	0.43	0.40	1.00	0.53	0.47	0.35	0.41	-0.42	-0.44	-0.50	-0.47
VT	0.55	0.46	0.48	0.53	1.00	0.57	0.61	0.71	-0.56	-0.61	-0.56	-0.59
SF	0.65	0.68	0.50	0.47	0.57	1.00	0.71	0.62	-0.45	-0.47	-0.52	-0.42
RE	0.67	0.77	0.55	0.35	0.61	0.71	1.00	0.60	-0.39	-0.32	-0.40	-0.34
MH	0.51	0.45	0.37	0.41	0.71	0.62	0.60	1.00	-0.62	-0.70	-0.77	-0.69
HADS-D	-0.37	-0.30	-0.16	-0.42	-0.56	-0.45	-0.39	-0.62	1.00	0.72	0.64	0.74
HADS-A	-0.32	-0.18	-0.24	-0.44	-0.61	-0.47	-0.32	-0.70	0.72	1.00	0.76	0.81
A-State	-0.36	-0.26	-0.22	-0.50	-0.56	-0.52	-0.40	-0.77	0.64	0.76	1.00	0.76
A-Trait	-0.34	-0.16	-0.11	-0.47	-0.59	-0.42	-0.34	-0.69	0.74	0.81	0.76	1.00

Figure 2. Correlation coefficients between SF-36v2 scores and HADS and STAI scores
Domains on the 36-Item Short Form Health Survey, version 2: PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; and MH, mental health; HADS: Hospital Anxiety and Depression Scale; STAI: State-Trait Anxiety Inventory
shadow shows the correlation coefficient.

Given these findings, we analyzed the impact of their children's presymptomatic diagnosis (PT) and its effects on the participants' anxiety. The participants were divided into 4 groups according to whether or not their children underwent PT and its effect: Group 1, children underwent PT, with both positive and negative effects; Group 2, underwent PT, with only positive effects; Group 3, underwent PT, with only negative effects; and Group 4, did not undergo PT. Group 3 was significantly less anxious than Group 2 and Group 4 .

In a between-group comparison (Kruskal Wallis test), anxiety was significantly lower in group 3 (p=0.0032), and a two-group comparison (Wilcoxon signed-rank sum test) between groups 2 and 3, and groups 3 and 4, showed significant differences in each (groups 2 vs. 3, p=0.0049; groups 3 vs. 4, p=0.0021). Significant differences were found for each (groups 2 vs. 3, p=0.0049; groups 3 vs. 4, p=0.0021) (Figure 3).

Furthermore, anxiety about passing the disease to their children and grandchildren was significantly higher (p=0.0293) in the group that received GC than the group that did not receive GC (Figure 4).

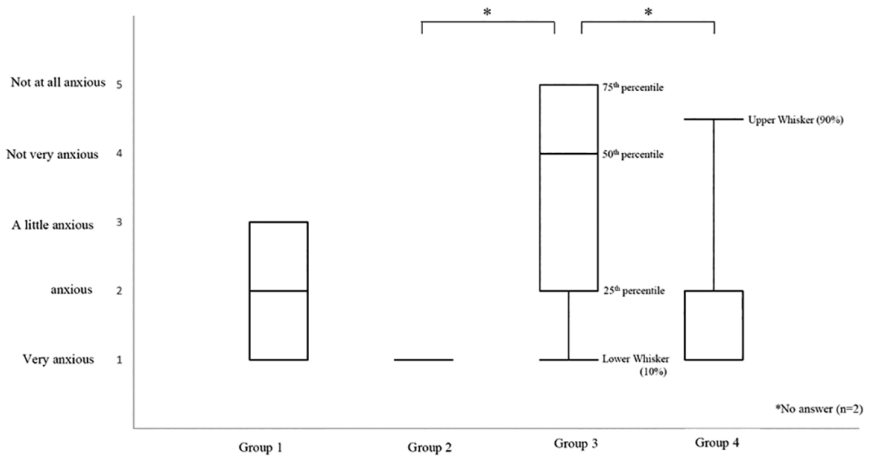

Figure 3. Anxiety caused by child's PT for multiple endocrine neoplasia type 1
Group 1 (n=7) : PT, with both positive and negative effects on anxiety
Group 2 (n=6) : PT, with only positive effects
Group 3 (n=7) : PT, with only negative effects
Group 4 (n=54) : No PT
Kruskal Wallis test: p=0.0032
Wilcoxon: groups 2 vs. 3, p=0.0049; groups 3 vs. 4, p=0.0021
PT: Presymptomatic genetic testing undertaken by participant's children

