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Lewy pathological study on α-synuclein in gastrointestinal tissues of prodromal Parkinson's disease

Q.-B. LU[1,2], Z.-F. ZHU[2], H.-P. ZHANG[2], W.-F. LUO[3]

[1]Department of Neurology, the Second Affiliated Hospital of Soochow Univer[illegible], Suzh[illegible]iangs[illegible] China
[2]Department of Neurology, Affiliated Jiangyin Hospital of Southeast Univ[illegible]y Me[illegible]al Colle[illegible] Jiangyin, Jiangsu, China
[3]Department of Neurology, the Second Affiliated Hospital of Soochow [illegible]rsi[illegible]Suzhou[illegible]iangsu, China

Abstract. – OBJECTIVE: In the gastrointestinal neural system, the emergence of Lewy Body (LB) is usually earlier than the clinical diagnosis of Parkinson (PD) motor symptoms. Therefore, this study is aimed to explore whether the LB in the gastrointestinal tract of prodromal PD patients.

PATIENTS AND METHODS: 98 paraffin embedded tissue specimens from 57 PD patients were collected in the Second Affiliated Hospital of Soochow University archives, as well as 98 tissue specimens of 90 non-PD patient[illegible] dergone surgical resection. The patho[illegible] sections were stained by the immune-[illegible]-chemistry method. The positive staining of[illegible] gregated α-Synuclein (a-α-syn) and phosph[illegible] ylated α-Synuclein (p-α-syn) in [illegible]intestin[illegible] tract were counted to analyze [illegible]ution o[illegible] the expression of a/p-α-syn i[illegible]e pro[illegible]mal PD patients before diagnosis [illegible]years, [illegible]years, 11-20 years).

RESULTS: According[illegible] re[illegible]om the im-munohistochemical [illegible]ining [illegible]-α-syn, 35 (52.23%) and 30 [illegible]8%) tissue [illegible]ks were positively staine[illegible]tively in tot[illegible] tissue blocks provide[illegible]om 3[illegible]dromal PD patients. And there w[illegible]46 (46.94%)[illegible]25 (25.51%) positive staini[illegible]98 tissue blo[illegible]om the control group. I[illegible] tissue blocks coll[illegible]ted from 18 PD patient[illegible]here w[illegible]19 (61.29%) and 15 (48.39%) tissue[illegible]ks [illegible] the a[illegible]-α-syn positive staining. Co[illegible]with p[illegible]D patients from the [illegible]l gro[illegible]he a[illegible]n positive rate was not [illegible]ntly [illegible] in the pre- and post-di-agnos[illegible]PD pati[illegible] (p>0.05). However, p-α-syn of bo[illegible]roups increased significantly (p<0.05). Als[illegible]e expression rate of a/p-α-syn [illegible]6-10-yea[illegible] group was lower than that in the [illegible]ear and 11-20-year, and the positive rate of th[illegible]year group was the highest (p<0.05).

C[illegible]LUSIONS: p-α-syn as the main component of Lewy body of nervous system in the gastrointestinal track may be used as a characteristic predictive marker of PD and the prevention of PD disease.

Key Words
Prodro[illegible]D[illegible]rointestinal [illegible]ue, Ð-Synuclein, Immunoh[illegible]ochemi[illegible]

[illegible]troduction

[illegible]inson[illegible]ease (PD) is a common neurodegene[illegible]disease worldwide. The main clinical manifestations of PD include resting tremor, [illegible]inesia, rigidity and postural gait disorders and [illegible]er conventional motor symptoms[1]. Also, many PD patients have non-motor symptoms including REM sleep behavior disorder, hyposmia, constipation and orthostatic hypotension, etc.[3,4]. It was found that the degeneration of dopaminergic neurons of the substantia nigra and the presence of Lewy body were the pathological signs of PD. Lewy Body contains high-density of aggregated α-synuclein (a-α-syn) and phosphorylated α-synuclein (p-α-syn)[5]. The study hypothesized that there is an unknown pathogen that may cause a physiological error folding in the gastrointestinal tract of the α-synuclein (α-syn) in the peripheral nervous system. The retrograde axon then passes through the vagus nerve to the dorsal motor nucleus of the vagus nerve, thereby causing damage to the brain tissues, including the black body[6]. Researches[7] recently discovered that the vagus nerve stem cutting operation can reduce the risk of PD, verifying the previous hypothesis. Therefore, the study of the regional pathology of Lewy Body (LB) nerve endings has become a hotspot in the field of PD research, and with the accelerated process of PD pathophysiology, this is helpful for us to demonstrate the feasibility of using PD tissue samples *in vitro* for the diagnosis of prodromal symptoms.

