Delay in the diagnosis of multiple endocrine neoplasia type 1: typical symptoms are frequently overlooked

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Abstract. The morbidity and mortality of individuals with multiple endocrine neoplasia type 1 (MEN1) can be reduced by early diagnosis of MEN1 and related endocrine tumors. To find factors contributing to early diagnosis, we collected clinical information on MEN1 patients through a MEN study group, “MEN Consortium of Japan” and analyzed the time of initial symptom-dependent detection of parathyroid tumors, gastro-entero-pancreatic neuroendocrine tumors (GEPNETs) and pituitary tumors, and that of tumor detection-dependent MEN1 diagnosis in 560 patients. Main tumors were identified up to 7.0 years after symptoms appeared and there was no difference in age at the diagnosis of GEPNETs alone between probands and family members. In patients with typical symptoms (peptic ulcers, urolithiasis, fasting hypoglycemia, bone fracture/loss and amenorrhea), the mean interval between symptom manifestation and tumor detection was extended up to 9.6 years. In particular, 21.7% (5/23) of patients with amenorrhea were diagnosed with pituitary tumors in under one year. In patients with peptic ulcers (from parathyroid tumors or GEPNETs) and urolithiasis (from parathyroid tumors), the interval was positively correlated with age at tumor detection. The interval between tumor detection and MEN1 diagnosis was also prolonged to approximately four years in patients with fasting hypoglycemia (from GEPNETs) and amenorrhea. A substantial delay in the diagnosis of symptom-related tumors and subsequent MEN1 and inadequate screening of GEPNETs in family members were indicated. A greater understanding of MEN1 may assist medical practitioners to make earlier diagnoses, to share patients’ medical information and to give family members sufficient disease information.

Key words: Multiple endocrine neoplasia type 1 (MEN1), Endocrine tumor, Diagnosis
tumors, pathologically identified as hyperplasia or adenoma, are the most common and frequent manifestation, occurring in more than 85-95% of patients with MEN1 [3-5]. GEPNETs, which mainly consist of gastrinomas (manifested as Zollinger-Ellison syndrome), insulinomas (also manifested as fasting hypoglycemia) and nonfunctioning tumors, occur in approximately 40-60% of affected individuals [3-5]. Anterior pituitary tumors are evident in about 30-50% of patients [3-5]. Among functioning tumors, prolactinomas, which induce hyperprolactinemia, are the most common. Amenorrhea, galactorrhea and infertility are typical symptoms in women, whereas hypogonadism and sexual dysfunction occur in men [1]. Nonfunctioning tumors also frequently develop. Germline mutations of the MEN1 gene, which encodes the tumor suppressor protein menin, are identified in most patients [3].

While prognosis of MEN1 has improved regularly, GEPNETs and thymic NETs can increase the risk of death because they have high potential for malignant transformation [4]. Indeed, some reports have shown that patients with MEN1 may have a shorter life expectancy due to these malignancies [6, 7]. The early diagnosis of MEN1 and disease-related endocrinopathy is therefore necessary to reduce morbidity and mortality. Patients diagnosed with MEN1 are fewer in number than predicted from the estimated prevalence and it therefore seems likely that many patients remain undiagnosed or are diagnosed only after a significant time-lag [8, 9].

In the present study we used a recently established clinical database of Japanese patients with MEN1 to evaluate factors contributing to the early diagnosis of MEN1 through an analysis of the interval between the appearance of initial symptoms and the diagnosis of MEN1 or MEN1-related main endocrine tumors.