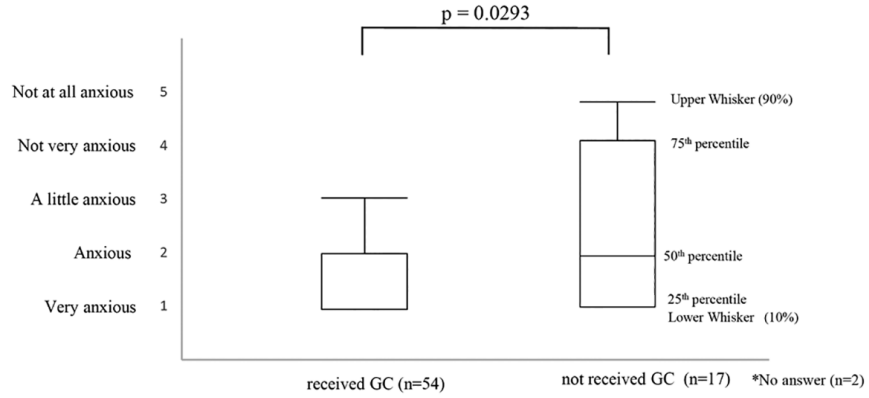

Figure 4. Anxiety about passing on the disease to their children or grandchildren according to received or not received genetic counseling (GC)

Discussion

In this study, we investigated the relationship between QOL and anxiety in Japanese patients with MEN1. The results of a questionnaire battery consisting of standardized assessments and an original disease-specific questionnaire were analyzed to identify patients' backgrounds and disease-specific anxieties. The highest component of anxiety concerned "transmission to children and grandchildren", which was significantly higher in the group that received GC compared to those who did not.

According to the Japanese manual of the STAI, high anxiety is defined as a score of 42 or more for state anxiety and 44 or more for trait anxiety in men and 42 or more for state anxiety and 45 or more for trait anxiety in women. In the present study, high anxiety was observed in women with MEN1. In terms of QOL, our patients with MEN1 had significantly lower general health scores than those of the normal Japanese population. A high negative correlation tendency was found between SF-36 MH score and each of the HADS-D, HADS-A, and STAI (A-State and A-Trait) scores, with A-State having the highest correlation coefficient. In addition to the inherently high tendency for anxiety shown on the STAI due to high illness-associated trait anxiety, the correlation between the SF36 and MH suggests that state anxiety might increase stress in daily life. HADS was developed with a focus on cognitive aspects, is unaffected by physical symptoms[18], and correlates highly with the SF-36 MH. Anxiety in patients with MEN1 could arise from physical impairment due to the disease itself as well as psychological issues, we considered HADS can be used as an indicator to assess psychological impact of patients with MEN1.

In relation to current concerns, many patients were "very anxious" or "anxious" about their health, the possibility of disease recurrence, and transmission of the disease to their children and grandchildren. In particular, 46 patients (60.5%) were "very anxious" about the possibility of their children and grandchildren developing the disease, suggesting that they were particularly anxious because of the hereditary nature of the disease. Anxiety due to being diagnosed with MEN1 may also be affecting patients' QOL.

It is important to note that patients who received GC were more anxious about transmission to the next generation than those who did not receive GC. There may be several possibilities to this result which was unexpected given the purpose of genetic counseling. The more anxious patient group might have received genetic counseling. Alternatively, it is possible that genetic counseling has increased patients' knowledge about the disease, making health and genetic concerns more tangible. Although some previous studies have described anxiety about the next generation because of the hereditary nature of the disease[6, 9], there are no studies, as far as we are aware, that mention a link between GC and a degree of anxiety.

