A probabilistic assessment of the diagnosis of paraganglioma/pheochromocytoma based on clinical criteria and biochemical/imaging findings

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Abstract
Paragangliomas (PGL) and pheochromocytomas (P) are rare neural-crest-derived neoplasms. Very recently guidelines on diagnosis and treatment of PGL/P have been presented by the US Endocrine Society. In the following overview we assessed the implementation of these guidelines with probabilistic reasoning (calculating with Fagan nomograms the post-test probability of PGL/P for a given pre-test probability). **Conclusion**: Biochemical evaluation of PGL/P showed excellent diagnostic characteristics with post-test probabilities that are very different from the pre-test probabilities, thus a positive biochemical test is usually indicative of disease whereas a negative one usually rules out disease. The post-test probabilities of anatomical and functional imaging modalities (i.e. in nuclear medicine) were different from the pre-test probabilities but to a lesser degree than the biochemical tests; furthermore in biochemically-proven PGL/P a negative imaging modality is not useful, while a positive one may indicate only one of multiple foci of metastatic/extra-adrenal disease. Thus, regarding imaging modalities, they should be combined in order to get the most of their characteristics for the localization of PGL/P.

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Introduction

Very recently guidelines on diagnosis and treatment of paragangliomas/pheochromocytomas/ (PGL/P) have been presented by the US Endocrine Society [1]. These tumors have an incidence of 0.2%-0.6% among subjects with hypertension. Their prevalence is reported to be approximately 0.3% in major U.S. academic centers. This figure we will use to consider as the initial pre-test probability of PGL/P [2]. According to Bayes' theorem prior information influences the interpretation of observations. In medicine, Bayesian methods incorporate known uncertainties and thus, induce a more realistic diagnosis [3]. Evidence-based medicine uses likelihood ratios, among others, to assess the utility or the futility of performing a certain diagnostic test. The testing modality's sensitivity and specificity, via the likelihood ratio, also known as Bayes' factor, determine whether a test result changes the probability of a disease. In the following overview we assess the implementation of the as above recent PGL/P guidelines using probabilistic reasoning and calculating with Fagan nomograms the post-test probability of PGL/P for a given pre-test probability.

Epidemiology

Due to the rarity of PGL/P, the epidemiological figures given in the previous section may not convey an exact estimate of the disease's prevalence. From the anamnesic/patient history, the classic triad of diaphoresis, palpitations and headache has a reported sensitivity of 89% and specificity of 67% for PGL/P and in the presence of hypertension 91% and 94%, respectively [2, 4]. Thus a person with this triad of symptoms plus hypertension has a 15-fold probability of suffering from PGL/P, whereas in case of having hypertension without the classic triad has a 10-fold probability of not suffering from PGL/P. A diagnosis is almost unequivocally ruled in with a likelihood ratio for a positive test >10 or ruled out with a likelihood ratio for a negative test <0.1) [5] (Figure 1a). These initial results are reassuring a better diagnosis but since not all patients have the above cluster of symptoms biochemical evaluation is necessary.

Biochemistry

It is known that PGL/P secrete catecholamines in an episodic manner while they continuously metabolize them into metanephrines [6]. For a *pre-test* probability of 0.3%, a plasma level of fractionated metanephrines more than 4 times higher than the upper normal levels (henceforth considered as those of biochemically-proven disease), assuming sensitivity of 97% (+LR = 8.85) and specificity of 89% (-LR = 0.03) has a post-test probability of 3.0% for PGL/P, whereas negative plasma metanephrines have a *post-test* probability of 0.0%. Thus, the *post-test* probability of PGL/P considerably increases, but less than 10-fold, whereas a negative test, below the lower normal limit, almost excludes the diagnosis of PGL/P (Figure 1b). Intermediate plasma metanephrine results, warrant dynamic evaluation using the clonidine test. If plasma metanephrines are not available, urine fractionated metanephrines are the second best choice for biochemical evaluation of suspected PGL/P. For a *pre-test* probability of 0.3%, elevated urine fractionated metanephrines, assuming sensitivity of 95% (+LR = 3.65) and specificity of 74% (-LR = 0.07) have a *post-test* probability of 1.0% for PGL/P, whereas negative urine metanephrines have a *post-test* probability of 0.0%. Approximately 5% of adrenal incidentalomas are PGL/P, which leads to a higher *pre-test* probability [1, 7], so that positive biochemistry findings make the diagnosis more probable, and negative biochemistry, as for example in a subject with an incidentaloma, points away from such a diagnosis (Figure 1b).

