

Increased prevalence of light chain monoclonal gammopathy of undetermined significance (LC-MGUS) in first-degree relatives of individuals with multiple myeloma

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Received 15 November 2011; accepted for publication 16 January 2012

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Summary

Previously, we reported increased risk of heavy-chain (HC) monoclonal gammopathy of undetermined significance (MGUS) among first-degree (1°) relatives of multiple myeloma (MM) or HC-MGUS probands. This study investigated whether there was comparable risk for light-chain (LC) MGUS among 911 relatives of the same HC-MGUS/MM probands versus a reference population of 21 463. Seventeen 1° relatives had LC-MGUS (adjusted prevalence = 1.7%, 95% CI = 0.9–2.6%). There was increased risk of LC-MGUS in relatives of MM probands (RR = 3.4, 95% CI = 2.0–5.5). We saw no increased risk in relatives of HC-MGUS probands. We conclude that the prevalence of LC-MGUS is significantly higher among 1° relatives of MM probands compared to the reference population.

Keywords: MGUS, myeloma, epidemiology.

Monoclonal gammopathy of undetermined significance (MGUS) is the most common clonal plasma cell proliferative disorder, present in over 3% of the population aged 50 years and older (Kyle *et al*, 2006). MGUS is a precursor for multiple myeloma (MM) and related diseases, with a rate of progression to malignancy of 1% per year (Kyle *et al*, 2002). The prevalence of MGUS increases with age, ranging from 1.7% in those in aged 50–60 years to >5% in those older than 70 years.

Most patients with MGUS have expression of immunoglobulin heavy chain (IgH); however, approximately 20% have no evidence of IgH expression (Kyle *et al*, 2006). These individuals are considered to have light chain MGUS (LC-MGUS), the precursor to LC-MM (Dispenzieri *et al*, 2010). LC-MGUS is defined by an abnormal kappa-lambda (κ - λ)

free light chain ratio (FLC-R), elevation of free light chain (FLC) level, and absence of expression of a monoclonal peak of IgH in the serum on immunofixation (Drayson *et al*, 2001; Dispenzieri *et al*, 2010). LC-MGUS is present in approximately 1% of the general population over the age of 50 years.

We recently reported a 2.6-fold increased risk of heavy chain (HC) MGUS in first-degree relatives of patients with HC-MGUS or MM (Vachon *et al*, 2009). There are currently no data on whether LC-MGUS is increased in first-degree relatives. Here, we sought to determine the prevalence of LC-MGUS in first-degree relatives of patients with MM and HC-MGUS, and to examine whether the prevalence of LC-MGUS differed in relatives of probands who have LC-MM compared with HC-MM.

Methods

Study probands

The study was approved by the Mayo Clinic Institutional Review Board and employed the same families that were studied to determine the prevalence of HC-MGUS in first-degree relatives of patients with MM and HC-MGUS (Vachon *et al*, 2009). HC-MGUS probands were recruited from a well-defined cohort of patients from Olmsted County, MN, who were identified as having HC-MGUS through a population-based prevalence study (Kyle *et al*, 2006). Serum samples were obtained from 21 463 (76.6%) of 28 038 enumerated residents aged 50 years or older. Of these, HC-MGUS was identified in 694 subjects (3.2%); 89 were derived from blinded samples and 301 were deceased, to give a total of 304 eligible living HC-MGUS probands. An invitation letter, consent form, and family history questionnaire soliciting contact information for first-degree blood-related family members aged 40 years and older were sent to each living HC-MGUS proband.

MM probands were recruited from patients seen at the Mayo Clinic between February 2006 and September 2007. Eligible patients were invited to participate via a letter distributed during their clinical appointment (Vachon *et al*, 2009). Consent forms and questionnaires, identical to those sent to MGUS probands, were sent to each consenting proband.

First-degree relatives

An invitation, risk factor questionnaire, and informed consent form were mailed to all first-degree relatives identified by probands. Upon receipt of the completed consent form, a blood collection kit was mailed to relatives for blood to be collected at a local facility and returned to Mayo Clinic for testing.

Serum protein electrophoresis, serum immunofixation, and free light chain assay

All serum samples were processed and analysed in an identical fashion in the same laboratory (Mayo Clinic Protein Immunology Laboratory, Rochester, MN, USA) as the population-based study of HC-MGUS in Olmsted County samples, which served as the reference population (Kyle *et al*, 2006). Serum protein electrophoresis and immunofixation were previously performed on all samples from first-degree relatives. Samples were tested using the serum FLC assay (FREELITE™, The Binding Site Ltd., Birmingham, UK) to measure κ and λ immunoglobulin FLC levels and to estimate serum FLC-R. The analytic sensitivity for the nephelometric FLC assay in the Mayo Clinic Protein Immunology Laboratory is 0.1 mg/l for a monoclonal κ or λ FLC (Katzmann *et al*, 2005). The standard definition of HC-MGUS and LC-MGUS used in prior Olmsted County prevalence studies were applied (Kyle *et al*, 2006; Dispenzieri *et al*, 2010). LC-MGUS was defined as an abnormal FLC-R (<0.26 or >1.65), the absence of heavy chain expression on serum

immunofixation, elevation of the involved light chain above the appropriate cut-off point, and absence of known myeloma or related malignancy.