It is to be noted that among the group who received GC (57/76 respondents: 75%), 51 (89%) mentioned that they found GC "helpful", indicating a positive view of GC. Genetic counseling is defined as "the process of helping people understand and adapt to the medical, psychological, and familial implications of the genetic contributions to disease"[23]. Due to the nature of MEN1, Marini et al. emphasized in their review article the importance of providing ongoing psychological support as well as new information about the disease even after the initial GC is provided[13]. They state that GC should be performed before and after genetic testing, with staff specializing in genetics providing psychological support for the management of results related to reproductive genetic test results and the psycho-social and economic aspects of the patient and their family. It is considered necessary to present regular surveillance in an easy-to-understand manner, to clearly state that medical care will be involved with the person in the long term, continue GC, establish a physical and emotional support system, and to provide a plan for the person to live with the condition with peace of mind regarding the anxiety caused by the diagnosis.

Berglund et al.[9] reported that 70% of MEN1 patients are pessimistic about the future, with anxiety about what might happen to themselves, their children, and their relatives. For medical staff involved in the treatment of MEN1, it is necessary to be fully aware of the need for understanding the constitution and surveillance of MEN1 and to decide who will play a hub role, who will be in total

control and who will be responsible for the patient's physical and mental state, as it is a multi-organ disease. There needs to be someone who is aware of the patient's physical and mental state. In other words, as also stated by Thakker et al, the main recommendation and suggestion for the best clinical and therapeutic management of MEN1 is to refer patients and their families to a specialized center for endocrine tumors. It would also lead to better QOL of patient and their families.

In a study by Giusti et al., MEN1 patients were shown to be moderately optimistic, corresponding to a normal quality of life despite the complex multi-neoplastic syndrome, and patients were able to receive treatment at specialized centers. It is closely correlated with being cared for, receiving individualized care and constant follow-up, and having access to facilities that can provide specialized care is closely correlated with patient care. It is an ideal model for post-diagnostic shock, and has been proven to contribute to maintaining a good health-related quality of life in MEN1 patients[16].

In studies of other inherited tumor syndromes with the same autosomal form of inheritance as MEN1, individuals with von Hippel-Lindow desease (VHL) have expressed concern about developing VHL-related tumors themselves or their family members developing them[24], and a report on Li-Fraumeni syndrome[24] indicated that such patients expressed greater concern about their family members developing cancer than they themselves developing it. In addition, a study of patients with several hereditary tumor syndromes reported that, while they felt it was possible to have a good QOL even with hereditary tumor syndromes, most felt that it was important not to pass the condition to the next generation[25].

A diagnosis of a hereditary tumor syndrome before the individual involved has given birth has an impact on reproduction. The fact that MEN1 patients had the highest rate of consideration of preimplantation genetic diagnosis, along with FAP patients, compared with patients with other hereditary tumors[26], suggests that, among the many existing hereditary tumor syndromes, MEN1 patients are particularly concerned about the impact on the next generation and wish to prevent transmission. MEN1 patients could benefit from GC because it helps them acquire the knowledge needed to obtain optimal care[7], and constant individualized care and follow-up can significantly improve their psychological status and perceptions of the disease[15]. In addition, given that MEN1 is a life-long disease and given the anxiety about the next generation identified here, continuous involvement with the patient through GC may ameliorate patients' anxiety and thereby help to maintain or even improve QOL.

Our current study have limitations in several points. The small sample size may limit to generalize these results. In addition, because the survey was cross-sectional, it was not possible to assess changes over time. It is also difficult to be certain about the consistency of feelings and anxieties immediately after disclosure of the genetic test results, because these are recalled retrospectively and not as real-time responses. Furthermore, this study was conducted during the COVID-19 pandemic. In view of the actual reported decline in QOL and mental health, including anxiety and depression, associated with COVID-19[27], we believe that the possibility that the overall QOL of the population was also affected should be considered. To better understand impact of MEN1 on psychological status to patients, additional study with larger number of participants may be necessary. Also, studies that track the psychological status of patients over time would also be necessary.