**Subjects and Methods**

**Patients and data collection**

We analyzed the clinical data of patients with MEN1 collected by the MEN Consortium of Japan, a voluntary research group which has established a national database for patients with MEN1. In brief, physicians and surgeons in Japan reported clinical information of their MEN1 patients according to questionnaires provided by the MEN Consortium. The required information included gender, birth date, family history, initial symptoms, the dates of lesion detection and diagnosis of MEN1, medical and surgical managements of all lesions and their outcomes, and both pathological and genetic information. As of April 2011, surveillance had been completed for 582 cases. After verification, 560 cases were considered to be eligible for the present analysis. The general characteristics of patients with MEN1 have been recently reported [5]. In brief, primary hyperparathyroidism, GEPNETs, and pituitary tumors were seen in 90.4%, 56.1%, and 47.5% of MEN1 patients respectively. Approximately 18% of probands were asymptomatic, while nearly two-thirds of family members had already developed clinical symptoms when the probands were diagnosed with MEN1. Frequent initial symptoms seen in both probands and family members were peptic ulcers, urolithiasis, hypoglycemia, bone fracture/loss and amenorrhea. Age at diagnosis was calculated by the date of diagnosis and birth date. Intervals were also calculated by age of appearance of initial symptoms and/or age at diagnosis. This study was approved by the Institutional Review Board of Shinshu University School of Medicine and other Universities/Facilities enrolled in this study.

**Statistical analysis**

We used the mean (S.D.) for analysis of the descriptive data. To find a significant difference in each item between probands (including apparently sporadic cases) and their family members, the Mann-Whitney’s U test was conducted. The correlation between age at tumor detection and diagnostic intervals was evaluated by Spearman’s rank correlation. A $p$ value of less than 0.05 was considered statistically significant.

**Results**

**Appearance of initial symptoms**

The mean age of appearance of initial symptoms in patients with MEN1 is shown in Table 1. Age-specific appearance of initial symptoms was observed to be 36.9% at 30 years, 59.4% at 40 years, 76.9% at 50 years and 92.3% at 60 years for all symptomatic patients (Fig. 1). Initial symptoms were recognized more by family members than by probands ($p<0.001$).

**Diagnostic timing of MEN1 and related main endocrine tumors**

The mean age at diagnosis of MEN1 or related classical endocrine tumors is shown in Table 1. The cumulative percentage of patients with tumors or MEN1 are also illustrated in Fig. 2. There were no great differ-
Delayed diagnosis of MEN1

The cumulative percentage of patients who had developed parathyroid tumors at the ages of 20, 30, 40 and 50 years were 4.3%, 22.6%, 43.9% and 65.2% respectively. Age-related penetrance of GEPNETs or pituitary tumors was almost equal to that of parathyroid tumors. However, parathyroid and pituitary tumors were diagnosed earlier in family members than probands ($p<0.001$).

The mean age at diagnosis of MEN1 was similar to those of the main endocrine tumors. The cumulative percentage of patients with MEN1 at the ages of 20, 30, 40 and 50 years were 6.7%, 24.4%, 44.7% and 64.4% respectively. Family members were also diagnosed as having MEN1 earlier than probands ($p<0.001$).

Interval between appearance of initial symptoms and diagnosis of MEN1

As mentioned above, representative initial symptoms were peptic ulcers, urolithiasis, hypoglycemia, bone fracture/loss and amenorrhea. The temporal relationship between the occurrence of the symptoms and the diagnosis of corresponding endocrine tumors (symptom−tumor) or between tumor detection and MEN1 diagnosis (tumor−MEN1) was analyzed. The age of appearance of typical symptoms and mean diagnostic intervals are shown in Tables 2 and 3, respectively.

Peptic ulcers as an initial symptom of parathyroid tumors or GEPNETs

Patients with parathyroid tumors and GEPNETs (gastrinomas) can develop peptic ulcers. The mean age of appearance of initial symptoms was in the fifth decade of life. There was no significant difference in the mean age of appearance of peptic ulcers between probands and family members.

Twenty (35.7%) of 56 patients were diagnosed with parathyroid tumors less than one year after the symptoms appeared, whereas more than 10 years elapsed before diagnosis in 17 patients (30.4%). However, 51 (81.0%) of 63 patients were diagnosed as having MEN1 in less than one year (Fig. 3a). The mean inter-
Table 2. Age of first appearance of typical symptoms

<table>
<thead>
<tr>
<th>Initial symptoms (causative tumors)</th>
<th>All</th>
<th>Probands</th>
<th>Family members</th>
<th>p valuea</th>
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a Probands vs family members
### Table 3 Diagnostic intervals

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<td>0.476</td>
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<td>No. of patients</td>
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<td>5.2 ± 10.9</td>
<td>2.8 ± 4.1</td>
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*a* Probands vs family members
val of peptic ulcers–parathyroid tumors was 7.3 years, but that of parathyroid tumors–MEN1 was only 0.4 years. Each interval was not significantly different between probands and family members.