Corresponding Author: Weifeng Luo, MD; e-mail: qc80855593tongz@163.com

Table I. Comparison of gender, age and tissue mass data in patients.

Index		Prodromal PD	PD	Control
Number of patients		39	18	90
Number of tissue		67	31a	98
Gender (m/f)		24/15	9/9	47/43
Mean age at diagnosis		70.53±13.12	65.15±15.47	-
Mean age at biopsy		63.34±10.44	68.73±11.42	65.22±8.13
a-α-syn	Positive tissue	35	19	46
	Mean age at biopsy	62.12±14.42	69.26±13.72	66.32±12.56
	Negative tissue	32	12	
	Mean age at biopsy	64.53±13.17	68.07±10.45	64 2.64
p-α-syn	Positive tissue	30	15	25
	Mean age at biopsy	63.40±11.92	69.02±13.85	64±10
	Negative tissue	37	16	73
	Mean age at biopsy	63.12±13.81	68.50±11.00	3

Note: a, 9 out of 31 tissues were from the 5 patients which were performed biopsy odromal stage

Decades ago, it was found that the LB exists in the enteric nervous system of PD and non-PD patients by hematoxylin and eosin staining[8]. Recently, the immunohistochemical studies[9] have confirmed that the LB can exist at the gastrointestinal tissue sites of typical PD patients. According to the reference, the researchers have detected the presence of LB in the gastrointestinal tract of the PD patients[10,11]. However, the potential pr in the development of α-syn histology are di t samples used by different immunohistochem methods and the difference of assessment crite of α-syn positive. By comparing e norma control group, the significant ier in the number of positive biopsies -syn (00%) is perhaps a more reliable te ndard has two main objective to te whether the intestinal nervou stem of tients with PD in the prodro ge has Lew thology; 2- the relative re between th positive rates of a-α-syn and p-α in gastrointestinal tissues of P d non-PD pa control group.

Pat ts an Methods

mple

5 tients ed in this study were enrolled ing Janu y 2013 to January 2015 from the ated Hospital of Soochow University (Suzhou, Jiangsu, China). A total of 98 in embedded tissue blocks was collected fro ncture biopsy or the excess parts of surgic removal (including 67 tissue blocks of the prodromal stage). All PD patients in this study were diagnosed as having a severe motor impairment. Tissue blocks of 39 patients had been surgically re d at prodromal stage (5 pati d surgical ion after diagnosis of P e first surgical removals of tissue blocks e performed or the rest 18 patients after diosed PD.

Co sa es

98 amples for the control group were collected from 90 non-PD patients. The patients control group had the same age, sex and pe issue with the PD patients in study group.

Ethical materials

All the experiments were approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University, and the isolated tissue blocks, which were surgically removed from the patients, were only used in this study. Patients or their family members have signed informed consent.

Comparison of gender, age and tissue mass data in patients

Patient demographics and tissue block information were listed in Table I.

Also, according to the basic information of patients, we divided the patients into 0-5-year group, 6-10-year group, and 11-20-year group. We summarized the distribution of a/p-α-syn positive and negative in 67 prodromal tissue blocks of PD patients.

Treatments of tissue samples

Tissue blocks were fixed in buffered formalin, then numbered and filed. From each tissue, slices of 3 μm thickness were cut-out and stained with hematoxylin and eosin staining (Abcam Co., Ltd.,

Table II. Distribution of a/p-α-syn positive staining location of Prodromal PD, PD and control group.

