Traditional Chinese Medicine Fulonggan (Terra Flava Usta) Improves the Clinical Syndrome and Comorbidity of Regressive Autism: A Case Report

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ABSTRACT

The occurrence of regressive autism is closely related to the disturbance of immunity and intestinal microbiota. The intestinal microbiota plays an important role in maintaining the balance of the human immune system, and also regulated central nervous system activity. Soil is a micro-ecological environment that contains the majority of all known microbial species. The number of species found in human feces is around 1/10 times of that found in soil. Therefore, soil can be considered as the microbial "seed bank". Our previous research indicated that everyday living environments are too clean, which, combined with the lack of contact with soil, results in the loss of a large number of microorganisms, and eating soil increased the gut microbial diversity and immune function in mice. As a special soil, Fulonggan (Terra Flava Usta) is a safe traditional Chinese medicine that has been used in the clinic for 1500 years. Here we report a case of 4.5-year-old male regressive autism with comorbidities of food allergy, allergic rhinitis, and constipation. Fulonggan was used to treat for 12 months from the age of 52 months to 63 months. For the first month of taking Fulonggan, he was also receiving the allergy medicine Singulair (montelukast). The constipation disappeared 5 days after taking Fulonggan, the allergic rhinitis disappeared 4 months later, and the food allergy disappeared after the treatment was stopped. Furthermore, the language skills, social skills, and mood were obviously better according to the Gesell Developmental Scale–Chinese Revised Version and Autism Behavior Checklist. At present, the child has returned to kindergarten. This report proposes a new method for the treatments of regressive autism and comorbidities including food allergy, allergic rhinitis, and constipation. The therapeutic method is effective and safe, and worth to be an alternative for regressive autism or allergy diseases.

Keywords: *Regressive Autism, Gut Microbiota, Immune Imbalance, Traditional Chinese Medicine, Case Study*

Introduction

Regressive autism occurs in children who show normal or near-normal early stages of development, after which all further development stops and previously acquired communication and/or social skills are lost (Duffy *et al*., 2014). Regressive autism has been reported to account for up to a third of all autism cases (Duffy *et al*., 2014). The onset of degenerative change has been reported to occur after a different event (such as trauma, disease, or an immune response) (Ozonoff *et al*., 2010) and is closely related to immune disorders, such as food allergy, asthma, and atopic dermatitis. Furthermore, the more serious the allergy is, the more serious the behavioral or emotional problems are (Masi *et al*., 2014) In addition, many people with autism have gastrointestinal problems, such as constipation, diarrhea, or foul-smelling stool (Gorrindo *et al*., 2012).

It has been reported that the intestinal microbiota is closely related to the occurrence of all the above allergic diseases and gastrointestinal problems (Ivanov and Honda, 2012). Microbial imbalance has been reported to lead to the overactivation of T-helper 1 and T-helper 17 cells, which results in damage to peripheral immune cells of the central nervous system and blood-brain barrier (Berer and Krishnamoorthy, 2012; Onore *et al*., 2012; Stolp *et al*., 2005). There is also a direct interaction between intestinal microflora and intestinal neurons (Barajon *et al*., 2009; Brun *et al*., 2013; Lai *et al*., 2020; Matheis *et al*., 2020), and this can regulate neural activity by regulating the hypothalamic pituitary adrenal axis (Sudo, 2012), and producing a large number of neurotransmitters, such as 5-hydroxytryptophan (Yano *et al*., 2015) and dopamine (De Vadder *et al*., 2014; Ray, 2014).

Immunomodulatory drugs (such as corticosteroids) are often used to treat regressive autism (McDougle *et al*., 2015). For patients with food allergy, dietary intervention and probiotic intervention have been reported to achieve a little effect on autism symptoms (Lange *et al*., 2015). However, there is very limited scientific evidence for the efficacy of these treatments (Lange *et al*., 2015).