GEPNETs were diagnosed almost simultaneously with the finding of ulcers in 16 (30.2%) of 53 patients and 21 (39.6%) of 53 patients were diagnosed with GEPNETs after more than 10 years. Those who were diagnosed with MEN1 in under one year accounted for 50 (86.2%) of 58 patients with GEPNETs (Fig. 3b). The mean time of peptic ulcers–GEPNETs was 9.6 years. However, the mean intervals of GEPNETs–MEN1 showed negative values in all patients’ and family members’ groups because MEN1 diagnosis was made from 1 to 15 years before GEPNETs were found through the detection of primary hyperparathyroidism in 20 patients (8 probands and 12 family members). There was a significant difference in the time of GEPNETs–MEN1 between probands and family members (p=0.022).

Urolithiasis as an initial symptom of parathyroid tumors
The mean age of the first appearance of urolithiasis was in the fourth decade of life. The symptoms were recognized in family members 8.6 years earlier than by probands (p=0.003).

Thirty (36.6%) of 82 patients were diagnosed as having parathyroid tumors less than one year after initial colic attacks, but in 26 (31.7%) of all patients 10 years and over elapsed before tumor diagnosis. MEN1 was diagnosed less than one year after detection of parathyroid tumors in 68 (71.6%) of 93 patients with tumors and more than 80% of probands or family members were diagnosed with MEN1 within five years (Fig. 3c). The mean number of years for diagnostic intervals of urolithiasis–parathyroid tumors and parathyroid tumors–MEN1 were 8.0 and 1.0 respectively. There were no significant differences in both diagnostic intervals between probands and family members.

Fasting hypoglycemia as an initial symptom of GEPNETs
Fasting hypoglycemia, which is a specific symptom of GEPNETs (insulinomas), appeared at a mean age of 29.8 years. There was no significant difference in age at symptom presentation between probands and family members. Twenty-one (53.8%) of 39 patients with hypoglycemia were diagnosed as having GEPNETs less than one year after the first attack and more than 10 years elapsed before tumor detection in five patients (12.8%). Fourteen (56.0%) of 25 probands and seven (50.0%) of 14 family members also had tumors detected in under one year. In contrast, the rate of diagnosis of MEN1 in less than one year was 59.5% of all patients with GEPNETs (Fig. 3d). The mean intervals of fasting hypoglycemia–GEPNETs and GEPNETs–MEN1 were 3.3 and 4.2 years respectively. Neither diagnostic interval was significantly different between probands and family members.

Bone fracture/loss as an initial symptom of parathyroid tumors
Bone fracture or loss was detected in the fifth decade of life. The period required for recognition of this symptom was greater than that of urolithiasis. There was no difference in the age of appearance of the symptom between probands and family members.

Parathyroid tumors were identified in less than one year in 16 (69.6%) of 23 patients with bone fracture or loss and after more than 10 years in only 2 patients (8.7%). Twenty-three (88.5%) of 26 patients were diagnosed with MEN1 less than a year after tumor detection and no patients were diagnosed with the disease after more than 10 years (Fig. 3e). The mean intervals of bone fracture/loss–parathyroid tumors and parathyroid tumors–MEN1 were 2.0 and 0.5 years respectively. There was no significant difference in either diagnostic intervals between probands and family members.

Amenorrhea as an initial symptom of pituitary tumors
Amenorrhea is often induced by hypersecretion of prolactin due to physiologic stimuli, systemic disorders or drugs, while it is also one of the symptoms related to pituitary tumors. Amenorrhea was recognized at a mean age of 30.5 years. While symptoms were present in probands 8.1 years later than in family members, the mean age in probands was not significantly different from that in family members. Surprisingly, 5 (21.7%) of 23 patients with amenorrhea were diagnosed with pituitary tumors less than one year after this symptom appeared, whereas in 5 patients (21.7%) more than 10 years elapsed prior to tumor diagnosis. One (10.0%) of 10 family members with amenorrhea had tumors detected less than one year, compared to four (30.8%) of 13 probands. Fourteen (58.3%) of 24 patients with pituitary tumors had MEN1 diagnosed in less than one year (Fig. 3f). The mean diagnostic intervals of amenorrhea–pituitary tumors and pituitary tumors–MEN1 were 7.0 and 4.1 years respectively, indicating that it was likely that the diagnosis of pituitary tumors and subsequent MEN1 was not readily made. There were no significant differences in both intervals between probands and family members.

