Prof. Dongsheng Fan: turn off the amyotrophic lateral sclerosis's disease gene

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With more and more celebrities all over the world jumping on the bandwagon of the Ice Bucket Challenge, amyotrophic lateral sclerosis (ALS) has been put in the spotlight. Though this event in a way had risen the awareness of ALS, there are still so many unsolved problems about it, such as the difficulty of accurate diagnosis and complete treatment. To discuss the hotspots and recent advances in this area, Annals of Translational Medicine has the pleasure to invite Prof. Dongsheng Fan (Figure 1), one of the leading experts on degenerative diseases of the nervous system in China, to unveil the "mystery" of ALS and find out what's newest about this disease. Prof. Fan will also work on a special issue about ALS as the guest editor of Annals of Translational Medicine subsequently.

Introduction

Professor Dongsheng Fan is currently the Chief of Neurology in the Peking University Third Hospital, a member of the standing committee of the Chinese Neurological Society, the vice-chairman of the Beijing Branch of the Chinese Academy of Neurology, a member of the Board of Directors of the World Stroke Organization (WSO), the vice president of the Neurology Branch of the Beijing Medical Doctor Association, the vice chairman of the Expert Committee of ALS project of the Chinese Medical Doctor Association, the deputy supervisor of the Electromyography and Clinical Neurophysiology group of the Chinese Neurological Society, and a committee member of the Neurological Genetic Disease study group of the Chinese Neurological Society. Professor Fan's major research areas are neurodegenerative diseases [including motor neuron diseases, Parkinson's disease (PD), and Alzheimer's disease (AD)], neuromuscular diseases, and cerebrovascular diseases.

ALS: still lacking a diagnostic gold standard

ATM: The Ice Bucket Challenge has made people focus on ALS. You are an expert in neurodegenerative diseases.

Figure 1 Professor Dongsheng Fan.

From a professional perspective, what are the disease characteristics of ALS?

Prof. Fan: Clinically, ALS, AD, PD, and multiple system atrophy (MSA) are all typical degenerative diseases of the nervous system. The basic characteristics of these diseases are progression with aging and the gradual loss of neuronal functions at a faster speed than normal individuals, thus affecting patients' daily activities. The prominent feature is that we currently have insufficient knowledge on the etiology of ALS; therefore, its pathogenesis is a hotspot in current basic neuroscience studies. Currently, the general viewpoint is that the development of these diseases is associated with the interactive reaction between genes and the environment. With increasing age, damage gradually accumulates, and quantitative changes become qualitative changes that result in the development of diseases. The aging of society plays an important role in this gradual increase in the incidence of these diseases.

It should be noted in particular that ALS is not a rare disease in China; rather, it is an uncommon disease. The concept of "rare disease" is more flexible. In countries with

small populations, ALS is a rare disease. However, in China, with its large population, the incidence of 2/100,000-4/100,000 (the newest reported data in the USA) is not low. Why does this point need to be emphasized? It is because scientific investigations into neurodegenerative diseases share commonalities. In countries with large populations, ALS should not be treated as a rare disease. Therefore, the relevant studies should be implemented more actively.

ATM: At present, what is the deficiency in the diagnosis of ALS?

Prof. Fan: Currently, the major issue in making the diagnosis may be the lack of a diagnostic gold standard. We hope to find specific biological markers to diagnose this disease. We know that the levels of the Aβ42 and tau proteins in the cerebrospinal fluid of AD patients have important meanings for early diagnosis in the clinic. However, no ALS-related pathophysiological marker that has diagnostic significance has been discovered.

ATM: What are the current main points of the differential diagnosis of ALS?

Prof. Fan: False positive and false negative results should be noted. The former are excess positive (false positive) signs such as muscle fasciculation, which can be present when normal individuals have excessively anxiety and fatigue. In addition, when patients come to the clinic, the anxiety of suffering from ALS and the pressure of expensive examinations will further aggravate fasciculation. To prevent misdiagnosis, some symptoms should not be overly emphasized or exaggerated to avoid increasing the psychological burden and economic pressure on patients.