Statistical analyses and considerations

Overall age- and sex- adjusted prevalence was estimated by standardization to the 2000 United States population. Age-specific prevalence was calculated by dividing the number of individuals with LC-MGUS in each age and sex group by the number of individuals in the group with an assayed serum sample. Age- and sex-specific rates of LC-MGUS from the Olmsted County LC-MGUS prevalence study were used as 'expected' rates for risk ratio (RR) calculations for comparisons of all first-degree relatives, and separately for relatives of each type of proband (HC-MGUS or MM) (Dispenzieri *et al*, 2010). Expected rates for individuals in the 40- to 49-year-old age group were estimated using linear interpolation, based on an assumed prevalence rate of 0 at age 30.

Results and Discussion

Characteristics of probands and relatives are given in Table I. LC-MGUS was identified in 17 (1.9%) of the 911 first-degree relatives, with an age- and sex-adjusted LC-MGUS prevalence

Table I. Baseline characteristics of probands and relatives.

Probands, <i>N</i> = 329, <i>n</i> (%)	MGUS proband, <i>n</i> = 97	MM proband, <i>n</i> = 232	Total
Male	48 (49.5)	126 (54.3)	174 (52.9)
Female	49 (50.5)	106 (45.7)	155 (47.1)
Age group, years, <i>n</i> (%)			
<40	0 (0)	6 (2.6)	6 (1.8)
40–49	0 (0)	30 (13.0)	30 (9.2)
50–59	20 (20.6)	79 (34.2)	99 (30.2)
60–69	48 (49.5)	75 (32.5)	123 (37.5)
70–79	26 (26.8)	38 (16.5)	64 (19.5)
80+	3 (3.1)	3 (1.3)	6 (1.8)
First-degree relatives, <i>N</i> = 911, <i>n</i> (%)	MGUS relatives, <i>n</i> = 247	MM relatives, <i>n</i> = 664	Total
Male	109 (44.1)	273 (41.1)	382 (41.9)
Female	138 (55.9)	391 (58.9)	529 (58.1)
Relationship to proband			
Parent	1 (0.4)	93 (14)	94 (10.3)
Sibling	101 (40.9)	392 (59)	493 (54.1)
Child	145 (58.7)	179 (27)	324 (35.5)
Age group, years, <i>n</i> (%)			
40–49	57 (23.1)	201 (30.3)	258 (28.3)
50–59	76 (30.8)	157 (23.6)	233 (25.6)
60–69	47 (19)	143 (21.5)	190 (20.9)
70–79	39 (15.8)	91 (13.7)	130 (14.3)
80+	28 (11.3)	72 (10.8)	100 (11)

MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma.

among all relatives of 1.7% [95% confidence interval (CI), 0.9–2.6%]. The adjusted prevalence of LC-MGUS was 0.6% (95% CI, 0.0–1.6%) for 247 relatives of 97 HC-MGUS probands and 2.1% (95% CI, 1.0–3.2%) for 664 relatives of 232 MM probands (32 LC-MM and 200 HC-MM) (Table II). Using identical techniques to detect LC-MGUS, the adjusted prevalence of LC-MGUS was 0.8% in Olmsted County (Table II) (Dispenzieri *et al*, 2010). Thus, the risk of LC-MGUS was significantly greater among all first-degree relatives than that in the Olmsted County reference population (RR = 2.7, 95% CI, 1.6 to 4.3). The increased risk of LC-MGUS was seen among the relatives of MM probands (RR = 3.4; 95% CI, 2.0–5.5); in relatives of HC-MGUS probands, the risk ratio was RR = 1.1 (95% CI, 0.3–4.5).

Of the 17 first-degree relatives in whom LC-MGUS was detected, 13 had overexpression of κ FLC and four had λ overexpression. In individuals with overexpression of κ , the median level of κ FLC was 2.69 (range: 2.02–10.10), the median level of λ FLC was 1.25 (range: 0.96–1.64), and the median FLC-R was 2.09 (1.72–7.43). In individuals with overexpression of λ , the median level of κ FLC was 1.04 (range: 0.28–1.95), the median level of λ FLC was 9.11 (range: 4.68–9.80), and the median FLC-R was 0.11 (range: 0.06–0.21).

Among MM probands, the prevalence increase in relatives of the 32 probands with LC-MM was 3.8; that of the relatives of the 200 probands with HC-MM was 3.3 (ratio = 1.2, 95% CI for the ratio = 0.3–5.1, $P = 0.85$). However, these estimates are based on small numbers and should be performed in larger family studies.

