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DIAGNOSIS AND TREATMENT OF ADDISON'S DISEASE IN A DOG

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ABSTRACT

A case of Addison's disease was diagnosed and treated has been described in this paper. In this case, the dog had poor mental state, vomiting, diarrhea, and dehydration. Laboratory examination showed that the dog had hyponatremia, hypochloremia and hyperkalemia, and that the serum sodium potassium ratio was as low as 15:1. Combined with the adrenocorticotropic hormone stimulation test, Addison's disease was diagnosed with metabolic acidosis, hepatitis, systemic infection and so on. Through symptomatic and etiological treatment, the dog basically returned to normal, but due to the degradation of primary adrenal functions, the dog needs to take glucocorticoid drugs for a long time.

***Keywords*:** Canine, Addison's disease, Primary degeneration of adrenocortical function

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1. INTRODUCTION

Addison's disease, also known as primary adrenal insufficiency, is caused primarily by primary immune-mediated adrenal cortex damage (Feldman et al. 2014), which leads to insufficient hormone secretion in the adrenal cortex, causing a chain reaction. The main symptoms of Addison's illness are anorexia, vomiting, diarrhea, dehydration, hyponatremia, azotemia, hypochloroemia and hyperkalemia(Van Lanen and Sande 2014).

The disease is generally common in young to middle-aged female dogs, ranging from 2 months to 14 years of age, with an average age of onset of 4 years. Compared with other diseases, the incidence of primary adrenal insufficiency in dogs is low and clinically rare. Therefore, due to the low specificity of the clinical symptoms of the disease, the diagnosis is difficult. In this case, the dog vomited, had diarrhea, refused food and water and was diagnosed with primary hypocorticalism or hypercortisolism through hematological tests, color ultrasound, and adrenocorticotropic hormone stimulation tests. Through a series of symptomatic therapies and hormone replacement therapies, the affected dog gradually recovered.

With the improvement of people's living standards, more and more people raise pets. Pets have gradually become an indispensable part of our life. This phenomenon requires the level of pet medical treatment to be continuously improved, and veterinarians to understand more about the clinically rare diseases. This project discusses a case of dog Addison's disease examination, diagnosis, treatment process analysis and related literature in order to provide a reference for clinical veterinarians to diagnose and treat the disease.

2. MATERIALS AND METHODS

2.1. Case information

The dog is female and 12 months old. The dog was measured and the results were: heartbeat of 70 beats/min, breathing of 25 times/min, body temperature of 36.1 degrees Celsius, and dehydration of 10%. The owner described the dog had abnormal condition for five days: On day 1, vomiting and no food intake; On day 2, vomiting and diarrhea. Started from day 3, the dog did not drink water, and showed poor mental state. The dog usually ate dog foods, occasionally went to the grass and had been injected eight vaccines.

2.2. Examination

2.2.1. Hematology tests

2.2.1.1. Complete blood count

The results (Table 1) showed that the canine had elevated red blood cells, hematocrit and hemoglobin, suggesting dehydration in the affected dog. Elevated white blood cells and neutrophils and elevated lymphocytes indicate inflammation in the dog.

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Table 1: Results of hematology in affected dog