The latter are false negatives. The presence of diseases that can induce ALS-like syndromes such tumors, hyperthyroidism, and rheumatic autoimmune diseases should be carefully screened for. In contrast to ALS, the treatment of ALS mimics should mainly focus on controlling the etiology. In addition, follow-up is very important. For example, one patient came to the clinic presenting typical ALS symptoms. After half year of follow-up, the rheumatic autoimmune disease-related indicators in this patient significantly increased. This patient was then treated for rheumatic diseases; all of the indictors recovered to normal, and the ALS symptoms had not progressed after more than ten years. It was hard to say that the simultaneous presence of ALS and rheumatic autoimmune diseases in this case was just a coincidence. Therefore, a distinction should be made between primary and secondary ALS disease. In another case, one patient was discovered to have hyperthyroidism during the treatment for ALS. After treating the hyperthyroidism, the ALS disease was also improved. Sometimes we read news of "ALS was cured"; actually, it was more like "an ALS mimic was cured"; the clinical symptoms that resemble ALS were improved.

Electromyography "plays a leading role"

ATM: Electromyography seems to have an important role in the diagnosis of ALS.

Prof. Fan: In early clinical diagnosis, electromyography can "explore" sub-clinical indicators. For example, one patient only senses abnormal lower limbs while the upper limbs are normal. Through electromyography, it can be found that the upper limbs already have neurogenic muscle damage. The features of ALS in electromyography are universal rather being limited to local muscle atrophy. Therefore, a standardized electromyography examination should be systemic. If a patient only feels "terrible" in the hand muscles, electromyography should also be performed in other locations. For example, hand muscle atrophy in patients with cervical spondylosis is caused by cervical compression. They are mainly local lesions and will not present the feature of universal atrophy that is present in ALS. At this point, systemic electromyography is very important to differentiate between ALS and other diseases. However, the diagnosis of ALS is not entirely dependent on electromyography. For patients with mid- and late-stage ALS with typical symptoms, electromyography is not necessary; however, by this time, these patients have already missed the best time window for treatment.

Electromyography is regarded as an extension of the physical examination in the Department of Neurology. General auxiliary examinations such as nuclear magnetic resonance imaging (MRI) can suggest conditions such as spinal cord compression in patients. However, whether the final diagnosis is cervical spondylosis still depends on whether the structural changes are consistent with the changes in neurological function. An experiment in Japan used screws to tighten the cervical vertebrae of dogs, and the results showed that the dogs were paralyzed if the screws were tightened by 30% at one time. The MRI results for that experiment showed that the cervical vertebrae compression of the dog was not "serious". However, if the

screws were slowly tightened by 70% in one year and only 30% of the cervical vertebrae space was left, the dog did not have any specific clinical manifestation and was still alive and mobile. However, the MRI results showed that the cervical vertebrae compression area was very large. Electromyography is not a simple auxiliary examination. Although clinical physical examination does not find muscle fasciculation and atrophy, the electromyography results may already show muscle atrophy, which has important clinical implications.

Anti-sense oligonucleotides (ASOs) turn off mutation points

ATM: In September of this year, Peking University Third Hospital launched its "Charity project for helping ALS patients use science and technology" to develop molecular genetic testing package for ALS. Would you please introduce this technology for us?

Prof. Fan: For diseases such as AD, PD, or ALS, approximately 10% of patients have an obvious family history. The disease-related genes in these patients can be traced. Studies have shown that SOD1, TARDBP, FUS, and C9ORF72 in European populations (common in Europe but rare in China) are the four most common disease-related genes in ALS. Through studies of the 10% of patients with these disease-related genes, our understanding of these diseases in the other 90% of patients will be deeper. Current study results show that the onset of ALS may be associated with protein abnormalities. The TDP-43 protein encoded by the TARDBP gene is present in the cell nucleus under normal conditions. When abnormalities occur, this protein can translocate out of the nucleus and precipitate in the cytoplasm. After a long time, cells cannot bear the burden and undergo necrosis. In addition to gene mutations, the environment can also cause abnormalities in this protein. These results have important significance for the study of sporadic cases of ALS.