Localization

Further radiological and/or nuclear medicine evaluation is necessary in subjects with biochemically-proven PGL/P as up to 17% of these patients may have extra-adrenal and/or metastatic disease. This means a higher *pre-test* probability [8]. Anatomical imaging with computed tomography (CT) and magnetic resonance imaging (MRI) has sensitivity of approximately 94%, while it may sometimes be as low as 57% and specificity of 70% [9]. Evaluated with CT/MRI, assuming sensitivity of 94% (+LR = 3.13) and specificity of 70% (-LR = 0.09), a positive CT/MRI has a *post-test* probability of 39.0%, whereas negative CT/MRI has a *post-test* probability of 2.0%. Thus, a lesion identified in a scan image in a subject with elevated metanephrines is probably a PGL/P. Nevertheless, the absence of lesions on a precise region in an anatomical image may lower the *post-test* probability of PGL/P but this is by no means reassuring since in this case there is a biochemically-diagnosed disease. Further assessment necessitates nuclear medicine imaging. Scintigraphy with iodine-123-meta-iodobenzylguanidine (^{123}I-MIBG) has a sensitivity of 56%-88% and a specificity of 70%-100%, with the worse diagnostic values noted for extra-adrenal, recurrent and/or metastatic disease. Positive lesions are probably PGL/P, however absence of ^{123}I-MIBG uptake - in case of biochemically-proven disease – may be false-negative (Figure 2a). Positron emission tomography with fluorine-18-fluorodeoxyglucose (^{18}F-FDG PET) has a reported sensitivity of 74%-100% and a specificity of 80%-90% [1, 10-12] and allows for a better diagnostic localization compared to ^{123}I-MIBG (Figure 2b).

In conclusion, biochemical evaluation of PGL/P show excellent diagnostic characteristics with *post-test* probabilities that are very different from the pre-test probabilities, thus a positive biochemical test is usually indicative of disease whereas a negative one usually rules out disease. The post-test probabilities of anatomical and functional imaging modalities (i.e. in nuclear medicine) are different from the pre-test probabilities but to a lesser degree than the biochemical tests; furthermore in biochemically-proven PGL/P a negative imaging modality is not useful, while a positive one may indicate only one of multiple foci of metastatic/extra-adrenal disease. Thus, regarding imaging modalities, they should be combined in order to get the most of their characteristics for the localization of PGL/P.