Findings that fecal microbial transplants could effectively treat Clostridium difficile infection highlights the possibility of using the human microbiome as a feasible therapeutic strategy for gut microbiota related diseases (Khoruts and Sadowsky, 2011). Fecal microbial transplants have also been explored clinically in the treatment of autism (Kang *et al*., 2017). However, the intestinal microbiota is a highly stable complex population, and many experiments have shown that it is difficult to change (Ivanov and Honda, 2012). Therefore, there is an urgent need for a better treatment to improve the intestinal microbiota and function.

The “hygiene hypothesis” indicated that the incidence of asthma or other allergic diseases (Ball

et al., 2000) in developed countries are higher than the developing countries, and higher in urban areas than in rural areas. The epidemiology of autism also conforms to the hygiene hypothesis (Becker and Schultz, 2010). The "microflora hypothesis" proposed that an over-clean environment limits infants' contact with microbes, which affect colonization of microbiota in the infant's gut, and that this clean environment therefore further disrupts immune system development and ultimately causes allergies (Wold, 1998). In support of this, several studies have reported that the diversity of intestinal microbiota in rural areas was higher than that in developed countries (Yatsunenko *et al*., 2012).

To identify which environmental factors affect intestinal microorganisms and to what extent, using mice, we verified in a previous study that a low cleanliness living environment increases the diversity and changes the structure and composition of the intestinal microbiota just as well as diet does (Zhou *et al*., 2016). This work was supported by findings from Ottman *et al*. (Ottman *et al*., 2019). In a subsequent experiment, we increased the microbes in the cages of mice to analyze its impact on the mouse intestinal microbiota; the simple increase of the microbes in the living environment had no significant impact on the mouse gut microbiota (Bai *et al*., 2016). However, the increase of contact with soil has altered the structure and composition of the gut microbiota of mice (Zhou *et al*., 2018), and this effect of soil on gut microbiota is comparable with that of diet (Zhou *et al*., 2018). Our further research indicated eating soil increased the gut microbial diversity and immune function in mice (Zhou *et al*., 2021). Grieneisen *et al*. also reported that soil has changed composition of the intestinal microorganisms of gorillas (Grieneisen *et al*., 2019).

Soil is the microecological environment with the most microbial species on earth (Grieneisen *et al*., 2019). Indeed, the number of microbial species found in human feces is about 1/10 times that found in soil (Blum *et al*., 2019). A large proportion of bacteria (~80%) found in soil are in a dormant state (about 20% of bacteria in the human intestine are in a dormant state). When microorganisms meet the environment suitable for their survival, they start to multiply in large numbers; this explains why soil has been called the "seed bank" of microorganisms (Lennon and Jones, 2011).

Humans and the soil share a close relationship. It is a custom in many countries to eat soil, such as Cameroon and Kenya, which can be used as food or to supplement some mineral elements (Sing and Sing, 2010). In addition, in ural areas, a common behavior of children is to eat non-food materials, including soil, as a means to explore and evaluate their environment (Abrahams, 2003).

Li Shizhen (1518-1593), a Chinese traditional medical scientist in the Ming Dynasty, said that "water is the source of everything, and soil is the mother of all things" in the book of Compendium of Materia Medica. This book stated that water is the source of drinking and soil is the source of food. Not

only that, it claimed that all soil can be used as medicine, tonifying the spleen and stomach, dispelling cold and dampness, promoting the growth of muscles and hemostasis, and reducing swelling and detoxification. Fulonggan (Terra Flava Usta), a kind of soil, was first recorded in the book of Supplementary Records of Famous Physicians, which was compiled by Tao Hongjing of Liang Dynasty (456-536 AD), and has been used safely in the clinic for more than 1500 years. Fulonggan (Terra Flava Usta), also known as zaoxintu, comes from the middle bottom of the clay stove that has been only used to burn firewood. After calcining for many years, the clay in the middle bottom of the stove turns red on the outside and yellow in the middle.

