Applying a new decision threshold to an old test: Does the measurement of plasma metanephrines in patients fasting & supine improve diagnostic sensitivity?

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GP-03-06

BACKGROUND & AIMS

Recently published Endocrine Society Clinical Practice Guidelines on Phaeochomocytoma and Paraganglioma (PPGL) recommend measuring fractionated plasma free metanephrines (PMets) with patients in the supine position using appropriately defined reference intervals. These recommendations were based on the superiority of sampling after supine rest versus sampling in the seated position without preceding rest. The endorsed upper reference limits (URL) for plasma normetanephrine (NMN) and metanephrine (MN) are 610pmol/L and 310pmol/L respectively[1].

Studies have shown higher diagnostic sensitivities using the latter pretesting criteria [2,3]. This protocol is resource intensive and arguably impractical in clinical practice. In our institution blood samples for PMets are collected with patients seated with preceding cannulation and rest (30 minutes) using reference intervals established accordingly (URL for plasma NMN :1180pmol/L and plasma MN: 510pmol/L).

The aim of this study was to retrospectively evaluate the diagnostic performance of the Endocrine Society decision thresholds for PMets in patients who underwent screening for PPGL in our institution between 2009-2014.

METHODS

A retrospective review of all PMets carried out in our institution from 2009-2014 was performed. Patient details were obtained through chart review and interrogation of radiology and laboratory computer based systems. Fractionated PMets (NMN and MN) were measured using Liquid Chromatography Tandem Mass Spectrometry. The newly recommended Endocrine Society cut-offs for PMets were applied to these data. Statistical analysis was performed using R (V3.2.0). Summary statistics included means and standard deviations for continuous variables and frequencies and percentages for categorical variables. The diagnostic sensitivity and specificity was then calculated for plasma NMN and MN using both the current laboratory and the recently endorsed Endocrine Society decision thresholds for PMets.

RESULTS

A total of 183 patients were included in this study, 82 females and 101 males. The mean age of participants was 53.4 (SD 16.3). Chart review determined that 5 of 183 (2.7%) patients had histologically confirmed PPGL (males, n=4). The most common indication for screening was hypertension (n=121 or 66.1%) and adrenal adenoma (n = 32 or 7.5%).

The current laboratory reference interval for PMets, established in seated and rested patients, gave a diagnostic sensitivity and specificity of 100% and 98.9% respectively with two false positive cases. Application of the Endocrine Society recommended reference interval for PMets resulted in a diagnostic sensitivity of 100% and a diagnostic specificity of 84.8% with a total of forty seven false positive results. Importantly, irrespective of the PMets reference interval applied to our cohort, no case of PPGL would have been missed. The most common diagnoses associated with false positive results occurred in individuals with hypertension (n=22, 47%), primary hyperaldosteronism (n=10, 21.2%) and obstructive sleep apnoea (n=4, 8.5%).