Location	Prodromal PD (n=39)			PD (n=18)			Control (n=90)		
	N	a-α-syn	p-α-syn	N	a-α-syn	p-α-syn	N	a-α-syn	p-α-syn
Nasal area	2	0	0	1	1	1	3	0	
Oral area	5	3	1	3	0	0	8	1	2
Salivary glands	3	2	3	1	1	0	4	2	1
Esophagus	16	3	2	7	2	4	23		2
Stomach	21	10	9	10	7	4	31	18	
Small intestine	7	6	6	1	1	1	8		
Appendix	5	5	5	3	3	2	8	8	
Colon	8	6	4	5	4	3	13	5	
Total	67	35	30	31	19	15			25

Bristol, UK), and verified the anatomic locations by standard histopathological evaluation. Tissue blocks had to be excluded if contained abnormal tissues, and other sections of the tissue blocks were used for immunohistochemical staining.

Immunohistochemical methods

The brain tissues of this study were derived from the late PD patients with typical Lewy pathological features and other patients who died from other causes of neurological disorders (pro-vided by the Department of Pathology of t ond Affiliated Hospital of Soochow Univ y, Suzhou, Jiangsu, China). In the pilot experi of this study, the ranges of corresponding spec antibody (Abcam Co., Ltd., Bris) concen trations which according to a in a -α-syn in brain tissue samples we :40 ~1 00 and 1:100 ~1:6000, respectivel four the antibody was dilute ith os, strong staining of LB was duced, b staining of other brain tissues ot detected syn and p-α-syn were a ed for 8 m by using the protease a tric ac fer was carried out for 24 min gen repair at 5°C. The anti-a-α-syn/p- n rabbit monoclo antibody were 1:200 ions, a ncubated at 37°C for 32 min.

Th nd eratio f ready-to-use immunohistoch y Elivi Plus broad spectrum zhou ma oTech Co. Ltd., Fuzhou, ujia hina) ed and stained the first antibod strict ac ordance with the instructions. Pho saline (PBS) buffer instead of rst antibody was as a negative control. brain tissues from deceased PD patients wi y pathology were considered as positive contro samples, and the brain tissues from deceased non-PD patients as negative controls. Different markers of immunohistochemistry staining of adjacent parallel sections, including CD34 (endothelial), CD68 ro es), CD56 (autophagy phocytes a ural tissues), CD117 (st cells) and prominent vesicular proteins (nerv s) were used to analyze the eactivity a entation of the α-syn st ng.

tistical An sis

e SPSS19 oftware (SPSS Inc., Chicago, IL,) w sed for the statistical analysis. A X^2 used to analyze the categorical variables in the Table. Multivariate analysis was ed by using logistic regression. Differ- ce ith a value of $p<0.05$ were considered statistically significant.

Results

Positive staining and evaluation results

We performed a double blind, clinical classification of stained sections. The positive brain tissue control group showed the expected strong reactivity, linear Lewy neurite and larger circular LB separation staining (Figure 1). In some cases, non-specific staining was found when the surrounding tissue samples were stained. Additional dilution studies were carried out from the surrounding tissues of the selected samples. The studies confirmed that the non-specific staining of the peripheral tissues of the samples and the neural tissues can be distinguished. When there was a clear and strong immunohistochemical staining signal, the signal was identified as positive reaction. In the Lewy neurite, the nerve plexus or the dense granular staining was used as the positive lower limit of the α-syn (Figures 2-3). According to the results and our consensus, we determined the presence of a-α-syn/p-α-syn pathology.