In this report, we used the Traditional Chinese Medicine Fulonggan to treat a child with regressive autism complicated with allergies.

Case Report

Diagnosis

The case was a male patient who was diagnosed with ASD at the age of 39 months in September 2017 (Fig. 1). He initially visited a doctor because his language had regressed at the age of 35 months and he had become unable to speak as he had done before. He could only say 7-8 Chinese words in a short sentence, and he primarily expressed rejection and requests by screaming by the age of 52 months. With the degradation of language, he rapidly lost communication skills and normal behavior deteriorated. He bit other children and exhibited obviously abnormal behavior, after which he had to leave ordinary kindergarten.

The boy had a food allergy that became apparent at the age of 1 month, and allergic rhinitis at the age of 30 months or so. His allergic rhinitis occurred at any time, and the allergens were unknown. He had serious constipation from very early on. After his language began regressing at 35 months old, his sleep was not good; he found it difficult to fall asleep and was easily woken up. He was awake for around 2 hours per night and was restless after waking up.

He had always eaten too little food and had a lean body. He had dietary bias and liked meat from an early age. After the diagnosis of autism, he began to suffer from eating toys, paper, and cartons. He had an abnormal mood, was irritable, and was often angry without any apparent cause. He suffered from hyperactivity and sometimes urinated in bed or in his pants. His visual reactions also gradually became abnormal, whereby he avoided looking at other people and made nearly no eye contact. He then developed a poor imitation ability. He had had a poor motor ability and a poor development of gross and fine motor skills since he was very little.

His food-specific IgG serum antibodies were detected at the age of 48 months, and it was found he was allergic to 11 types of food, including watermelon, mango, cantaloupe, eggs, and milk, etc. (Table 1). He stopped eating these allergic foods and began to take allergy medicine. His mother said that, after this intervention, his symptoms were slightly relieved, but His autism-related symptoms were still serious. At the age of 51 months, his development was measured using the Gesell Developmental Scale–Chinese Revised Version (GDS) in a hospital in Jinan city (China). His adaptive behavior DQ (Development Quotient) score was 45, which means moderate growth retardation, his gross motor DQ score was 41 (moderate growth retardation), his fine motor DQ was 45 (moderate growth retardation), his language DQ was 38 (severe growth retardation), and his personal-social behavior DQ was 41 (moderate growth retardation) (Table 2). The Autism Behavior Checklist (ABC) was completed by his mother before treatment and he received an ABC score of 82, which was indicative of autism.