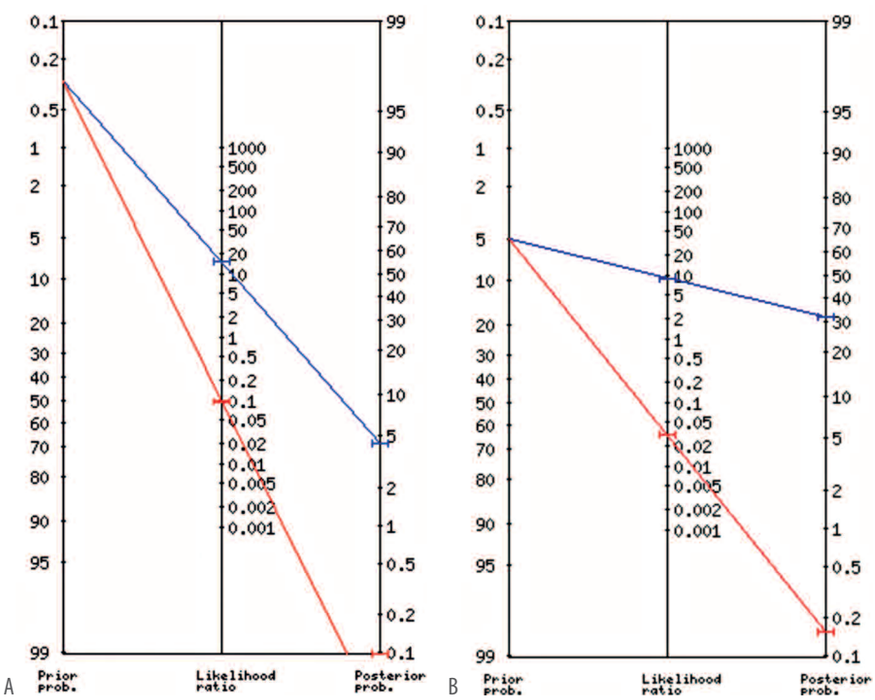

Figure 1. A. Fagan nomogram for a pre-test probability of 0.3%. The PGL/P triad of symptoms, assuming sensitivity of 91% (likelihood ratio for a positive test [+LR] = 15.00) and specificity of 94% (likelihood ratio for a negative test [-LR] = 0.10) have a post-test probability of 4.0% for PGL/P, whereas the absence of the PGL/P triad, has a post-test probability of 0.0%
B. With a pre-test probability of 5.0%, an adrenal incidentaloma in a patient with elevated plasma fractionated metanephrines, assuming sensitivity of 97% (+LR = 8.85) and specificity of 89% (-LR = 0.03) has a post-test probability of 32.0% for PGL/P, whereas negative plasma metanephrines have a post-test probability of 0.17% (modified from figures drawn with Diagnostic Test Calculator; http://araw.mede.uic.edu/cgi-bin/testcalc.pl).

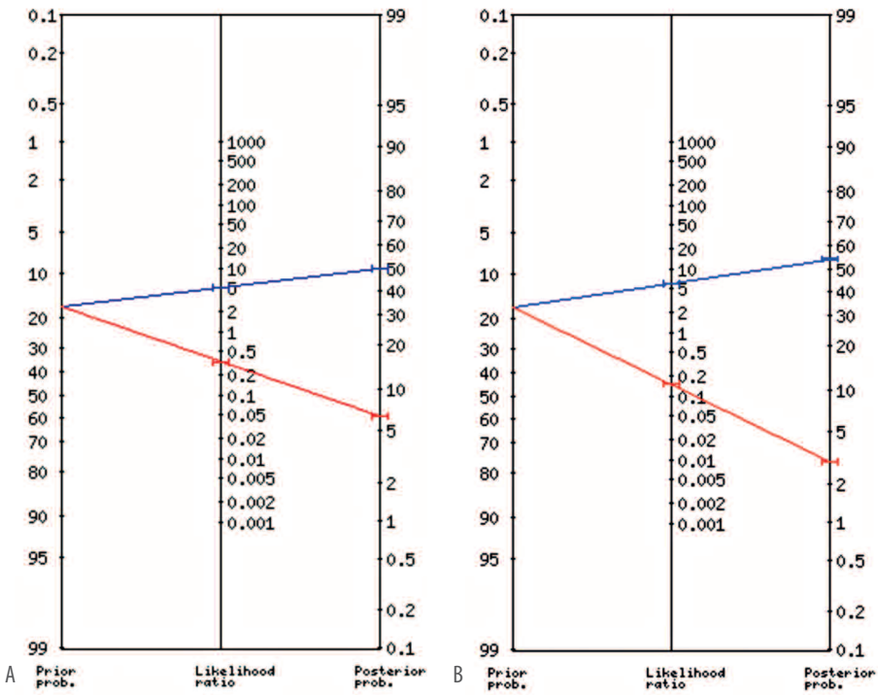

Figure 2. Fagan nomograms for biochemically-proven PGL/P with pre-test probability of 17.0% for extra-adrenal/metastatic disease. A: Evaluated with ^{123}I-MIBG, assuming sensitivity of 72% (+LR = 4.80) and specificity of 85% (-LR = 0.33), positive ^{123}I-MIBG, has a post-test probability of 50.0%, whereas negative ^{123}I-MIBG, has a post-test probability of 6.0%. B: Evaluated with ^{18}F-FDG PET, assuming sensitivity of 87% (+LR = 5.80) and specificity of 85% (-LR = 0.15), positive ^{18}F-FDG PET has a post-test probability of 54.0%, whereas negative ^{18}F-FDG PET has a post-test probability of 3.0%.

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The authors declare that they have no conflicts of interest.

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