While research studies usually involve patients who participate in research for the benefit of future patients with the same disease, this study may help to maintain or improve the QOL of the individuals who actually participated or those who currently have a MEN1 diagnosis. Despite the variety of hereditary tumor syndromes, concern about transmission to the next generation is similar for all genetic diseases and although this study is specific to MEN1, the same effect of GC on transmission fears may be true for patients with other hereditary tumor syndromes. We believe that the nature of GC should be re-examined and that medical practitioners should provide support from all angles so that patients can maintain a better QOL.

Appendix

MEN1-specific questionnaire

Please check all that apply and complete the following questions in parentheses.

Do you have a partner? ☐ Yes ☐ No

Do you have children? ☐ Yes ☐ No
If Yes, how many children do you have and how many of them are minors? ( )

Do you have grandchildren? ☐ Yes ☐ No
If Yes, how many grandchildren do you have and how many of them are minors? ( )

Do you have siblings? ☐ Yes ☐ No
If Yes, how many siblings do you have and how many of them are minors? ( )

No	Question	Choices
1	Have you been diagnosed with MEN1?	☐ Yes ☐ No
2	How many years have passed since you were diagnosed with MEN1?	☐ Less than 1 year ☐ More than 1 year but less than 3 years ☐ More than 3 years but less than 5 years ☐ More than 5 years but less than 10 years ☐ More than 10 years but less than 15 years ☐ More than 15 years but less than 20 years ☐ More than 20 years but less than 25 years ☐ More than 25 years but less than 30 years ☐ More than 30 years ☐ Don't remember
3	What is the reason you were diagnosed with MEN1? (multiple choices allowed)	☐ Primary hyperparathroidism ☐ Neuroendocrine neoplasm ☐ Pituitary tumor ☐ Genetic testing ☐ Don't remember ☐ Other ( )
4	Do you have any relatives with MEN1 symptoms?	☐ Yes → Q5 ☐ No → Q6
5	Who has MEN1 symptoms?	☐ Parent ☐ Sibling ☐ Child/Children ☐ Grandchild/Grandchildren ☐ Grandparent ☐ Don't remember ☐ Uncle/Aunt ☐ Cousin ☐ Nephew/Niece ☐ Other ( )
6	Has any of your relatives received presymptomatic genetic testing?	☐ Yes →Q7 ☐ No
7	Who is that and what was the result of the test?	☐ Father → ☐ Positive ☐ Negative ☐ Mother → ☐ Positive ☐ Negative ☐ Child → ☐ Positive ☐ Negative ☐ Sibling → ☐ Positive ☐ Negative ☐ Grandchild → ☐ Positive ☐ Negative ☐ Grandfather → ☐ Positive ☐ Negative ☐ Grandmother → ☐ Positive ☐Negative ☐ Uncle/Aunt → ☐ Positive ☐ Negative ☐ Cousin → ☐ Positive ☐ Negative ☐ Other → ☐ Positive ☐ Negative
8	Which of your relatives diagnosed with MEN1 has the severest symptoms ?	☐ Yourself ☐ Parent ☐ Child ☐ Sibling ☐ Grandchild ☐ Grandparent ☐ Uncle/Aunt ☐ Cousin ☐ Nephew/Niece ☐ Don't know

9 What are (were) the symptoms of the person you answered in Q8?

☐ Died of MEN1-related disease
☐ Several operations
☐ Single operation
☐ Presymptomatic operation
☐ Difficulty in daily life
☐ Don't know
☐ Other

10 Did you receive genetic counseling?

☐ Yes →Q11
☐ No. →Q14

11 When did you receive the genetic counseling?

☐ Before genetic testing
☐ Within a year after genetic testing
☐ Over a year but within 10 years after genetic testing
☐ Over 10 years after genetic testing

12 Did someone accompany you during genetic counseling?

☐ Yes (☐ Partner ☐ Parent ☐ Child ☐ Other)
☐ No

13 Was genetic counseling helpful for you?

☐ Yes (☐ acknowledgement/information
☐ psychological/feelings ☐ Other)
☐ No
☐ Don't remember