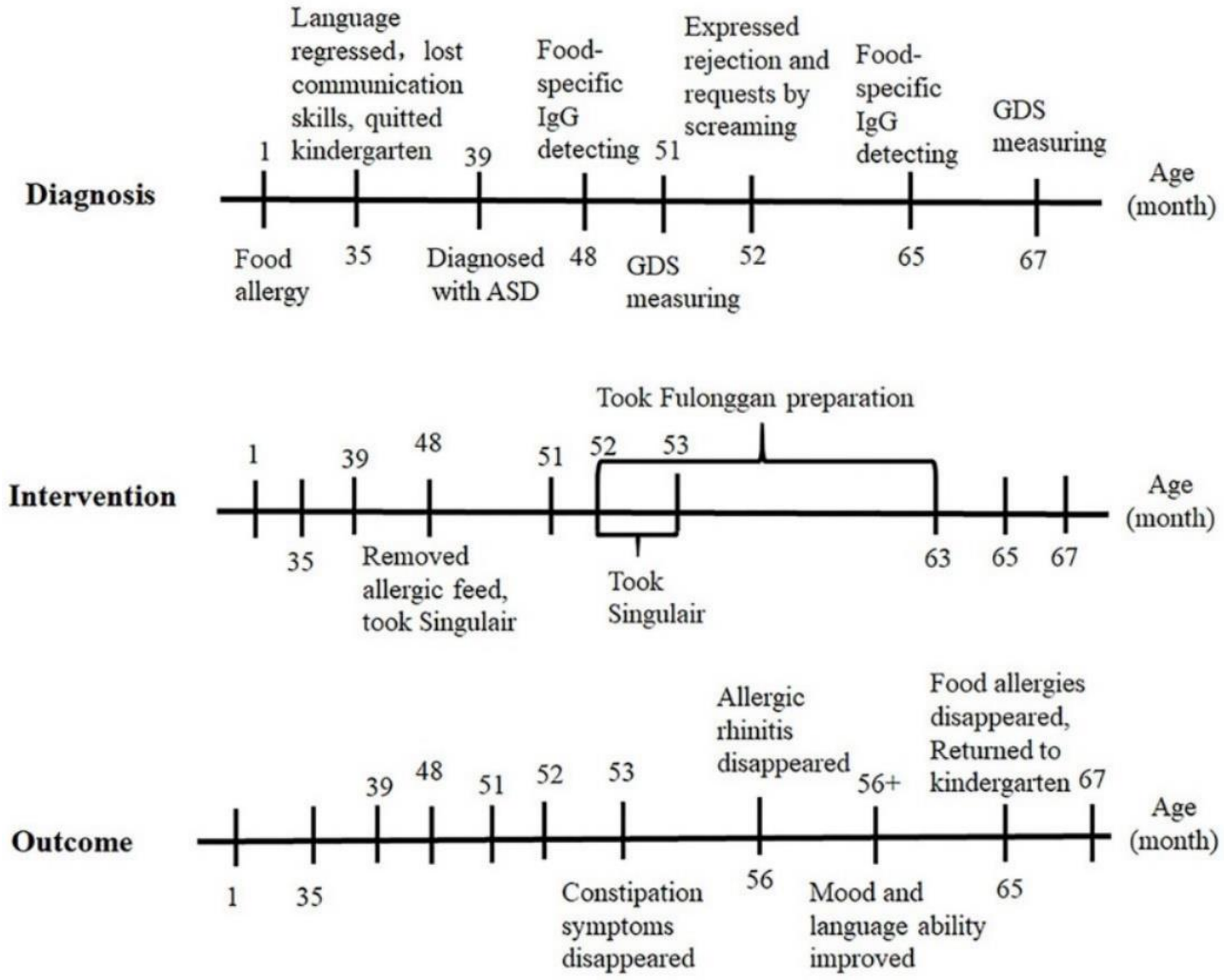

Figure 1: the time line of diagnosis, treatment and outcome. The patient began to regress at 35 months age, and he was diagnosed with autism at 51 months. Then he took Fulonggan during the age of 52-63 months, and some complications disappeared from the age of 53 months.

Table 1: Detection of food-specific IgG antibodies at the age of 3 and 5 years.