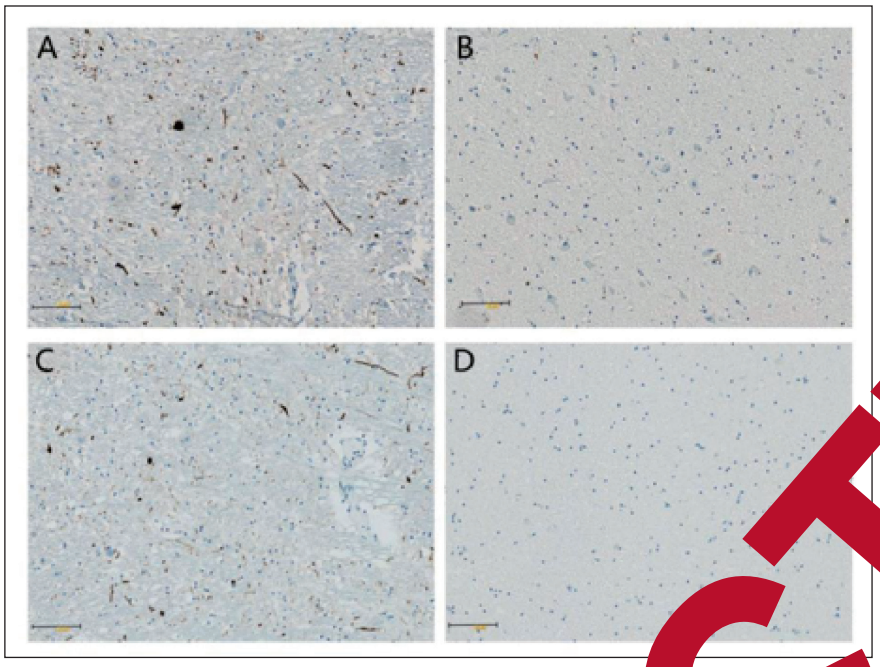

Figure 1. Typical staining of brain tissue sections. Note: Immunohistochemical staining of a-α-syn and p-α-syn of brain tissue sections of late PD patients (**A**, **C**) and late non-PD patients (**B**, **D**). PD ... linear Lewy neur... positive brown ...ng (**A**, **C**). ... negative con... up did not hav... phenomenon ... ...ne staining (**B**, **D**). ...le=100 ...

Comparison of positive rates of a/p-α-syn in different parts of prodromal PD, PD and control group

The immune response is located in th... mucosa, submucosal ganglion, muscle nerv... er and intramuscular ganglion. The positive sta... was located in the same parts of the PD gr... and the control group. Althoug... staini... reactions appeared in the mu... la... f some tissues, the most significant ...tive st... ng was ... in the a... of intestinal and submucosal ga... (Fig...). Also, some p-α-syn staining of PD ... and control group were found that non- neuronal non-specific staining was discovered in the epithelial layer of gastric biopsy. This ... immune response was easy to be distinguished from normal cranial nerve structure, and was not classified as positive α-syn staining.

According to the immunohistochemical staining for a-α-syn, we found that 24 (35 tissue

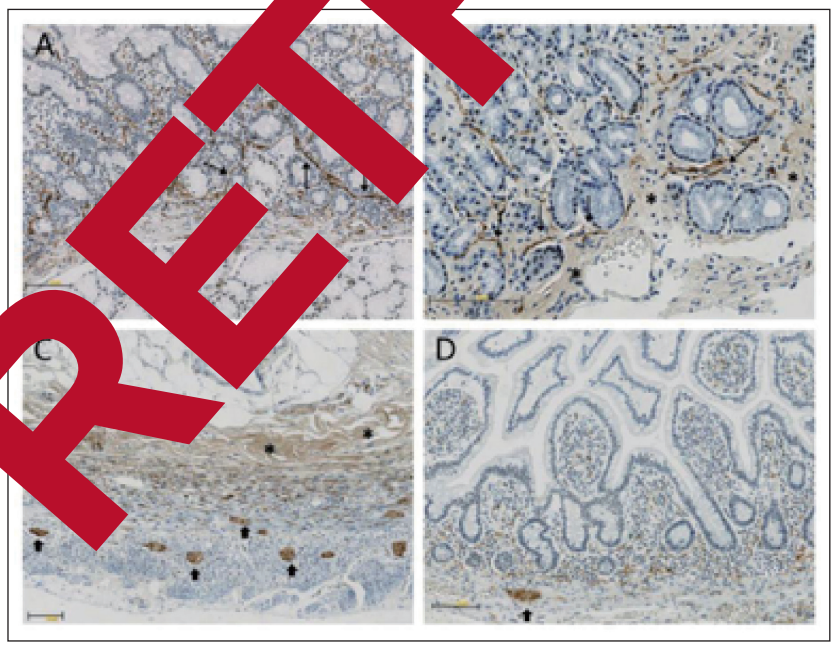

Figure 2. Typical staining of gastrointestinal tract samples (1). Note: Immunohistochemical staining of a-α-syn in gastrointestinal tract. **A**, Duodenum of controls; **B**, Pylorus in prodromal PD patients; **C**, Appendix of controls; **D**, Small intestine of PD patients. The thin and thick arrows represent the neurite and the nerve plexus. The asterisk represents nonspecific amplification in non nerve tissue. Scale=100 μm.