Many factors affect the prevalence of HC-MGUS, including age, sex, race, pesticide exposure, obesity, and family history (Kyle *et al*, 2006; Landgren *et al*, 2006, 2007; Vachon *et al*, 2009). LC-MGUS is a newly described entity, and is the precursor for LC-MM. Factors that influence the development of LC-MGUS and its risk of progression are largely unknown. The Olmsted County LC-MGUS prevalence study described an increased prevalence in men (1.0%) compared with women (0.6%) (Dispenzieri *et al*, 2010). The same study revealed a significant increase in prevalence of LC-MGUS with increasing age (Dispenzieri *et al*, 2010).

We have previously shown that first-degree relatives of individuals with HC-MGUS or MM have a 2.6-fold increased prevalence of HC-MGUS (Vachon *et al*, 2009). Here, we describe for the first time the increased prevalence of LC-MGUS in first-degree relatives of patients with MM. Unlike HC-MGUS, increased prevalence was not seen in the first-degree relatives of HC-MGUS probands. Furthermore, the increased risk of LC-MGUS was not unique to LC-MM probands. The overall age- and sex-adjusted rate of all MGUS in first-degree relatives (both LC-MGUS and HC-MGUS) is 9.0%, based on prior data (Vachon *et al*, 2009).

Our findings support a possible genetic predisposition for LC-MGUS. A major limitation of our study is that, at the time of data collection, LC-MGUS was an undefined identity; therefore, we collected data only for probands with HC-MGUS and their first-degree relatives. Additionally, given that we did not have information on renal failure status in subjects, it is possible that the prevalence of LC-MGUS

Table II. Prevalence of LC-MGUS in first-degree relatives of MGUS and MM probands compared with Olmsted County, MN residents.

Age, years	All relatives			Olmsted County		
	Total no.	No. with LC MGUS	Prevalence (95% CI)	Total no.	No. with LC MGUS	Prevalence (95% CI)
40–49	258	1	0.4 (0.0–2.2)			
50–59	233	3	1.3 (0.3–3.8)	7167	36	0.5 (0.4–0.7)
60–69	190	3	1.6 (0.3–4.6)	5330	40	0.8 (0.5–1.0)
70–79	130	6	4.6 (1.7–10.0)	3850	43	1.1 (0.8–1.5)
80+	100	4	4.0 (1.1–10.2)	2010	27	1.3 (0.9–2.0)
Total	911	17	1.9 (1.1–3.0)	18357	146	0.8 (0.7–0.9)
Total, adjusted*	911	17	1.7 (0.9–2.6)	18357	146	0.8 (0.7–0.9)
Relatives of MGUS proband				Relatives of MM proband		
40–49	57	0	0.0 (–)	201	1	0.5 (0.0–2.8)
50–59	76	0	0.0 (–)	157	3	1.9 (0.4–5.6)
60–69	47	1	2.1 (0.1–11.9)	143	2	1.4 (0.2–5.1)
70–79	39	0	0.0 (–)	91	6	6.6 (2.4–14.4)
80+	28	1	3.6 (0.1–19.9)	72	3	4.2 (0.9–12.2)
Total	247	2	0.8 (0.1–2.9)	664	15	2.3 (1.3–3.7)
Total, adjusted*	247	2	0.6 (0.0–1.6)	664	15	2.1 (1.0–3.2)

LC, light chain, MM, multiple myeloma; 95% CI, 95% confidence interval.

*Rates for monoclonal gammopathy of undetermined significance (MGUS) determined by serum protein electrophoresis, age- and sex-adjusted to the 2000 US total population.

may have been slightly overestimated. Future work should examine LC-MGUS prevalence and risk in relatives of LC-MGUS probands, as there may still be increased risk in these individuals. Planned additional work will examine the prevalence of these conditions in second- and third- degree relatives. Individuals with LC-MGUS have a lower progression rate to malignancy (0.3%/year) compared with IgG, IgA or IgM HC-MGUS (1.0%/year), but their risk is roughly comparable to low-risk IgG MGUS, which has been defined as an M-spike of <15 g/l and a normal FLC ratio (0.25%/year) (Rajkumar *et al*, 2005; Dispenzieri *et al*, 2010). This knowledge, coupled with our findings, could help inform clinical monitoring and treatment of LC-MGUS.

Acknowledgements

This work was supported in part by the National Cancer Institute, National Institutes of Health, Bethesda, MD (CA107476, CA100707, CA 83724) and by the NIH/NCRR CTSA Grant Number TL1 RR024152. Also supported in

part by the Jabbs Foundation, Birmingham, United Kingdom and the Henry J. Predolin Foundation, USA.

Authorship contribution

A.J.G., C.M.V., and S.V.R. conceived the study and wrote the paper with comments from all coauthors; C.M.V. was responsible for study design and overseeing the project; R.A. K. helped in strategizing the project, contributed study populations, and interpreted study findings; R.A.K. and J.A.K. determined MGUS diagnoses for all relatives; S.L.S., T.M.T., D.R.L., and C.L.C. performed all statistical analyses and contributed to their interpretation; T.K.P. assisted with data collection and was responsible for all blood processing; A.D. and S.K.K. provided scientific input and interpretation of analyses; all coauthors read and approved the paper.

Conflict-of-interest disclosure

The authors declare no competing financial interest.

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