14 Did you undergo genetic testing to get a diagnosis of MEN1

☐ Yes →Q15
☐ No. →Q21

15 How many years have passed since you underwent genetic testing?

☐ Less than 1 year
☐ More than 1 year but less than 3 years
☐ More than 3 years but less than 5 years
☐ More than 5 years but less than 10 years
☐ More than 10 years but less than 15 years
☐ More than 15 years but less than 20 years
☐ More than 20 years but less than 25 years
☐ More than 25 years but less than 30 years
☐ More than 30 years
☐ Don't remember

16 Did someone accompany you during genetic testing?

☐ Yes (☐ Partner ☐ Parent ☐ Child ☐ Other)
☐ No

17 Was there an attendant at the time of disclosure of results?

☐ Yes (☐ Partner ☐ Parent ☐ Child ☐ Other)
☐ No

18 Do you remember what was explained to you at the time when you were told your results and what conversations you had with your Dr or Genetic counselor?

☐ Remember well
☐ Remember vaguely
☐ Don't remember well
☐ Don't remember at all

19 To what extent did you feel the following immediately after being told the results of your genetic test (getting your genetic diagnosis)?

1. Shocked
2. Anxious
3. Reassured
4. Sad
5. Glad
6. Could not think about anything
7. Don't remember
8. Confusion
9. Convinced
10. Other ( )
11. Other ( )

Note: For each item (1 to 11), check one of the five boxes that best applies
☐ Very much
☐ Much
☐ Quite a bit
☐ No much
☐ Not at all

20 Were you anxious about the following after being told the results of your genetic test (getting your genetic diagnosis)?

1. My health
2. My life
3. Future treatment
4. Possible recurrence
5. Communication with healthcare providers
6. Relationship with partner
7. Impact on family
8. My marriage
9. Passing on the disease to my children and grandchildren
10. Impact on work
11. Medical costs
12. Vague anxiety
13. About ( )
14. About ( )
16. Don't remember.

Note: For each item (1 to 16), check one of the five boxes that best applies
☐ Very much
☐ Much
☐ Quite a bit
☐ No, it isn't.
☐ Not at all

21 Are you currently anxious about any of the following because you have MEN1?

1. My health
2. My life
3. Future treatment
4. Possible recurrence
5. Communication with healthcare providers
6. Relationship with partner
7. Impact on family
8. My marriage
9. Passing on the disease to my children and grandchildren
10. Impact on work
11. Medical costs
12. Vague anxiety
13. About ( )
14. About ( )

Note: For each item (1 to 16), check one of the five boxes that best applies
☐ Very much
☐ Much
☐ Quite a bit
☐ No, it isn't.
☐ Not at all

22 Are you a member of a patient or party associations?

☐ Yes
☐ No

23 Do you have people or places (e.g., at patient or party associations) where you can talk about your concerns and worries about having MEN1?

☐ Yes →Q24
☐ No

24 Who can you talk to (where)?

25 Please let us know about your requests, dissatisfaction with the medical care you are receiving, and your expectations of medical care because of having MEN1.

Acknowledgment

We would like to thank the patients who participated in this study.

We declares no conflict of interest.