Detect items	Units	Test Results on Days				Reference value range
		1	3	6	10	
Red blood cell count	10^{12}/L	10.52↑	8,97↑	7.28	6.44	5.65-8.87
Hematocrit	%	72.2↑	60.9	48.6	42.9	37.3-61.7
Hemoglobin	g/dL	25.1↑	21.4↑	17.5	15.1	13.1-20.5
Average volume of erythrocytes	fL	68.6	67.9	66.8	66.6	61.6-73.5
Average hemoglobin content of erythrocytes	pg	23.9	23.9	24.0	23.4	21.2-25.9
Average red blood cell hemoglobin concentration	g/dL	34.8	35.1	36.0	35.2	32.0-37.9
Platelet distribution width	%	21.5	20.1	18.0	15.9	13.6-21.7
Reticulocyte ratio	%	0.4	0.2	0.2	0.1	NA
Reticulocyte count	k/μL	40.0	16.1	11.6	6.4↓	10.0-110.0
Reticulocyte hemoglobin	pg	24.1	24.3	24.1	24.4	22.3-29.6
White blood cell count	10^9/L	23.43↑	15.26	16.71	18.82↑	5.05-16.76
Neutrophil Percentage	%	65.9	68.9	64.7	57.5	NA
Lymphocytes Percentage	%	25.8	24.5	28.1	31.2	NA
Monocytes Percentage	%	3.8	4.6	4.8	6.6	NA
Eosinophils Percentage	%	4.4	1.7	2.3	4.6	NA
Basophils Percentage	%	0.1	0.3	0.1	0.1	NA
Neutrophil counts	10^9/L	15.44↑	10.51	10.81	10.82	2.95-11.64
Lymphocyte counts	10^9/L	6.05↑	3.74	4.69	5.87↑	1.05-5.10
Monocyte counts	10^9/L	0.88	0.7	0.81	1.25↑	0.16-1.12
Eosinophil counts	10^9/L	1.04	0.26	0.39	0.87	0.06-1.23
Basophil counts	10^9/L	0.02	0.05	0.01	0.01	10.00-0.10
Platelet counts	K/μL	244	113↓	154	213	148-484
Average platelet volume		14.4↑	15.0↑	13.6	12.4.	8.7-13.2
Platelet volume distribution width	fL	20.2↑		15.5	12.2	9.1-19.4
Platelet hematocrit	%	0.35	0.17	0.21	0.26	0.14-0.46

Note: "↑" indicates an increase in the number of indicators; "↓" indicates a decrease in the number of indicators. NA=Not Available.

2.2.1.2. Blood biochemical tests

The results (Table 2) showed that the detection values of creatinine, urea, and phosphorus ions in this dog were high, indicating that the dog had kidney disease. The serum bicarbonate was low, indicating that the dog had metabolic acidosis caused by kidney disease. C-reactive protein was high, showing an inflammatory infection. Elevated NH3 concentrations and aspartate aminotransferase indicated liver damage. Decreased sodium and chloride concentrations and elevated potassium levels showed hyponatremia, hypochloroemia, and hyperkalemia, which are typical electrolyte disturbances with adrenal hypokinesia (Kalenyak and Heilmann 2018).

2.2.2. Color ultrasound of the abdomen

The color ultrasound examination (Fig. 1) showed that the liver contour was smooth, the parenchymal echo was uniform, the liver was sharp, and no abnormal nodular foci were seen. The gallbladder was full, the walls were smooth, and no abnormal echoes were seen in the cavity. The contours of the spleen were smooth, the parenchymal echo was uniform, and no abnormal nodular foci were seen. The contours of both kidneys were smooth, the cortical echoes were uniform and the boundaries of the cortical medulla were clear. The size of the left kidney was about 5.85cm * 3.24cm, and the size of the right kidney was about 6.79cm * 2.89cm. No significant structural and echo abnormalities were seen in the bladder, pancreas, and gastrointestinal tract.

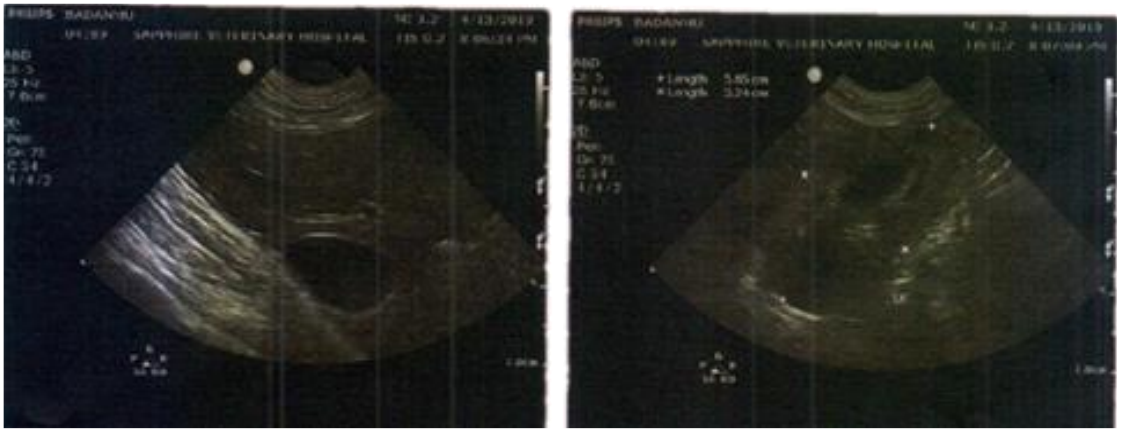

Fig. 1: Ultrasonography Images of dog suffering from Addison's disease.