The correlation between age at tumor diagnosis and diagnostic intervals in individuals with an initial symptom
To clarify the cause of the delayed diagnostic pro-
Fig. 3  Diagnostic intervals in patients with typical initial symptoms
Intervals were divided into two periods; between the appearance of each specific initial symptom and the detection of tumors, and between the detection of tumors and the diagnosis of MEN1. Data are shown for probands and apparently sporadic cases, family members of the probands, and all patients with each symptom. (a) urolithiasis–parathyroid tumors–MEN1 (b) peptic ulcers–parathyroid tumors–MEN1 (c) peptic ulcers–GEPNETs–MEN1 (d) fasting hypoglycemia–GEPNETs–MEN1 (e) bone fracture/loss–parathyroid tumors–MEN1 (f) amenorrhea–pituitary tumors–MEN1.
cess, the timelines for the presentation of amenorrhea, the detection of pituitary tumors and the diagnosis of MEN1 were evaluated in individuals with amenorrhea (Fig. 4a). The interval between age at symptom appearance and that at tumor detection tended to be longer when the tumors were identified above the age of 20. The interval between age at tumor identification and that at MEN1 diagnosis seemed to be also longer after the patients had reached the age of 15 (Fig. 4b). The other symptoms had similar diagnostic intervals.

The correlation between age at the time of detection of tumors and diagnostic intervals was also examined. The interval of peptic ulcers–parathyroid tumors or GEPNETs, and that of urolithiasis–parathyroid tumors were positively correlated with age at tumor detection, meaning that the later age at tumor detection is, the greater the interval of symptom–tumor is. The interval of tumor–MEN1 was negatively correlated with age at tumor detection in the case of fasting hypoglycemia alone, partly because the age at the diagnosis of MEN1 was earlier than that of finding of GEPNETs by detection of other MEN1-related tumors (Table 4).

Fig. 4 Diagnostic intervals in individuals with amenorrhea
(a) The timelines for the appearance of amenorrhea, the detection of pituitary tumors and the diagnosis of MEN1 in each patient. (b) The relationship between age at the detection of pituitary tumors and that at the appearance of amenorrhea or between age at the diagnosis of MEN1 and that at the detection of tumors.
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is 8.1 years earlier than that in the present study, whereas
the mean time elapsing from the appearance of this
symptom to the diagnosis of MEN1 was 17.2 years [12].
Another study in the same country also found that mean
onset of the first clinical signs or symptoms occurred
7.6 years before diagnosis of MEN1 [11]. In an analysis
of three apparently unrelated Brazilian MEN1 clusters,
the age at diagnosis of HPT was 40.68 years on average
although the first episode of renal calculi occurred at an
average age of 23.14, which is approximately 12 years
earlier than that in the present study [13]. Moreover, in
a study in the Netherlands, the median interval between
the occurrence of the first manifestations and MEN1
diagnosis was 9.5 years [14].

The present analysis raises two considerable and debat-
able issues regarding the presentation of initial symp-
toms and the timing of diagnosis between probands and
family members for the early diagnosis of MEN1. One
is that early recognition of symptoms does not necessar-
ily contribute to early diagnosis of tumors and subse-
quent MEN1. In other words, typical symptoms linked
to MEN1 diagnosis are overlooked. The time-to-diag-
nosis of MEN1 depending on amenorrhea due to pitu-
itary tumors was strikingly prolonged despite the recog-
nition of symptom at younger age. Also, in the case of
fasting hypoglycemia, early diagnosis of GEPNETs and
subsequent MEN1 was not necessarily made although
the diagnostic interval of GEPNETs−MEN1 was neg-
atively correlated with age at tumor identification. In
patients with peptic ulcers from GEPNETs, tumor diag-
nosis was obviously delayed though MEN1 diagnosis
was made before or shortly after tumor identification.

