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

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.

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. Positive lesions are probably PGL/P, whereas absence of 123I-MIBG uptake - in case of biochemically-proven disease – may be false-negative (Figure 2a). Positron emission tomography with fluorine-18-fluorodeoxyglucose (18F-FDG PET) has a reported 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 123I-MIBG uptake - in case of biochemically-proven disease – may be false-negative (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额外腺病. 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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Bibliography