Inspect item	Result (2018)	Result (2019)	Measure
1. Rice	22.7 (0)	9.89 (0)	U/ml
2. Wheat	10.0 (0)	11.91 (0)	U/ml
3. Corn	33.4 (0)	6.85 (0)	U/ml
4. Soybean	18.9 (0)	12.84 (0)	U/ml
5. Watermelon	92.5 (+1)	44.73 (0)	U/ml
6. Apple	10.9 (0)	2.80 (0)	U/ml
7. Mango	103.6 (+2)	9.27 (0)	U/ml
8. Banana	7.2 (0)	12.34 (0)	U/ml
9. Renegade	5.5 (0)	3.82 (0)	U/ml
10. Cantaloupe	101.9 (+2)	28.6 (0)	U/ml
11. Grape	10.0 (0)	5.78 (0)	U/ml
12. Pomelo	10.3 (0)	3.18 (0)	U/ml
13. Olive	52.0 (+1)	10.91 (0)	U/ml
14. Orange	65.1 (+1)	5.05 (0)	U/ml
15. Peach	60.6 (+1)	43.96 (0)	U/ml
16. Pineapple	19.0 (0)	9.51 (0)	U/ml
17. Durian	43.1 (0)	5.63 (0)	U/ml
18. Strawberry	31.7 (0)	4.92 (0)	U/ml
19. Egg	95.4 (+1)	7.65 (0)	U/ml
20. Chicken	9.6 (0)	2.15 (0)	U/ml
21. Beef	17.8 (0)	4.48 (0)	U/ml
22. Mutton	8.5 (0)	3.52 (0)	U/ml
23. Pork	6.7 (0)	1.83 (0)	U/ml
24. Turkey	8.9 (0)	4.82 (0)	U/ml
25. Mushroom	21.7 (0)	12.05 (0)	U/ml
26. Tomato	124.9 (+2)	40.12 (0)	U/ml
27. Spinach	41.9 (0)	11.29 (0)	U/ml
28. Petits pois	53.6 (+1)	34.59 (0)	U/ml
29. Milk	232.8 (+3)	52.98 (+1)	U/ml
30. Sesame	44.3 (0)	14.43 (0)	U/ml
31. Cashew	7.9 (0)	6.58 (0)	U/ml
32. Peanut	5.0 (0)	1.85 (0)	U/ml
33. Clam	16.4 (0)	8.48 (0)	U/ml
34. Codfish	17.7 (0)	10.70 (0)	U/ml
35. Crab	9.9 (0)	18.12 (0)	U/ml
36. Trichiurus	11.3 (0)	13.28 (0)	U/ml
37. Lobster	7.5 (0)	25.85 (0)	U/ml
38. Salmon	15.4 (0)	18.08 (0)	U/ml
39. Sardine	50.1 (+1)	10.82 (0)	U/ml
40. Pectinid	21.8 (0)	6.95 (0)	U/ml

41. Shrimp	14.0 (0)	22.64 (0)	U/ml
42. Grass carp	15.5 (0)	19.28 (0)	U/ml
Note: Result (2018) is the detection result on May 18, 2018 and Result (2019) is on October 13, 2019			

Table 2: Child development examination using GDS at the ages of 51 and 67 months.

Domain	Developmental age (months)		Developmental quotient		Assessment	
	2018	2020	2018	2020	2018	2020
Adaptability	23.1	30.57	45	46	Moderate growth retardation	Moderate growth retardation
Gross motor	21	30.8	41	46	Moderate growth retardation	Moderate growth retardation
Fine motor	23.33	27.77	45	42	Moderate growth retardation	Moderate growth retardation
Language	19.6	28.47	38	42	Severe growth retardation	Moderate growth retardation
Personal-social	21	27.77	41	42	Moderate growth retardation	Moderate growth retardation
Note: Examination time: September 11, 2018 and January 3, 2020						

Interventions

At the age of 48 months, his allergies were identified and removed from his diet, and the allergy medicine Singulair (montelukast) was taken (Fig. 1). From this age, he also started sensory integration therapy training, which he continues to receive. At the age of 51 months, his development was measured using the GDS in a hospital.

He took Fulonggan (Beijing Tongrentang) preparation powder, 10 grams/day) for 12 months from the age of 52 months to 63 months. For the first month of taking Fulonggan, he was also receiving the allergy medicine Singulair. He started eating food that he had been allergic to after he had stopped taking the Fulonggan preparation. After 2 months of discontinuation of Fulonggan preparation, his serum IgG was further examined, and after 3.9 months, the development checklist was checked with the GDS in the same hospital. At same time, the ABC was completed by his mother.

He had two colds at the start of taking Fulonggan medicine. For the first cold, compound diclofenac sodium chlorphenamine maleate and antibiotic cefaclor were taken for 5 days. For the second cold, the same medicines were taken for 3 days. During the cold period, Fulonggan preparation continued to be taken.