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Table 2: Blood biochemical tests of affected dog

Parameter	Units	Test Results on Days		Reference value range
		1	6	
Creatinine	μmol/L	475↑	94	44-159
Urea	mmol/L	633↑	5.4	2.5-9.6
Urea nitrogen	mg/dL	33	14	NA
Phosphorus ions	mmol/L	6.58↑	1.42	0.81-2.20
C-reactive protein	mg/L	94.3↑	41.2↑	0.0-10.0
Aspartate aminotransferase	U/L	72↑	32	0-50
NH_3	μmol/L	176↑	NA	0-98
Phosphokinase	U/L	851.↑	77	10- 200
Ca^{2+}	mmol/L	1.14↓	NA	1.2 1.50
pH (ven)		7.08↓	NA	7.31-7.42
HCO_3 (ven)	mmol/L	14.3↓	NA	20.0-29.0
PCO_2 (ven)	mmHg	53.0↑	NA	32.0-49.0
AnGap	mmol/L	25	NA	NA
tCO_2 (ven)	mmol/L	15.8↓	NA	21.0-31.0
Na	mmol/L	138.0↓	NA	144.0-160.0
K	mmol/L	9.2↑	NA	3.5-5.8
Cl	mmol/L	108.0↓	NA	109.0-122.0

Note: "↑" indicates an increase in the number of indicators; "↓" indicates a decrease in the number of indicators. NA=Not Available.

2.2.3. Other tests

To further exclude other differentially diagnosed diseases, a urine test was performed and the results (Table 3) showed elevated urine glucose indicating diabetes mellitus, low urine specific gravity, and positive occult blood, indicating nephritis. An adrenocorticotropic hormone stimulation test using an endocrine and rapid test reagent analyzer showed results (Table 4) consistent with Addison's disease.

Table 3: Results of urinalysis in affected dog

Parameter	Test results
pH	5.0
white blood cell	negative
Urine protein	negative
Urine sugar	100 mg/dL
Ketone body	negative
Urinary biliary progen	normal
Bilirubin	negative
Occult blood in the urine	10 Ery/μL
Urine color	Pale yellow
Transparency	clear
Specific gravity of urine	1.007

Table 4: Results of adrenocorticotropic hormone stimulation test

Result	Reference Range (nmol/L)	and interpretation
<14nmol/L	<55	If clinically supported, the results are consistent with Addison's disease
	55-170	Uncertain
	170-470	Normal
	470-600	There may be Cushing's syndrome
	>600	If clinically supported, the results are consistent with Cushing's syndrome

3. RESULTS

3.1. Diagnosis

The results of the canine hematological examination showed that it had hyponatremia, hypochloroemia, and hyperkalemia and the serum sodium-potassium ratio is as low as 15:1 (the range of normal serum sodium-potassium ratio is 27:1 to 40:1 (Wei and Jin 2019)), which is a typical symptom of primary adrenal insufficiency. Combined with the results of the ACTH stimulation test, the dog was diagnosed with Addison's disease.

3.2. Treatment

3.2.1. The course of treatment

Dogs were treated with kidney disease based on the principles of correcting hyponatremia, hypochloremia, and hyperkalemia, regulating electrolyte abnormalities and controlling infection.

On the first day of treatment, the dog had a poor mental state, and undiagnosed Addison's disease. The treatment on day 1 is mainly by regulating electrolyte disorders, liver protection, antiemetics, treatment of kidney disease, and infection control. Body temperature, heart rate, and respiratory rate were measured every 2 hours. Kept the dog warm, and fed dog food according to one-half of the recommended amount.

The Prescription on day 1 is as follows: 0.9% NaCl solution 100mL + 50% sodium bicarbonate solution 40mL (iv/1 h), 5% glucose solution 60mL + 10% calcium gluconate 20mL (iv/1 h), 0.9% NaCl solution 250mL (iv/1 h/10 group), amoxicillin clavulanate potassium injection 1.0mL, vitamin C injection 10mg (2 times/day), metronidazole (2 times/day), 1 bag of lactulose, 2.0mL of antithretic acid, Renal Kang 4g, vitamin B complex 2.0mL + vitamin B1 1.0mL, and 1 tablet of glycoberide (4g) (2 times/day)

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On the second day of treatment, the affected dog vomited once, and urinated heavily. Addison's illness was not diagnosed. Measured body temperature, heart rate, and respiratory rate every 4 hours. Paid attention to the vomiting of the affected dog. Fed dog food according to the recommended amount, and divided the amount for 6 times. Blood gas was measured at 8 pm.The prescription on day 2 is as follows: 5% glucose solution 60mL + 10% calcium gluconate 20mL (iv/1 h), 0.9% NaCl solution 200mL (iv/1 h/group), 0.9% NaCl solution 50mL + 5% sodium bicarbonate solution 20mL (iv/1 h), 0.9% NaCl solution 200mL + 5% glucose solution 50mL (iv/4 h), 0.9% NaCl solution 50 mL + 5% sodium bicarbonate solution 20mL (iv/1). h), 0.9% NaCl solution 200mL + 5% glucose solution 50mL (iv/4 h), 2 tablets of doxycycline, 50mL + metronidazole 1 tablet (2 times/day), Renkang 4g, sucralfate 1 packet, antithrepressine 2.0mL, multivitamin B 2.0mL + vitamin B1 1.0mL and glycobide (4g) 1 tablet (2 times/day).

On the third day of treatment, the affected dog showed a general mental state, no vomiting, mushy stool, flushing of both eyes, heart rate of 90 beats per minute, body temperature of 38-38.1 degrees Celsius, respiratory rate of 22-24 beats per minute, and no intake. Temperature, heart rate, and respiratory rate were measured every 4 hours and the dog was given 180g of prescription food for the kidneys. The prescription on day 3 is as follows: 0.9% NaCl solution 160mL + 5% glucose solution 40mL (iv/3 h/3 group), 0.9% NaCl solution 220mL + 5% glucose solution 30mL (iv/4h/3group), vitamin B complex 2.0mL, doxycycline 2 tablets (2times/day), ursodeoxycholic acid (50mg) 6 tablets, amoxicillin clavulanate potassium tablets (2times/day) 1 tablet (2times/day), glycobelin (4g) 1 tablet (2times/day) and renal kang 6g.

On the fourth day of treatment, the affected dog showed a general mental state. Stool was formed and there was trace amount of blood in the stool. Temperature, heart rate, and respiratory rate were measured every 4 hours and 180g of dog food were fed. The prescription on day 4 is as follows: 0.9% NaCl solution 160mL + 5% glucose solution 40mL (iv/3.5 h/3 group), vitamin B complex 2.0mL, 2 tablets of doxycycline (2 times/day), amoxicillin clavulanate potassium tablets (250mg) 1 tablet (2times/day), glycoberide (4g) 1 tablet (2times/day), renal kang 6g, 5% NaCl solution 50mL + 10% calcium gluconate 15mL (iv/1h), 5% glucose solution 210mL + 50% Glucose 30mL + insulin 12 iu (iv/3 h), 0.9% NaCl solution 240mL + 5% glucose solution 10mL (iv/3.5 h/2 group), and Fu Neng ingot (0.1mg) 4 tablets.

On the fifth day of treatment, the affected dog showed an average spirit. Body temperature, heart rate and respiratory rate were acceptable The dog had strong feeding food, a lot of urination, mucus on the surface of the stool, and a weight of 20.2kg. Body temperature, heart rate, and respiratory rate were measured every 4 hours to determine whether there was vomiting or stool. Feed the dog kidney prescription food 200g, and divided the food into 6 times.

The prescription on day 5 is as follows: 0.9% NaCl solution 220mL + 5% glucose solution 30mL (iv/4 h/3 group), 2 tablets of doxycycline (2 times/day), amoxicillin clavulanate potassium tablets (250mg) (2 times/day), vitamin B complex 2.0mL, glycobelin (4g) 1 tablet (2 times/day), and Funeng lozenges (0.1mg) 4 tablets.