Discussion

The present study is a nationwide investigation of
the diagnosis of MEN1 and MEN1-related endocrine
tumors using the clinical data of more than 500 Japanese
patients with MEN1. In the present study, initial symp-
toms appeared in 50% of patients by the fourth decade
of life. Parathyroid tumors were the most frequent man-
ifestation and hence the symptoms related to HPT, such
as urolithiasis, peptic ulcers, and bone fracture/loss,
were frequent in symptomatic cases. As for the diagno-
sis of three main tumor types and MEN1, the mean age
at diagnosis was in the fifth decade of life, supporting
previous reports that the mean age at diagnosis was in
the fourth to fifth decade of life [4, 10-18].

In 1991, a factual investigation of 106 Japanese
patients with MEN1 was conducted [19]. The first
clinical manifestations were symptoms associated
with HPT such as nephrolithiasis (32%), pituitary
tumors (26%), peptic ulcers (28%) and hypoglycemia
(13%), which appeared at an average age of 34.4 years
in familial MEN1 and 33.3 years in sporadic cases.
However, the mean age at MEN1 diagnosis was 46.2
years in familial cases and 41.3 years in sporadic ones,
indicating that many years elapsed before diagnosis of
MEN1 depending on the symptoms. There is little dif-
ference between these results and our data, indicating
that MEN1 diagnosis is still delayed, i.e. little or no
progress has been made in early diagnosis.

Delayed diagnosis of MEN1 has also been observed
in other countries. A study in the U.S. showed that the
mean age at onset of urolithiasis to be 26.9 years, which
is 8.1 years earlier than that in the present study, whereas
the mean time elapsing from the appearance of this
symptom to the diagnosis of MEN1 was 17.2 years [12].
Another study in the same country also found that mean
onset of the first clinical signs or symptoms occurred
7.6 years before diagnosis of MEN1 [11]. In an analysis
of three apparently unrelated Brazilian MEN1 clusters,
the age at diagnosis of HPT was 40.68 years on average
although the first episode of renal calculi occurred at an
average age of 23.14, which is approximately 12 years
earlier than that in the present study [13]. Moreover, in
a study in the Netherlands, the median interval between
the occurrence of the first manifestations and MEN1
diagnosis was 9.5 years [14].

The present analysis raises two considerable and debat-
able issues regarding the presentation of initial symp-
toms and the timing of diagnosis between probands and
family members for the early diagnosis of MEN1. One
is that early recognition of symptoms does not necessarily
contribute to early diagnosis of tumors and subse-
quent MEN1. In other words, typical symptoms linked
to MEN1 diagnosis are overlooked. The time-to-diag-
nosis of MEN1 depending on amenorrhea due to pitu-
itary tumors was strikingly prolonged despite the recog-
nition of symptom at younger age. Also, in the case of
fasting hypoglycemia, early diagnosis of GEPNETs and
subsequent MEN1 was not necessarily made although
the diagnostic interval of GEPNETs−MEN1 was neg-
atively correlated with age at tumor identification. In
patients with peptic ulcers from GEPNETs, tumor diag-
nosis was obviously delayed though MEN1 diagnosis
was made before or shortly after tumor identification.