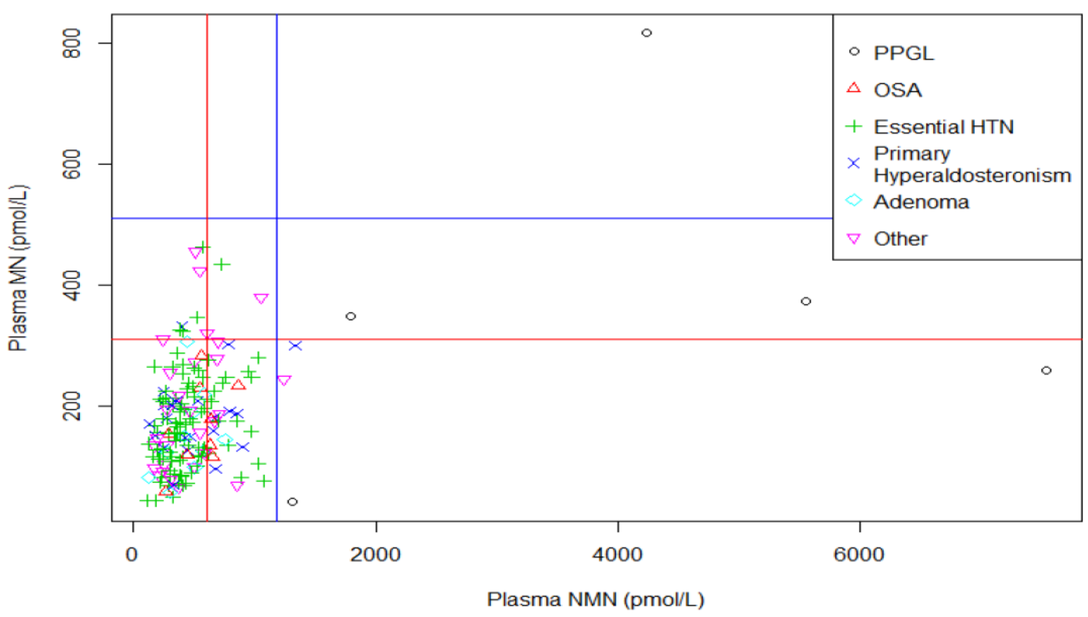

Figure 1. Fractionated free PMets in all patients investigated for PPGL
Current laboratory URLs for PMets
Endocrine Society URLs for PMets

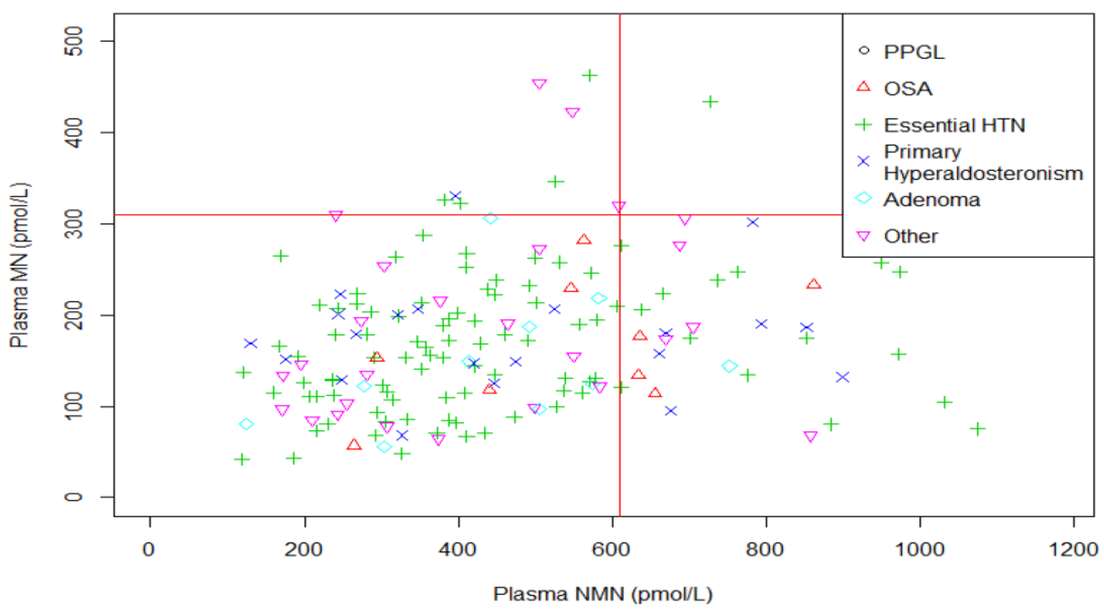

Figure 2. Schematic representation of patients with a false positive test result using the Endocrine Society URLs for PMets.

CONCLUSIONS

Our findings are reassuring as they confirm that the diagnostic sensitivity of the existing more pragmatic testing protocol employed in our institution over the 5-year period of this review, has to-date, not yielded a false negative result in the potentially life threatening condition of PPGL. Further, application of the Endocrine Society reference intervals derived after supine rest did not improve diagnostic sensitivity but did reduce diagnostic specificity resulting in forty five additional false positive results. Together with not missing a diagnosis our protocol avoided further patient follow-up and the associated economic implications.

We acknowledge a limitation of the current study is its retrospective design. Notably, in our institution the sampling protocol includes a 30 minute rest period prior to phlebotomy. A prospective study is required to validate our findings and to investigate whether preceding rest is the critical factor contributing to the non-inferior diagnostic sensitivity of our protocol when compared with that of the Endocrine Society.

REFERENCES

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17 ECE 6--GP-03
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DOI: 10.3252/pso.eu.17ece.2015
Poster presented at: ECE2015 16–20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY