Is Arginine Test a Reliable Tool for Differential Diagnosis of Multiple System Atrophy?

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Gardner et al evaluated the arginine growth hormone (GH) stimulation test in cerebellar-type multiple system atrophy (MSA-C) patients as compared with those with idiopathic late-onset cerebellar ataxia (ILOCA) and familial ataxia.[1] In contrast to our previous results,[2] they did not find any correlation between GH response to arginine and diagnosis.

There are several aspects of the Gardner et al study that deserve attention.

The case series investigated is too small to draw any conclusion. In the study in which we proposed the arginine test as a diagnostic tool for the differential diagnosis between idiopathic Parkinson disease (PD) and MSA, we enrolled a number of MSA-C patients that was double that of Gardner's study. The lack of results in Gardner's study could be due to the small series studied. Moreover, Gardner and coworkers concluded that the arginine test is not reliable for diagnosing MSA-C only on the basis of absence of any significant difference in peak GH response to arginine. In our study, 25 of 26 patients (96%) with MSA-C had GH peak after arginine under the cut-off level of 4μg/l, established by receiver operating characteristic (ROC) analysis.[2] Gardner et al did not calculate a cutoff level; however, by carefully analyzing their Figure, we observed that 8 of 12 (67%) MSA-C patients had a GH peak lower or close to 4μ/l, as compared to 8 of 21 (38%) patients with ILOCA and familial ataxia.

The inclusion of obese patients is a major methodological flaw, as body weight is a strong predictor of GH response to any stimulation test.[3–5] Considering the significant negative correlation between peak postarginine GH and weight, observed in their study, it is thus highly likely that weight is the major determinant for the variability of GH response to arginine. In a subanalysis, they excluded subjects with a body mass index (BMI) $\geq$28 (about 50% of all ataxic patients), further reducing the sample size to the point that no statistical analysis would have any value.

The authors stated that GH deficiency (GHD) had been excluded by performing growth hormone-releasing hormone (GHRH) plus arginine test. To exclude GHD, they used a cut-off of 4.1μ/l, based on a report on a US population of 39 patients with hypothalamic-pituitary disease and 34 healthy controls.[3] This is surprising, considering that GHRH plus arginine test is a very potent test, inducing the release of the complete pituitary reserve of GH. In a series of 408 healthy subjects of our region who performed the GHRH plus arginine test, a GH cutoff value ranging from 4 to 11.5μg/l according to age

and BMI was found for a diagnosis of GHD.[5] On analysis of the mean levels of GH peak after GHRH plus arginine reported by Gardner et al in their Table 2, the large standard deviations in both patients and controls demonstrated that a consistent number of subjects had abnormal GH peak, making it unlikely that they can be considered normal and not GHD.

Recently, the reliability of the arginine test in the differential diagnosis of MSA has been confirmed by Zhang et al, who studied GH response to arginine and clonidine in 24 patients with parkinsonian MSA (MSA-P) as compared with 26 patients with PD.[6] By ROC analysis, they found that the arginine test had a sensitivity of 78% and a specificity of 73%, whereas the clonidine test had a sensitivity of 82% and a specificity of 76%. When these tests were combined, the specificity in the differential diagnosis of MSA-P from PD increased to 92%.[6]

In conclusion, we still consider the arginine test a valid research tool that deserves further analysis to understand its potential role in the differential diagnosis between MSA-C and ILOCA.

Potential Conflicts of Interest

Nothing to report.

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