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Stimulation of growth hormone release in multiple system atrophy, Parkinson's disease and idiopathic cerebellar ataxia

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Abstract Clonidine has been proposed to differentiate multiple system atrophy (MSA) from idiopathic Parkinson's disease (IPD), as it does not increase growth hormone (GH) release in MSA. We studied GH release in response to clonidine in 7 IPD patients, 6 MSA patients, 4 patients affected by idiopathic late-onset cerebellar ataxia (ILOCA) and 8 healthy controls. In addition, we investigated the effects of GH releasing hormone plus arginine (GHRH-Arg) on GH release in the same patients. Both clonidine and GHRH-Arg raised serum GH levels in all groups examined. Clonidine failed to differentiate MSA from IPD and ILOCA. GHRH-Arg showed a lower increase of serum GH in MSA patients than in other groups, even if such difference was not statistically significant. We suggest that stimulation of GH release with GHRH-Arg rather than clonidine could differentiate MSA from IPD and ILOCA, but this hypothesis would need to be confirmed by further investigations.

Multiple system atrophy (MSA), idiopathic Parkinson's disease (IPD) and idiopathic late-onset cerebellar ataxia (ILOCA) are sporadic neurodegenerative disorders. Differential diagnosis between MSA and IPD and between MSA and ILOCA may sometimes be difficult, but is important for prognosis and treatment. Clonidine is an α2-adrenoceptor agonist that raises serum growth hormone (GH) concentrations in healthy subjects. Kimber et al. reported that clonidine does not increase GH levels in MSA patients and this finding clearly differentiates MSA from IPD [1]. More recently, Clarke et al. failed to show any difference in the GH response to clonidine in patients with MSA and IPD [2]. To clarify these discordant data, we studied GH response to stimulation not only with clonidine but also with growth hormone releasing hormone plus arginine (GHRH-Arg), as this test is considered more reliable in adults [3].

Eight healthy controls, 7 patients with IPD not receiving levodopa or dopamine agonists for at least 1 month, 6 patients with MSA according to accepted criteria [4], and 4 patients with ILOCA were included in the study. After fasting overnight, an antecubital vein was cannulated. Patients rested supine for 30 min and a baseline blood sample was taken. Clonidine and GHRH-Arg were administered on two different days. Clonidine (2 μg/kg) was administered orally and blood samples taken every 15 min for 2 hours. Blood pressure and heart rate were recorded at the same intervals. Arginine (30 g in 100 ml) was infused from 0 to 30 min, and GHRH (100 μg) was injected as an intravenous bolus at 30 min. Blood samples were collected at 0, 30, 45, 60, 90, 120, 150 min. Blood samples were centrifuged and the plasma stored at –20° C pending analysis of serum GH. Basal concentrations of insulin-like growth factor-1 (IGF-1) and IGF-binding protein-3 (IGFBP-3) were also measured. For statistical analysis we used mean peak GH responses and areas under the curves (AUC) for each group. Groups were compared by analysis of variance (ANOVA) and Newman-Keuls test.

Both clonidine and GHRH-Arg increased serum GH levels in all groups examined. Basal GH, IGF-I and IGFBP-3 levels were comparable between groups. Mean peak GH responses and AUC results for each group are reported in Table 1. After clonidine administration, there was no significant difference between the groups in peak GH responses or AUC. After GHRH-Arg administration, no significant difference was found between the groups, but the mean peak GH response and AUC in MSA patients were lower than in other groups (p=0.0 and p=0.08, respectively).

Discussion

Clonidine is a centrally active α2-adrenoceptor agonist used for testing GH responses in children. Recently, it has been proposed to differentiate MSA from IPD [1], possibly due to a depletion of catecholaminergic neurons of the intermediate reticular formation of the ventrolateral medulla which project to the hypothalamic nuclei [5].

GHRH-Arg is considered to be the safest and most reliable test throughout the adult lifespan [6]. This test, however, was never used to differentiate MSA from IPD patients. As arginine stimulates GH serum release mainly by suppressing endogenous somatostatin secretion, we wondered if even this pathway was involved in MSA.

Our results with regard to clonidine test are discordant from the previous ones [1, 2]. After clonidine administration, GH levels increased in both MSA and IPD patients. We did not find any difference in GH responses to clonidine between MSA and IPD, and neither did clonidine test differentiate MSA from ILOCA. After GHRH-Arg administration, on the

Table 1 Peak growth hormone (GH) responses and areas under the curve (AUC) after clonidine and GHRH-Arg tests. Values are means (SE)

Test	Control (n=8)	MSA (n=6)	IPD (n=7)	ILOCA (n=4)
Clonidine				
Peak GH response (ng/ml)	21.1 (3.5)	24.1 (6.9)	20.3 (7.0)	24.8 (4.0)
AUC (ng/ml min)	732.3 (126.8)	784.6 (262.7)	956.5 (326.5)	825.8 (134.0)
GHRH-Arg				
Peak GH response (ng/ml)	30.0 (3.0)	19.6 (3.5)	26.8 (5.0)	36.4 (3.1)
AUC (ng/ml min)	921.5 (101.7)	614.2 (200.1)	972.9 (211.7)	1419.8 (196.5)

MSA, multiple system atrophy; *IPD*, idiopathic Parkinson's disease; *ILOCA*, idiopathic late-onset cerebellar ataxia

contrary, we observed a significant trend to a lower GH response in MSA than in other groups

We suggest that clonidine GH stimulation is not a good test to differentiate MSA from IPD and ILOCA. Further investigations are necessary to confirm the utility of GHRH-Arg test as a diagnostic tool in MSA.

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