Outcome

His constipation symptoms disappeared about 5 days after taking Fulonggan preparation, and from then he had one stool every day, and the stool shape and color were normal (Fig. 1). After taking Fulonggan preparation for about 4 months, his allergic rhinitis essentially disappeared and has not recurred to date. After the disappearance of his allergic rhinitis, his sleep gradually returned to normal

and is now fine. At same time, his pica symptoms disappeared. After he stopped taking Fulonggan preparation, he began to eat some food he had been allergic to, and did not experience food allergy symptoms.

His mood is basically good and he has few unexplained tantrums. He still has some hyperactivity and dietary bias. He eats a little more than before and is now a little fatter than before treatment. His language ability has obviously improved, and he uses more and more active language and can use language to express rejection and request. His athletic ability has obviously improved. His gross and fine movement abilities have improved, which may be associated with the sensory integration therapy training. His visual reaction has obviously improved. He now occasionally makes eye contact. Therefore, imitation ability has also improved.

After 2 months of discontinuation of Fulonggan, a serum IgG test was carried out. Serum IgG showed that his food allergies had essentially disappeared; from the original 11 foods to which he was allergic, he only remained allergic to milk (and to a lesser extent than before) (Table 1).

After 4 months of discontinuation of Fulonggan, his change in behavior was tested using the GDS. All the Development Age indexes of the four abilities were obviously better than those of the test at 51 months old. However, considering that his age is also increasing, the DQ was a little disappointing, except for the obvious increase of the DQ value of language ability (Table 2). However, the ABC score was 42, which means that his autism symptoms almost disappeared after using Fulonggan. At present, he has returned to kindergarten.

Discussion

Constipation was the first problem to be solved after using Fulonggan. According to the patient's mother, he had a gastrointestinal reaction 24 hours after using the medicine, and constipation disappeared completely in about 5 days. This is consistent with the response of intestinal microbiota to food. David *et al*. reported that the human gut microbial community structure differences were apparent 1 day after the animal-based diet reached the gut if they had fed on a plant-based diet before (David *et al*., 2014). Combined with our previous studies on the relationship between soil and intestinal microbiota (Zhou *et al*., 2018), it can be inferred that Fulonggan improves constipation symptoms by acting on the intestinal microorganisms of the patient.

Taking Fulonggan preparation is obviously effective in the treatment of allergic rhinitis and food allergy. Allergic disease is caused by a human immune system imbalance (Ball *et al*., 2000; Ege *et al*., 2011; Stein *et al*., 2016; Strachan *et al*., 1989), and its epidemiology conforms to the "hygiene

hypothesis" (Ege *et al*., 2011). Our results seem to support the theory that soil in our living environment regulates and maintains the immune balance in humans through changing and retaining /keeping the diversity and the composition of intestinal microbiota, as required.

In this study, the Traditional Chinese Medicine Fulonggan was selected because, as a special soil, it has a clinical application history of 1500 years and a high safety. This study examined a new use of the drug and used it to treat a case of regressive autism, based on earlier studies on the impact of soil on intestinal microbiota (Bai *et al*., 2016; Ottman N, 2019; Zhou *et al*., 2018; Zhou *et al*., 2016).

The efficacy, mechanism, and protocol of Fulonggan in the treatment of regressive autism needs to be further explored by large-scale animal experiments and clinical trials. All in all, this report provides a new idea for the treatment and prevention of autism.

Conclusion

This case report indicates the use of Fulonggan combined with antiallergic western medicine to optimize the cure of regressive autism and comorbidities of allergic diseases. The therapeutic method is effective and safe, and might be an alternative for regressive autism or allergy diseases.

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Author Contributions

DZ, PX, ZZ, NL, and ZB were responsible for collection and assembly of the clinical data. DZ, YD, ML and ZB performed data analysis. DZ, XS, and ZL contributed to writing.

Statement

The patient has provided informed consent for publication of the case

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