Table 4 Correlation between age at tumor detection and diagnostic intervals

<table>
<thead>
<tr>
<th>Diagnostic intervals</th>
<th>No. of patients</th>
<th>rs</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcers−parathyroid tumors</td>
<td>56</td>
<td>0.267</td>
<td>0.047</td>
</tr>
<tr>
<td>Parathyroid tumors−MEN1</td>
<td></td>
<td>0.031</td>
<td>0.822</td>
</tr>
<tr>
<td>Peptic ulcers−GEPNETs</td>
<td>51</td>
<td>0.465</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GEPNETs−MEN1</td>
<td></td>
<td>-0.263</td>
<td>0.062</td>
</tr>
<tr>
<td>Urolithiasis−parathyroid tumors</td>
<td>79</td>
<td>0.304</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parathyroid tumors−MEN1</td>
<td></td>
<td>-0.131</td>
<td>0.251</td>
</tr>
<tr>
<td>Fasting hypoglycemia−GEPNETs</td>
<td>37</td>
<td>0.262</td>
<td>0.117</td>
</tr>
<tr>
<td>GEPNETs−MEN1</td>
<td></td>
<td>-0.415</td>
<td>0.011</td>
</tr>
<tr>
<td>Bone fracture/loss−parathyroid tumors</td>
<td>20</td>
<td>-0.283</td>
<td>&gt;0.050</td>
</tr>
<tr>
<td>Parathyroid tumors−MEN1</td>
<td></td>
<td>-0.038</td>
<td>&gt;0.050</td>
</tr>
<tr>
<td>Amenorrhea−pituitary tumors</td>
<td>23</td>
<td>0.410</td>
<td>&gt;0.050</td>
</tr>
<tr>
<td>Pituitary tumors−MEN1</td>
<td></td>
<td>-0.395</td>
<td>&gt;0.050</td>
</tr>
</tbody>
</table>

rs: rank correlation coefficient
For patients with parathyroid tumors, urolithiasis, bone fracture or loss, and peptic ulcers were the symptoms leading to MEN1 diagnosis soon after the tumors were found. From these facts, it is supposed that the interval between the onset of symptoms and tumor detection may be prolonged in part because some patients did not wish to consult a doctor by themselves in spite of having symptoms. Moreover, it is also assumed that family members may not have sufficient knowledge of the disease from which the probands are suffering.

The second issue is that both the mean age of appearance of typical symptoms and the mean age at diagnosis of parathyroid and pituitary tumors or MEN1 were significantly lower in family members than in probands, whereas the mean age at diagnosis of GEPNETs was not. This finding may partly reflect the earlier recognition of symptoms in family members. It is natural that family members can more rapidly identify symptoms based on probands’ experiences and genetic analysis. However, in our data, like the two other tumor types, there was no significant difference in diagnostic intervals of GEPNETs between probands and their family members. It has been previously demonstrated that GEPNETs were found at a younger age and with shorter delay between symptom presentation and tumor diagnosis in familial cases than in sporadic ones [20]. Hence, our data suggest that prospective screening and surveillance strategies for GEPNETs might be inadequate for family members.

Considering the circumstances mentioned above, we infer that the important factors causing delayed diagnosis and inadequate tumor screening are on the side of health care professionals. Indeed, Christopoulos et al. [12] have cited a lack of further examination beyond the scope of standard urological investigation in patients with urolithiasis by urologists and emphasized the responsibility of urologists suspecting HPT to appropriately refer patients for formal endocrinology consultations. It should be recognized that medical practitioners, such as physicians and co-medical staff, may insufficiently understand the characteristics of MEN1 and related disorders. In addition, the genetic testing of MEN1 for family members before the manifestation of tumors is not general in our country and a special screening strategy for family members has not been clearly shown in the existing guideline for management of MEN1. Given these facts, for appropriate screening of related endocrine tumors, we should consider improved sharing of medical information on patients and their family members among medical practitioners who examine the same patients and provide not only probands but also the family members with sufficient information of MEN1.

That said, we recognize that there are limitations of the collection and analysis of our data. The clinical data were collected with both qualitative and quantitative questionnaires, some portions of which were less informative. In the case of patients having a long history of MEN1, there is the possibility of fragmentary data collection since they may change physicians and/or hospitals. In fact, not all data were necessarily complete and thus we had to extract only the analyzable data.

In conclusion, there is a long interval not only between the appearance of initial symptoms and the diagnosis of MEN1-related endocrine tumors but also between tumor detection and MEN1 diagnosis, resulting in delayed diagnosis of MEN1 and related endocrine tumors. The symptoms of MEN1 related diseases can first be diagnosed and treated by urologists, gastroenterologists, and gynecologists, among other specialists. However, there may exist a lack of acknowledgement of MEN1 and related endocrinopathy and insufficient sharing of medical information on the same patients and their family members among involved medical practitioners. Providing family members with information of MEN1 is also insufficient. Further steps should be taken not only to promote understanding of MEN1 and prepare an environment for optimal medical information sharing among medical professionals but also to accelerate the education of family members by health care professionals.

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Disclosure

The authors have nothing to disclose.
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