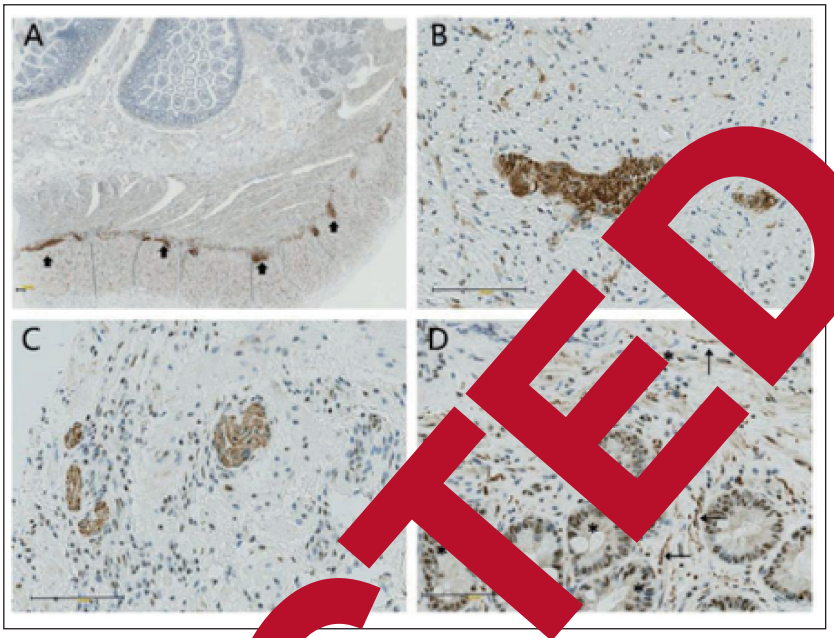

Figure 3. Typical staining of gastrointestinal tract samples (2). Note: Immunohistochemical staining of p-α-syn in gastrointestinal tract. **A**, Intestinal tissues of PD patients; **B**, Nerve plexus of appendix in controls; **C**, Gastric nerves of PD patients; **D**, Esophagus of PD patients. The thin and thick arrows represent the neurite and the nerve plexus. The asterisk represents nonspecific amplification in non nerve tissue. Scale=100 μm.

blocks) of 39 (67 tissue blocks) prodromal PD patients had a positive stain, the proportion was 61.54% (52.23%). 43 (46 tissue blocks) of 90 (98 tissue blocks) patients in the control group had a-α-syn positive stain, with proportion of (46.94%). In 31 tissue blocks of 18 PD patients after diagnosis, there were 11 (19 tissue blocks) PD patients had a-α-syn positive stain, with proportion of 61.11% (61.29%). Compared to the control group, the increase of α-syn positive rate in patients at prodromal stage and after diagnosis was not significant (p>0.05).

According to the immunohistochemical staining for p-α-syn, we found that 22 (tissue blocks) of 39 (67 tissue blocks) prodromal patients had a positive stain, with proportion of 56.41% (44.78%). In the control group, 3 (25 tissue blocks) of 90 (98 tissue blocks) patients had a-α-syn positive staining with a proportion of 3.56% (25.51%). There were 9 (15 tissue blocks) cases of p-α-syn positive stain in total 31 tissue blocks from 18 PD patients, the proportion was 50.00% (48.39%). Compared to the control group, the increase of α-syn positive in patients at prodromal stage and after diagnosis was significant (p<0.05). The distribution of α-syn positive stain locations of groups was shown as Table II.

Comparison of the time distribution of positive diagnosis of a/p-α-syn

The distribution of positive/negative diagnosis time was shown as Figure 4. The positive expression rate of a-α-syn and p-α-syn in 6-10-year group was lower than that in 0-5-year group and 1[illegible]-year group and the 0-5-year group was the high[illegible] (p<0.