References

1. Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML; Endocrine Society. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012; 97: 2990-3011.
2. Pieterman CRC, Valk GD. Update on the clinical management of multiple endocrine neoplasia type 1. Clin Endocrinol (Oxf) 2022; 97: 409-423.
3. The Editorial Committee of The Guidebook of Multiple Endocrine Neoplasia. ed. The guidebook for management of multiple endocrine neoplasia. Tokyo: Kanehara & Co., Ltd.; 2013 (in Japanese).
4. Brandi ML, Gagel RF, Angeli A, Bilezikian JP, Beck-Peccoz P, Bordi C, Conte-Devolx B, Falchetti A, Gheri RG, Libroia A, Lips CJ, Lombardi G, Mannelli M, Pacini F, Ponder BA, Raue F, Skogseid B, Tamburrano G, Thakker RV, Thompson NW, Tomassetti P, Tonelli F, Wells SA Jr, Marx SJ. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001; 86: 5658–5671.
5. Bassett JH, Forbes SA, Pannett AA, Lloyd SE, Christie PT, Wooding C, Harding B, Besser GM, Edwards CR, Monson JP, Sampson J, Wass JA, Wheeler MH, Thakker RV. Characterization of mutations in patients with multiple endocrine neoplasia type 1. Am J Hum Genet 1998; 62: 232–244.
6. Strømsvik N, Nordin K, Berglund G, Engebretsen LF, Hansson MG, Gjengedal E. Living with multiple endocrine neoplasia type 1: Decent care-insufficient medical and genetic information: A qualitative study of MEN 1 patients in a Swedish hospital. J Genet Couns 2007; 16: 105–117.
7. Peipert BJ, Goswami S, Yount SE, Sturgeon C. Health-related quality of life in MEN1 patients compared with other chronic conditions and the United States general population. Surgery 2018; 163: 205–211.
8. van Leeuwaarde RS, Pieterman CRC, Bleiker EMA, Dekkers OM, van der Horst-Schrivers AN, Hermus AR, de Herder WW, Drent ML, Bisschop PH, Havekes B, Vriens MR, Valk GD. High fear of disease occurrence is associated with low quality of life in patients with multiple endocrine neoplasia type 1: Results from the Dutch MEN1 Study Group. J Clin Endocrinol Metab 2018; 103: 2354–2361.
9. Berglund G, Lidén A, Hansson MG, Oberg K, Sjöden PO, Nordin K. Quality of life in patients with multiple endocrine neoplasia type 1 (MEN 1). Fam Cancer 2003; 2: 27–33.
10. You YN, Thompson GB, Young WF Jr, Larson D, Farley DR, Richards M, Grant CS. Pancreatoduodenal surgery in patients with multiple endocrine neoplasia type 1: Operative outcomes, long-term function, and quality of life. Surgery 2007; 142: 829–836; discussion 836.e1.
11. Peipert BJ, Goswami S, Helenowski I, Yount SE, Sturgeon C. Financial burden is associated with worse health-related quality of life in adults with multiple endocrine neoplasia type 1. Surgery 2017; 162: 1278–1285.
12. Goswami S, Peipert BJ, Helenowski I, Yount SE, Sturgeon C. Disease and treatment factors associated with lower quality of life scores in adults with multiple endocrine neoplasia type I. Surgery 2017; 162: 1270–1277.
13. Marini F, Giusti F, Tonelli F, Brandi ML. Management impact: Effects on quality of life and prognosis in MEN1. Endocr Relat Cancer 2017; 24: T227–T242.
14. van Leeuwaarde RS, Pieterman CRC, May AM, Dekkers OM, van der Horst-Schrivers AN, Hermus AR, de Herder WW, Drent ML, Bisschop PH, Havekes B, Vriens MR, Valk GD. Health-related quality of life in patients with multiple endocrine neoplasia type 1. Neuroendocrinol 2021; 111: 288–296.
15. Giusti F, Cioppi F, Fossi C, Marini F, Masi L, Tonelli F, Brandi ML. Quality of life in Italian patients with multiple endocrine neoplasia type 1 (MEN 1): Results of an extensive survey. Orphanet J Rare Dis 2021; 16: 16.
16. Division of Mental Health and Prevention of Substance Abuse World Health Organization, Tazaki M, Nakane Y. ed. Japanese version of WHO QOL26. Tokyo: Kanekoshobo; 1997 (in Japanese).
17. Fukuhara S, Suzukamo Y. Manual of SF-36v2 Japanese version. Kyoto: iHope International Inc.; 2004, 2019.
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361–370.
19. Spielberger CD, Smith LH. Anxiety (drive), stress, and serial-position effects in serial-verbal learning. J Exp Psychol 1966; 72: 589–595.
20. Spielberger CD, O'Neil HF Jr., Hansen DN. Anxiety, drive theory, and computer-assisted learning. Prog Exp Pers Res 1972; 6: 109–148.
21. Nakazato K, Mizuguchi T. Development and validation of Japanese version of State-Trait Anxiety Inventory: A study with female subjects. Japanese joural of psychosomatic medicine 1982; 22: 107–112 (in Japanese).
22. Nakazato K, Shimonaka Y. A cross-sectional study of development of anxiety in adult lifespan. Japanese Journal of Educational Psychology 1989; 37: 172-178 (in Japanese).
23. The National Society of Genetic Counselors' Definition Task Force: Resta R, Biesecker BB, Bennet RL, Blum S, Hahn SE, Strecker MN, Williams JL. A new definition of genetic counseling: National society of genetic counselors' Task force report. J Genet Couns 2006; 15: 77-83.
24. Lammens CRM, Bleiker EMA, Verhoef S, Hes FJ, Ausems MGEM, Majoor-Krakauer D, Sijmons RH, van Der Luijt RB, van Den Ouweland AMW, van Os TAM, Hoogerbrugge N, Gómez García EB, Dommering CJ, Gundy CM,

