Disease and treatment factors associated with lower quality of life scores in adults with multiple endocrine neoplasia type I

Sneha Goswami, BA,[a] Benjamin J. Peipert, BA,[a] Irene Helenowski, PhD,[a] Susan E. Yount, PhD,[b] *and* **Cord Sturgeon, MD, MS,[a]** *Chicago, IL*

Background. *Physical and psychosocial morbidity of multiple endocrine neoplasia type-1 is ill-defined. How disease and treatment-related factors relate to patient-reported outcomes including health-related quality of life is unknown. We hypothesized that disease and treatment burden negatively impacts health-related quality of life in adults with multiple endocrine neoplasia type-1.*
Methods. *Adults (≥18 years) with multiple endocrine neoplasia type-1 completed an online survey of demographics, disease features, treatments, and Patient-Reported Outcomes Measurement Information System 29-item profile measure, and scores were compared with normative US data. Multivariable modeling was performed to evaluate factors associated with decreased health-related quality of life.*
Results. *Multiple endocrine neoplasia type-1 patients (*n = *207) reported worse health-related quality of life compared with US normative data in all health-related quality of life domains (*P < *.001). Persistent hypercalcemia after parathyroid surgery was associated with higher levels of anxiety, depression, fatigue, and decreased social functioning (*P < *.05). Patients <45 years of age at diagnosis reported worse physical and social functioning (*P < *.01). Traveling >50 miles for doctor appointments and ≥20 doctor appointments/year (*P < *.05) were associated with worse health-related quality of life. History of pancreatic neuroendocrine tumors was not associated with worse health-related quality of life.*
Conclusion. *This is the largest study to assess clinical and treatment factors associated with health-related quality of life in multiple endocrine neoplasia type-1. Persistent hyperparathyroidism, increased travel distance and frequency of doctor appointments were all associated with worse health-related quality of life. (Surgery 2017;■:■-■.)*

From the Departments of Surgery[a] and Medical Social Sciences,[b] Northwestern University Feinberg School of Medicine, Chicago, IL

Multiple endocrine neoplasia type-1 (MEN1) is a hereditary endocrine cancer syndrome (also known as Wermer syndrome) with an incidence of 1 in 30,000.[1] Mutations in the *MEN1* gene causing truncation or absence of the tumor suppressor protein menin underlie MEN1, resulting in the development of multiple endocrine and nonendocrine tumors.[2] MEN1 is inherited in an autosomal dominant manner and has a penetrance of 94% by age 50.[3] Although the disease is highly penetrant, its

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Reprint requests: Cord Sturgeon, MD, MS, Department of Surgery, Northwestern University Feinberg School of Medicine, 676 North Saint Clair Street, Suite 650, Chicago, IL 60611. E-mail: cord.sturgeon@nm.org.

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expressivity is highly variable, with >20 endocrine and nonendocrine tumors described in this population. The manifestations of MEN1 are difficult to predict, as few genotype-phenotype correlations exist.[4] The classic triad of MEN1 is primary hyperparathyroidism (primary hyperparathyroidism [PHPT]; 95% to 99% penetrance), pancreatic neuroendocrine tumors (pNETs; 30% to 80% penetrance), and anterior pituitary adenomas (15% to 90% penetrance).[5] Other manifestations include foregut carcinoids, adrenal tumors, and cutaneous lesions. Although MEN1 is a rare condition, there is evidence that it is often underdiagnosed and underrecognized in the clinical setting.[6]

Treatment of MEN1 varies depending on the extent and severity of disease. There is no clear evidence that early intervention leads to better outcomes, and the optimal timing of surgery for treatment of primary hyperparathyroidism remains unclear. There also is considerable controversy surrounding best practices for treatment of pNETs, with very little consensus about the management of small nonfunctioning tumors.[7] Additionally, it is unknown whether medical or surgical treatment of gastrinomas leads to better outcomes.[8]

Previous studies have reported that PHPT is associated with decreased physical and mental health.[9-17] Furthermore, a recent study found that patients with neuroendocrine tumors (NET) report worse quality of life (QOL) than the general population.[18] Because PHPT and pNETs are 2 of the primary manifestations of MEN1, these studies suggest that MEN1 patients may experience worse health-related quality of life (HRQOL). Previous studies examining HRQOL in MEN1 patients had small sample sizes ($n \leq 50$), were performed in highly specific settings, or yielded conflicting results.[19,20] Additional research is required to enhance our understanding of the QOL in individuals with MEN1. To date, there have been no studies that examine clinical factors associated with worse HRQOL scores in individuals with MEN1.

Our aim was to (1) evaluate HRQOL in a large sample of MEN1 patients and (2) to identify factors associated with worse HRQOL using patient-reported outcome data. We hypothesized that individuals with MEN1 would report worse HRQOL than the general US population. We also hypothesized that increased severity of disease, number and success of surgical interventions, and treatment-related factors would be associated with HRQOL in MEN1.

METHODS

We developed a survey comprised of questions addressing patient demographics, disease features, treatment, and finances with input from individuals with MEN1 through collaboration with American Multiple Endocrine Neoplasia Support (AMENSupport), a support group for people with all forms of MEN. The survey was piloted by 4 MEN1 patients and 4 clinicians and the content was modified based on specific feedback. Respondents answered questions about their diagnosis of MEN1, their current age and age of diagnosis, history of pNETs or PHPT, and treatment history. The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) 29-item profile measure (PROMIS-29) was used for HRQOL assessment. The PROMIS-29 measures dimensions of mental, physical, and social health across 7 domains (depression, anxiety, pain interference, physical function, fatigue, satisfaction with social role participation [ie, social function], and sleep disturbance) plus one 11-point rating scale for pain intensity.[21-26] The metric for PROMIS measures is the T-score, which has a mean of 50 and standard deviation of 10. The PROMIS-29 (and most PROMIS measures) are centered on the US general population census of 2000.[25] Thus, a T-score of 50 represents the mean response for the general US population (standard deviation = 10).[27] Worse HRQOL is reflected by higher scores in the domains of anxiety, depression, fatigue, pain interference, and sleep disturbance and lower scores in the physical functioning and social function domains.

Adults diagnosed with MEN1 were recruited online through AMENSupport for a 6-month study period (April to October 2016). The public survey URL was distributed online, primarily through the AMENSupport website and social media pages. Individuals were eligible to participate in the study if they were ≥18 years of age, reported a diagnosis of MEN1, and completed an electronic consent. The cohort of respondents to this survey has been designated the AMENSupport MEN1 Cohort. Nonoverlapping data from the AMENSupport MEN1 Cohort have been reported in 2 other articles.

Study participants completed the 2-part questionnaire online on REDCap, a secure, web-based platform for collecting and managing survey data for research purposes.[28] Participants were excluded from our analysis if they did not complete both parts of the 2-part questionnaire. Responses were recorded anonymously by assigning