Discussion

According to a series experiments of brain tissue samples, this study confirmed that the pathological aggregation of α-syn in different gastrointestinal sites can be detected in the 20 years before the development of clinical symptoms of PD. Through the immunohistochemical stain of a-α-syn and p-α-syn, we found that when only p-α-syn staining was performed, the numbers of positive staining from prodromal PD biopsy samples were significantly higher in comparison with the control group. The previous study[12] suggested that, by study of gastrointestinal tissues of prodromal PD patients, 3 cases of 33 patients (9%) had p-α-syn positive reaction. By contrast, there were 22 of 39 (56.41%) cases of prodromal PD patients had p-α-syn positive staining in this study. Even though the two studies had the similar design and staining of p-α-syn, results showed significant differences. The difference of results can be affected by various factors which including different tissue types, different immunohistochemical staining methods, different pretreatment methods of tissue samples and the differences in the evaluation criteria of α-syn positive staining. It was extremely imperative that all tissue samples, which were detected in

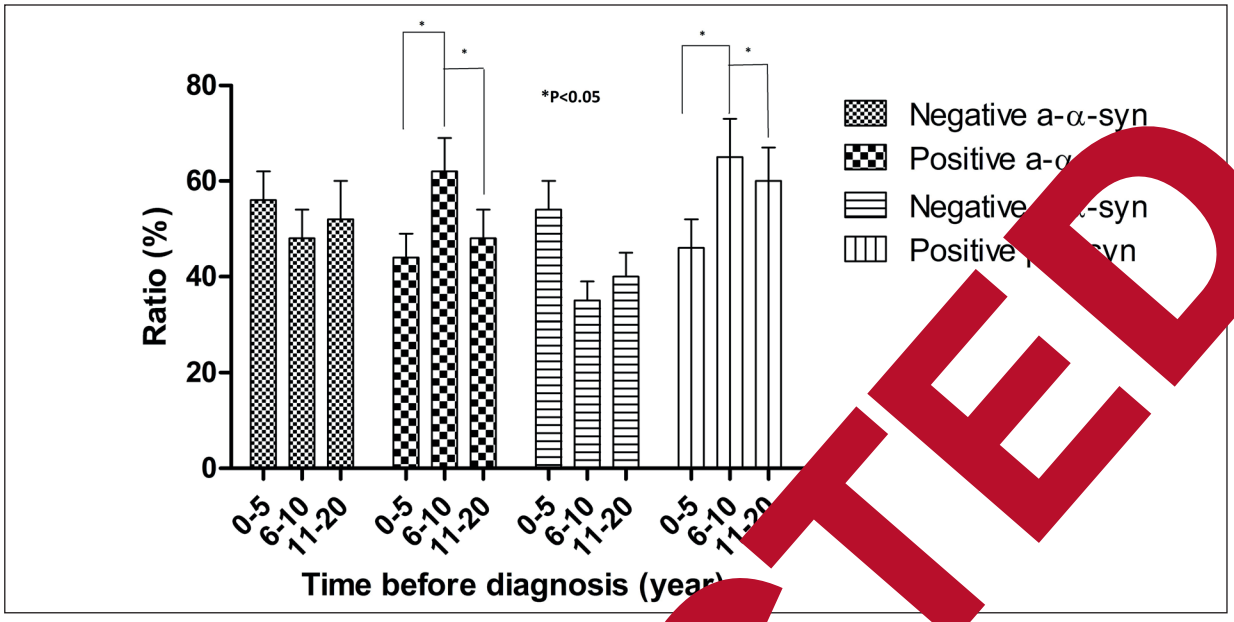

Figure 4. Distribution of positive/negative tissue blocks at prod l a-α-syn and syn. Note: The time intervals before diagnosis of PD were 0-5 year (n=29), 6-10 year (n=23), 11-20 yea 15).