Aaronson NK. Psychosocial impact of Von Hippel-Lindau disease: Levels and sources of distress. Clin Genet 2010; 77: 483–491.

25. Lammens CRM, Bleiker EMA, Verhoef S, Hes FJ, Ausems MGEM, Majoor-Krakauer D, Sijmons RH, van Der Luijt RB, van Den Ouweland AMW, van Os TAM, Hoogerbrugge N, Gómez García EB, Dommering CJ, Gundy CM, Aaronson NK. Psychosocial impact of Von Hippel-Lindau disease: Levels and sources of distress. Clin Genet 2010; 77: 483–491
26. Lammens CRM, Aaronson NK, Wagner A, Sijmons RH, Ausems MGEM, Vriends AHJT, Ruijs MWG, van Os TAM, Spruijt L, Gómez García EB, Kluijt I, Nagtegaal T, Verhoef S, Bleiker EMA. Genetic testing in Li-Fraumeni syndrome: Uptake and psychosocial consequences. J Clin Oncol 2010; 28: 3008–3014.
27. Rich TA, Liu M, Etzel CJ, Bannon SA, Mork ME, Ready K, Saraiya DS, Grubbs EG, Perrier ND, Lu KH, Arun BK, Woodard TL, Schover LR, Litton JK. Comparison of attitudes regarding preimplantation genetic diagnosis among patients with hereditary cancer syndromes. Fam Cancer 2014; 13: 291–299.
28. Chen J, Gong CL, Persson U, Gu NY. A cross-country comparison of health-related quality of life in the United States, Sweden, and Norway during the first year of the COVID-19 pandemic. Arch Public Health 2023; 81: 58.

多発性内分泌腫瘍１型（MEN1）患者における心理的影響と遺伝カウンセリング（GC）：生活の質に関する懸念への対応

宮﨑幸子[1)]，隅田健太郎[1)]，伊藤雅憲[2)]，山崎雅則[3)]，内野眞也[4)]，櫻井晃洋[1)]

[1)] 札幌医科大学医学部 遺伝医学
[2)] アステラス製薬株式会社 デジタル・アナリティクス＆テクノロジー エンタープライズインサイト＆デジタルソリューショングループ
[3)] 信州大学医学部 内科学教室 糖尿病・内分泌代謝内科
[4)] 医療法人野口記念会野口病院 外科

多発性内分泌腫瘍１型（MEN1）は常染色体顕性遺伝性の疾患であり，さまざまな内分泌臓器および非内分泌臓器に腫瘍を生じ，横断的かつ長期的な医療管理を必要とする．MEN1 患者では，医療に対する不安だけでなく遺伝性の疾患であることから，不安が生活の質（QOL）に影響を及ぼす．本研究では MEN1 が患者に与える心理的影響と遺伝カウンセリング（GC）の影響について検討した．予備調査を行った後，日本の 3 つの医療機関と患者会から募集した MEN1 患者に質問票を送付した．76 名の患者からの回答を分析した（回答率 54％）．QOL（SF-36v2）の「心の健康」と不安尺度（HADS，STAI）の間に高い相関係数が認められ，不安の最も高い要素は「子や孫への影響」に関するもので，GC を受けた群で有意に高かった．MEN1 患者では QOL が低いことが報告されている．GC は遺伝的情報に加えて心理的サポートを提供するが，提供される追加情報が不安を増大させる可能性がある．このように，遺伝性疾患における GC の有用性は広く認識されているが，個人にとっての価値を確保するためには，各人の背景や精神状態を考慮し，その可能性のあるリスクを念頭に置くことが必要である．