On the seventh day of treatment, biochemical test results (Table 5) were low in cholesterol and high in C-reactive protein, suggesting systemic inflammation. There were no obvious abnormalities in the blood gas ion analysis. The prescription on day 7 is as follows: Amoxicillin clavulanate potassium tablets (250mg) 1.5 tablets (2 times/day), and Fuenerium tablets (0.1mg) 1 tablet.

On the ninth day of treatment, the dog showed food induction, normal stool, normal mental fitness, body temperature, heart rate, and respiratory rate were acceptable. Measured body temperature, heart rate, and respiratory rate every 4 hours, and fed 200 g of dog food and one ordinary can. The prescription on day 9 is as follows: amoxicillin clavulanate potassium tablets (250mg) 1.5 tablets (2 times/day), and Funeng lozenges (0.1mg) 4 tablets.

On the tenth day of treatment, the affected dog had normal mental health, normal body temperature, heart rate and respiratory rate, and the dog was discharged from the hospital with re-examination after one week.

On the sixteenth day of treatment, the overall condition of the affected dog was good. Substitute therapy was given with four enrichment lozenges daily.

3.2.2. Laboratory test results

3.2.2.1. Changes in the results of the blood routine examination

The changes in the blood routine are shown in Table 1, and after ten days of treatment, the blood routine results showed that the affected dog had a mild inflammatory infection.

3.2.2.2. Changes in blood biochemical results

The changes in blood biochemical results before and after treatment are shown in Table 2. After 6 days of treatment, there were no obvious abnormalities except for systemic infection.

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3.2.2.3. Changes in blood biochemical results

The changes in blood biochemical results before and after treatment are shown in Table 5. After 6 days of treatment, there was no obvious abnormality in the blood biochemical test results.

Table 5: Changes in blood biochemical test results

Parameters	Test Results on Days						Reference value range
	1	2	3	4	5	6	
pH (ven)	7.08↓	7.29↓	7.31	7.27	7.33	7.39	7.31-7.42
HCO_3 (ven) (mmol/L)	14.3↓	16.0↓	17.1↓	17.0↓	22.3	20.7	20.0-29.0
PCO_2 (ven) (mmHg)	53.0↑	36.0	37.0	32.0	46.0	38.0	32.0-49.0
AnGap (mmol/L)	25	21	23	18	19	20	
tCO_2 (ven) (mmol/L)	15.8↓	17.0↓	18.2↓	17.9↓	23.6	21.8	21.0-31.0
N (mmol/L)	138.0↓	144.0	145.0	136.0↓	147.0	147.0	144.0-160.0
K (mmol/L)	9.2↑	6.2↑	6.3↑	6.7↑	5.1	5.4	3.5-5.8
Cl (mmol/L)	108.0↓	113.0	112.0	108.0↓	111.0	112.0	109.0-122.0

Note: "↑" indicates an increase in the number of indicators; "↓" indicates a decrease in the number of indicator.

4. DISCUSSION

Primary adrenal insufficiency is usually caused by a lack in glucocorticoid secretion or mineralocorticoid secretion or both secretions. It is common in young to middle-aged female dogs (Liu et al. 2017). The most common clinical symptoms are depression, dehydration, weakness, and hypothermia(Guzmán Ramos et al. 2022). Hyperkalemia, hyponatremia, and hypochloremia are typical electrolyte changes for adrenal hypocortex (Kalenyak and Heilmann 2018). The disease is rare and difficult to diagnose, and an adrenocorticotropic hormone stimulation test is required for diagnosis. However, the adrenocorticotropic hormone stimulation test cannot distinguish between primary and secondary adrenal hypocortex. Secondary adrenal hypocoticism is due to destructive pituitary or hypothalamic damage or prolonged use of exogenous glucocorticoids (iatrogenic) resulting in decreased adrenocortical hormone secretion by the pituitary gland, which in turn leads to decreased glucocorticoid secretion, while mineralocorticoid secretion is normal (Lv et al. 2022). These two disorders can be distinguished clinically by checking whether the serum sodium-to-potassium ratio is decreased, with a serum sodium-to-potassium ratio decreasing in primary adrenal hypocortex and staying normal in secondary adrenal hypocortex (Wei and Jin 2019). Clinical symptoms combined with an adrenocorticotropic hormone stimulation test and a decrease in serum sodium-potassium ratio can confirm the diagnosis of the disease.