this study, were not entirely based on cli al diagnosis, but rather focused on the experi results. Despite what type of immunohisto n-istry method and the positive staining evalua criteria was used, we found that there was a la amount of p-α-syn accumulation obviou a-α-syn changes in the gastr tract of prodromal PD patients. M of the revious works mainly focused on t nical PD patients, and the ti sa ere usua taken from the same or multi arts of each patient. These stu ay be ado different approaches, lead to radictory co clusions. To exclude the methodo al differences, we selected on athology sli m each tissue. Although had a slightly low positive rate of α-syn atient e results obtained from the prodr PD ients w e consistent with the previous ch res Physiological α-syn, vs a ol the protection of nerve idn has a of functions in the central nervo ystem a enteric nervous system[13]. In the rmal people, it was found that n be detected in about 10-12% in the brain of the people over the age of 60, which sug d that the LB was possibly the outcome of the hange of α-syn with the increase of age. There was no significant clinical significance for Parkinson's disease, such condition was incidental DLB (dementia with LB)[14]. Also, α-syn may be involv e deposition of the nervous system in a variety of neurodegenerative diseases, such tau disease and multiple system atrophy[15]. cc ng to the 233 community sources found at autopsy, 24.9% individuals with α-syn positive, of which 8% individuals was suffering from AD, 2% individuals suffering from multiple system atrophy, and 1% individuals with atypical α-syn protein disease[16]. However, the pathologic α-syn polymerization was involved in various neurodegenerative diseases including PD[17]. Therefore, it was very important to distinguish between physiological and non-physiological α-syn (a-α-syn/p-α-syn) by immunohistochemical detection of α-syn.

Through the detection of a variety of α-syn antibodies, previous researchers have found that the positive rates of cerebral Lewy pathology were similar, but the non-specific staining was common. The sensitivity and specificity of antibodies, and the different types of pretreatment of tissue samples may also influence the final results of immunohistochemical staining. The detection rate of Lewy neurite was increased 25 times after pretreatment of brain tissue with proteinase K[18]. Also, compared with the non-physiological α-syn polymer, Proteinase K can decrease the expression of α-syn in physiological monomer, but when the α-syn fibrosis or phosphorylation can resist the effect of protease K[19]. Only low polymerization state α-syn with moderate degree of sensitiv-

ity to K protease maybe the precursor of fibrosis dense LB, and the LB contains high-density p-α-syn[20]. We used protease pretreatment combined with conventional α-syn and p-α-syn antibodies, to visualize the pathology of Lewy pathology. This binding mode showed excellent sensitivity and specificity of antibodies against brain tissue samples from PD patients and non-PD controls (Figure 1). Gastrointestinal dysfunction is very common in PD patients. Such symptom may be related to the presence of Lewy pathology in the gastrointestinal tract. Through the studies of PD patients with positive Lewy pathology, we found that dysfunction of dopaminergic neurons and decreased function of the submucosal ganglion in the intestinal mucosa were common in these patients. In contrast, some studies have reported that the number of neurons in the colon tissue of Lewy patients with positive PD has not changed. Some works[21,22] have suggested that the number of ganglion neurons or neurons in the colon of PD patients with positive Lewy pathology has not changed. However, it should be noted that the quantification of enteric nervous system is difficult, and often produce highly variable results. The gastrointestinal dysfunction in PD patients may be due to the presence of a-syn in presynaptic terminals, because of prominent functional damage. Besides, cell loss and Lewy pathology were found to be present in the dorsal vagal nucleus of the majority of PD patients, suggesting that the parasympathetic controlled the intestinal function. This was confirmed by positron emission tomography studies. Compared with the control group, the intestinal acetylcholinesterase activity in patients with early PD was significantly decreased.

In this study, we performed immunohistochemical staining in one paraffin slice from each tissue block. In control group, more tissue samples were normal in histological examination. Previous studies[23] have reported that pathological tissue samples did not show a higher positive rate of α-syn. There were differences comparing with the results of our study, because we used the formalin fixation and paraffin embedding in these studies. Therefore, it is not able to use immunofluorescence double labeling staining to provide a better verification method for co-location. In Figure 4, it showed that the positive rate of a/p-α-syn tissue samples in different time group was close to the clinical diagnosis. However, uneven distribution of tissue types in 3 different groups may cause deviation. 6-10-year group contained a large proportion of esophageal samples, it was also often diagnosed as α-syn negative. This may explain why the positive expression rate of tissue samples of 6-10-year group was lower than comparing the 11-20-year group. Previous studies have shown that esophageal tissue has a high positive rate. However, these studies used the biopsy samples and our samples were derived from superficial biopsy and surgical resection.

Conclusion

We used immunohistochemical staining to detect the pathological changes of gastrointestinal system in the PD patients. The positive staining rate of p-α-syn in the prodromal stage was significantly higher than that in non-PD tissues, and it was concluded that the p-α-syn as the main component of LB can be used as a characteristic predictive marker for PD.

Conflict of interest

The Authors declare that they have no conflict of interests.

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