The molecular genetic testing package developed by Peking University Third Hospital mainly targets familial ALS to precisely identify that the onset of the disease is caused by which mutated position in which exon of which gene. Next, ASO technology is used to "turn off" the mutated points in gene using synthesized small molecules, which is so-called gene-targeted drug treatment. This technology is applicable in populations with family histories, age of onset younger than 30 years, living parents, and gene mutations. The direct benefits to patients are the following: (I) if the efficacy of ASOs is confirmed, patients can benefit earlier; and (II) for gene carriers prior to disease onset (the development of disease is associated with genetic penetrance and the environment), early detection is helpful for early prevention. By avoiding adverse factors such as excessively strenuous exercise, consuming a large amount of monosodium glutamate, and specific working environments, carriers can delay disease onset or even avoid disease onset entirely. In addition, carriers who have already undergone genetic testing can receive treatment immediately upon disease onset without awaiting the expression of typical clinical symptoms. Early intervention leads to better treatment efficacy.

ATM: For ALS that cannot be cured, would you please give some humanistic care suggestions?

Prof. Fan: Chinese doctors pay more attention to etiological diagnosis and treatment and usually ignore the issues related to the quality of life of patients. In Western countries, problems of ALS patients such as pain, respiration, sleep, and drooling are studied as major topics. We should help to improve not only the quality of life of patients but also the quality of life of the family members who take care of them.

Let patients participate in their own health management

ATM: Peking University Third Hospital has rich experience in the management of chronic diseases of the nervous system. Would you please introduce how your hospital implements chronic disease management in the neurological unit?

Prof. Fan: Chronic neurological diseases are mainly cerebrovascular diseases. The biggest problem is secondary prevention. When patients are admitted for treatment, diseases can generally initially be stabilized. However, with increased age and other risk factors, the recurrence rate can reach more than 9 times the rate in normal individuals. Therefore, we used the internet to establish a chronic disease management system to better prevent strokes. The main feature of this system is that it is open to patients. Patients can use their own accounts to log into the system through the internet at home. They can look up their characteristics such as blood pressure, blood lipid,

and medications entered by the hospital staff. They can also update the above indicators themselves after being discharged from the hospital. In addition, we provide BS software to specifically facilitate communication between doctors and patients. Rotating doctors are arranged to answer questions raised by patients in a timely manner. Thus, this system can increase medication compliance and reduce the doubts and mistakes of patients. For example, if secondary prevention requires lifelong medication use, a normal blood pressure and blood lipid panel does not indicate that the anti-hypertensive drug can be stopped. If a patient is worried about side effects and wants to stop the medication, we can instruct the patient to check their liver functions through the internet. The main feature of this system is that patients can participate in their own health management. Improvements in their disease indicators can be intuitively presented to patients to produce a sense of achievement for self-health management in the patients. Through this chronic disease management system, the recurrence rate of cerebrovascular disease in patients has decreased to 3% in our hospital (the yearly average recurrence rate of cerebrovascular disease in China can reach 12-15%). In addition, we also stratify patients. Patients at very high risk are reminded every 3 months to return for re-examination. Patients with many risk factors are referred to stroke follow-up clinics to reduce difficulties in their management.

In fact, this system is currently being upgraded. The next step is to develop a management system based on mobile terminals such as cell phones together with the School of Electronic Engineering and Computer Science of Peking University. The management of chronic diseases can be accomplished using cell phones; thus, this system is more convenient and popular.

ATM: Thank you very much!

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