In this case, the dog was about 12 months old., The dog had a low appetite, reduced drinking of water, poor mental state and symptoms such as vomiting, diarrhea, and dehydration, which had persisted for 5 days at the time of the dog's visit. Routine menstrual examination reveals elevated red blood cells, hematocrit, and hemoglobin, elevated white blood cells and neutrophils, and elevated lymphocytes, suggesting dehydration and inflammation in the dog (Wang 2021). Biochemical test results showed high detection values of creatinine, urea and phosphorus ions, low serum bicarbonate, high C-reactive protein, increased NH3 concentration and aspartate aminotransferase (AST), decreased sodium and chloride ion concentrations, and increased potassium ion concentrations. Aspartate aminotransferase (AST) is mainly distributed in hepatocyte mitochondria and a few in cytoplasm. When the causative factors lead to hepatocyte degeneration and increased cell membrane permeability, the main thing released from the cell is ALT. When liver cells are severely damaged and necrotic, AST is released in the mitochondria, resulting in a significant increase in serum AST. Creatinine detection can judge glomerular function, thereby judging the damage to the kidneys, the concentration of creatinine rises, suggesting that the glomeruli cannot effectively filter creatinine, the filtration effect decreases, which also suggesting that kidney function is damaged (Hokamp and Nabity 2016), finally suggesting that the canine may have severe impairment of liver function and abnormal renal function. It also causes metabolic acidosis and is accompanied by severe systemic inflammatory infection. Typical symptoms of Addison's disease include hyponatremia, hypochloremia and hyperkalemia. Due to the typical symptoms of Addison's disease, in order to further confirm the diagnosis, the ACTH stimulation test is the gold standard for diagnosing adrenal hypocotticism (Lennon et al. 2007). When ACTH stimulation test results are <14 nmol/L, Addison's disease can be confirmed in combination with the clinical manifestations of the dog.

Because Addison's illness was not diagnosed a few days before the visit, the treatment in the first several days is the correction of electrolyte disorders, acidosis, liver protection, antiemetics, kidney protection and infection control. Chronic adrenal insufficiency, regardless of the cause, can be given adrenocortical hormone once the diagnosis is established, and the drug's effect is expected to be good. Therefore, based on the previous prescription, a glucocorticoid drug, Funeng Lozenges, was added. After 6 days of treatment, the results of whole blood count (WBC) and the blood biochemical test of the affected dog basically showed no abnormalities. However, the C-reactive protein index was still high, suggesting that the affected dog still had systemic infection (Sproston and

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Ashworth 2018), and amoxicillin clavulanate potassium tablets should be used for more time. One week after the cure when the affected dog was re-examined, the indicators returned to normal. Because inadequate adrenocortical hormone secretion is an irreversible disease, subsequent treatment for the disease is mainly glucocorticoid replacement therapy, emphasizing lifelong treatment (Chifu and Hahner 2022). Dose adjustment can be made when the dog is under the stress condition (e.g., fever, surgery, or other medical conditions). A physician can be consulted if necessary.

5. Conclusion

Primary adrenal hypocorticism is clinically rare and difficult to diagnose. It is necessary to pay attention to the differentiation in the clinic. The adrenocorticotropic hormone (ACTH) stimulation test is used clinically to diagnose the disease. However, a combination of a decreased serum sodium-to-potassium ratio and other symptoms is required to confirm the diagnosis. Before the diagnosis is confirmed, symptomatic treatment should be performed for the patients to avoid the adrenal hypocortical crisis. With treatment, the prognosis of the affected animal is generally good. With appropriate glucocorticoid and/or mineralocorticoid replacement therapy, most affected dogs can recover and have a normal life.

Author's Contribution

Juan Chen: Writing - original draft, editing, data curation, methodology, examination and treatment. Ruiwan Mai and Jiaojiao Chang: Data collection, examination and treatment. Vincent Latigo: conceptualization, review and editing. Lin Li: Review, editing and supervision. Ping Liu: Resources, writing - review and editing, data curation and supervision.

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