Dear Editors and Reviewers:

Thank you for your letter and for the reviewer's comments concerning our manuscript entitled Elevated serum growth differentiation factor 15 in multiple system atrophy patients: A case control study. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer' s comments are as following:

Comments:

1. #According to this study and others, GDF15 seems generally elevated in neurodegenerative diseases, including MSA, PD, DLB, etc. This study deals with serum, while others (ex. ref 18) deal with CSF. Why serum in this study? Are there any other studies dealing with serum GDF15; and if so, in what neurodegenerative diseases? There happens to be data about CSF GDF15 in this study? Are there any data about serum GDF15 vs CSF GDF15 in neurodegenerative diseases, with respect to their superiority or inferiority for the differential diagnosis?

Answers: We are very sorry for our unclear report about this study deals with serum other than the CSF. In order to facilitate the development of the clinical trials, the identification of potential and non-invasive biomarkers is important. The ideal biomarker is detectable in easily accessible samples, i.e. blood, urine, saliva, or exhaled air, whether a subideal biomarker such as cerebrospinal fluid (CSF), muscle, liver, or heart requires more invasive procedures. And our recent study revealed that the mean serum GDF15 levels in the PD patients were significantly higher than those of the healthy control groups (ref.17). So, we investigated serum GDF15 in MSA patients in consideration of

the non-invasive and the easily accessed. According to comment, related content have been improved in the discussion part.

We are sorry not to deal with the GDF15 in CSF in this study, and it was not reported about the difference between the serum GDF15 and the CSF GDF15 in neurodegenerative diseases. It is interesting to know about superiority or inferiority in serum GDF15 and CSF GDF15 for the differential diagnosis? The reviewer gave us a new direction, which can be done in the future research.

2. #Supplement Table 1 is interesting, which, I guess, is ok by itself. But my bigger concern is as follows. For example, this table says hyper-intense putaminal rim, which is really a good diagnostic tool for MSA, is absent in 23 MSA-P and 14 MSA-C patients. My question is 'how about serum GDF15 levels in these patients (37 MSA patients in all)?' If it is sufficiently elevated (take >1075 pg/ml, for example, according to table 3), serum GDF15 is really a useful tool for the correct diagnosis of MSA. In this Supplement Table 1, we have a good array of items suggestive of MSA, for example, syncope/dizziness, sweating, urinary/sexual dysfunction, orthostatic hypotension, Babinski, hot cross bun sign, etc. I guess it possible to analyze statistically in the same way like, 'hyper-intense putaminal rim: MSA: no yes ＶＥＲＳＵＳ MSA: >1075 pg/ml <1075 pg/ml'. This analysis will enhance the value of this paper as well as serum GDF15 for the diagnosis of MSA.

Answers: As the Reviewer's good advice, we analyzed the serum GDF15 levels in the MSA patients with different clinical features. The serum GDF15 in patients with no hyper-intense putaminal rim is 1146.38±713.72 pg/ml, which suggest that serum GDF15 is really a useful tool for the correct diagnosis of MSA. The levels of the serum GDF15 in the MSA patients with or without the clinical features were shown in the following tables, which were

sufficiently elevated mostly(>1075 pg/ml). We have not found any significant difference between the yes or no subgroups of the clinical features. Some limitations exist and need to be improved upon in subsequent studies. Firstly, the sample size was limited, and it was difficult to obtain better insight into the correlation of the clinical features and the elevated serum GDF15 levels in MSA patients; Secondly, patients covering the broad range of disease stages are necessary. To further explore whether serum GDF15 levels are consistent with clinical manifestations requires studies with larger sample sizes in the future.

	sGDF15, pg/ml
Syncope/Dizziness	
NO	1446.45±961.39
YES	928.44±515.56
Urinary/sexual dysfunction	
NO	1211.25±847.83
YES	1151.22±782.90
Constipation	
NO	1135.54±1130.55
YES	1170.22±637.50
Wheezing/Apnea	
NO	1059.04±726.66
YES	1297.00±855.48
Sweating	
NO	1191.21±891.45
YES	1098.75±519.69
Orthostatic hypotension	
NO	1374.40±1076.71
YES	1066.88±611.97
Essential Tremor	
NO	1200.97±817.62
YES	1097.95±747.71
Rigidity	
NO	1036.33±840.36
YES	1201.46±773.84
Postural instability/ gait disturbance	
NO	1278.14±854.98
YES	1141.50±782.04
Loss of facial expression	

NO	1118.57±1027.01
YES	1168.10±752.72
Dysphonia	
NO	936.22±890.37
YES	1211.60±762.49
Lower limb weakness	
NO	1341.77±1067.23
YES	1095.75±661.76
Coordination test(+)	
NO	1086.00±878.49
YES	1245.83±673.12
Babinski-like responses/hyperreflexia	
NO	1224.44±913.47
YES	1041.65±456.54
Cognitive impairment	
NO	1126.85±835.61
YES	1336.13±439.25
Dysphagia (swallowing problems)	
NO	1047.87±694.43
YES	1261.12±858.12
Olfactory dysfunction	
NO	1111.36±813.58
YES	1298.54±711.33
Cortical atrophy	
NO	1179.07±800.37
YES	1002.20±686.91
Hyperintense putaminal rim	
NO	1146.38±713.72
YES	1206.17±1009.16
Cerebellum, brainstem atrophy	
NO	1208.84±952.72
YES	1111.21±577.56
Enlargement of the fourth ventricle	
NO	1207.00±833.68
YES	981.70±553.62
The Hot Cross Bun Sign	
NO	1128.47±843.67
YES	1222.29±680.55

3. I appreciated the reviewer telling us there were grammatical mistakes, and we have corrected them conscientiously.

I would like to re-submit to World Journal of Clinical Cases, and hope it is acceptable for publication in the journal.

Looking forward to hearing from you soon.

With kindest regards,

Yours sincerely
Yiming Liu