

Research Article

Development history, current situation and prospect of pediatric rheumatology in China

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Rheumatic diseases are a general term for a class of diseases that mainly invade joints, muscles, bones, soft tissues around joints (including tendons, synovium and ligaments, etc.) and blood vessels. More than 200 diseases are included. The development of pediatric rheumatology has gone through a long process, this paper sorts out the development process, current situation and existing problems of pediatric rheumatology, and looks forward to the future development of pediatric rheumatology. It is hoped that through a series of initiatives, the discipline will be promoted to benefit more children with rheumatism.

Keyword: Children, rheumatic diseases, rheumatology

1. INTRODUCTION

Rheumatic diseases are a group of disorders of unknown etiology, involving the muscles, bones, vessels and other tissues, that are chronic, inflammatory, and painful.

The evolution of the name "Rheumatic Diseases" has gone through a long process, with the term "Rheuma" appearing in the first century to refer to a flowing substance derived from mucus. The description of rheumatism was a group of clinical symptoms. With the development of science and technology, gout, rheumatic fever, rheumatoid arthritis, ankylosing spondylitis, SLE, scleroderma, and dermatomyositis were gradually understood. In 1942, Klemperer summarized these diseases as Collagen Disease based on the common feature of fibrosis in the connective tissue. Autoimmune disease refers to a group of diseases in which the immune system shows abnormal immune response to the body's own components, resulting in damage to its own tissues. Autoimmune diseases refer to a group of diseases caused by abnormal immune responses of the body's own components, resulting in damage to its own tissues. Rheumatic diseases is a general term for a group of diseases that mainly affect joints, muscles, bones, soft tissues around joints (including tendons, fascia and ligaments), and blood vessels. There are more than 200 diseases included.

Rheumatic diseases have been recorded in human history for thousands of years. As early as the 5th century B.C., the "Suwen" and "Lingshu" chapters of the earliest medical classics of China, the "Huangdi Neijing", mentioned the "Bi Zheng" or "Bi Syndrome", which refers to a type of disease characterized by joint and muscle pain. The bamboo slips unearthed from the tomb of the Marquis Yi of Zeng also mention "Ji Bi", indicating that "Bi Syndrome" had been widely used in traditional medicine as early as the Han Dynasty. In the Hippocratic

corpus of ancient Greece in the 4th century B.C., 18 typical manifestations involving joint disorders were described, five of which were related to gout. In the 1st century A.D., the term Rheuma appeared, which was similar to Atarhos (inflammation, cata) in Hippocrates, both of which meant "the flow of matter". In 1776, Scheele discovered uric acid, marking the beginning of the development of modern rheumatology [1].

With the development of pathology, people gradually recognize rheumatism as a systemic disorder affecting various systems of the body. From 1927 to 1934, Klinge discovered systemic connective tissue pathology in the course of researching rheumatism. Pathologist Klemperer, through summarizing his experience with systemic lupus erythematosus and scleroderma and Klinge's research, concluded that these ailments were the result of damage to the body's collagen system [2]. In 1941, Klemperer proposed the concept of "collagen disease". In 1952, Ehrlich suggested changing "collagen disease" to "connective tissue disease", a term that was widely used at the time. However, connective tissue disease could not encompass all of rheumatism, and thus the medical community today still advocates the use of the term "rheumatism".

Over the past three decades, the rapid advances made in biochemistry, immunology, cell biology, and molecular biology have enabled a profound and continual expansion of research into rheumatic diseases. Subsequently, the discovery of rheumatoid factor (1948), lupus cells (1948), and antinuclear antibodies (1950) paved the way for the application of corticosteroids and immunosuppressants in clinical treatment, heralding a period of rapid development in rheumatology and ushering research into the cellular and molecular level. It was not until 1570 that French physician Cuillaume Baillou first coined the term 'rheumatism' to describe a group of independent systemic musculoskeletal diseases. Then, in 1776, Swedish chemist Scheele isolated uric acid from the kidney stones of gout sufferers, a discovery that marked the beginning of 'modern rheumatology'. Finally, in 1859, London internist Alfred Baring Garrod first used the term 'Rheumatoid Arthritis' to describe rheumatoid arthritis [3]. Pediatric rheumatology was rarely described before 1800, and the discipline of pediatric rheumatology began much later, only in the nineteenth century [4].

2. RHEUMATOLOGY DEVELOPMENT IN CHINA

2.1 Development of Rheumatology

In the field of clinical internal medicine in China, Rheumatology is one of the youngest disciplines. The Chinese Rheumatology Association (CRA) was established in 1985 and later joined the Southeast Asia and Pacific Area League Against Rheumatism (SEAPAR, now APLAR) in 1988, thus becoming a member of the International League Against Rheumatism (ILAR). Over the past few decades, dozens of hospitals have set up rheumatology and immunology departments, with more than 30 provinces, cities and autonomous regions having established rheumatology societies in Beijing, Shanghai, Guangdong and Autonomous regions.

In 1996, the CRA established the Journal of Rheumatology, which was renamed the Chinese Journal of Rheumatology in 1997, providing rheumatologists with a platform to publish their research results and engage in academic exchanges. Over the past three decades, with the persistent efforts of several generations of rheumatology predecessors and colleagues, China's diagnosis and treatment of rheumatic diseases and research have caught up to and in some areas even achieved parity with the world's advanced level. Moreover, the past 30 years have been the most rapid period of development in rheumatology both domestically and internationally, with significant progress being made in the clinical diagnosis, treatment and basic research of rheumatic diseases.

2.2 Development of Pediatric Rheumatology in China

The development of pediatric rheumatology in our country began in the 1980s, when Professor Xiaohu He returned from the United States, establishing national first rheumatic immunology specialty and connective tissue disease laboratory at Beijing Children's Hospital, thus pioneering the cause of pediatric rheumatology in China. Since 2003, under the carry-on and carry-forward of Professor Li Caifeng's team, through various academic activities and mentorship, the development of pediatric rheumatology specialty has rapidly progressed from one specialty nationwide to more than 40 medical institutions opening rheumatic specialties; nearly 300 pediatric rheumatology professionals have been trained, some of whom have become leading figures in their respective hospitals or even regions. Through a variety of forms such as the National Learning Class of Pediatric Rheumatic Immunological Diseases and the International Forum of Pediatric Rheumatic Immunology, training of pediatric rheumatic immunology professionals from all over the country has been provided, along with assistance in the training of professional and transferred doctors from all provinces and cities; through teaching rounds, case sharing and other forms of training for frontline doctors, as well as going out and inviting in, consultations, referrals and non-paying visits, aid has been provided.

In recent years, Beijing Children's Hospital has taken the lead in establishing multiple specialty academic organizations domestically, which have played a positive role in promoting the development of pediatric rheumatic specialty. In 2014, the Cross-Strait Medical and Health Exchange Association Rheumatology and Immunology Children's Group was established; in 2018, the Futang Children's Medical Development Research Center Rheumatic Professional Committee was established. The center was established in August 2016 and is the largest children's medical research center in China. By March 2023, the center's member units had increased from 27 to 53; the Rheumatic Professional Committee's member units had increased from 27 to 35, with an additional 16 director units preparing to join the committee. In 2019, the Chinese Medical Association Pediatric Branch Rheumatic Group was established. In October 2019, the Chinese Physicians Association Rheumatic Committee was established. The specific cultivation methods of the Children's Rheumatic Group include: (1) Personnel training: standardized training for resident physicians, training for advanced physicians/nurses, and sending backbone personnel to famous international specialty hospitals for training; (2) Business cultivation: carrying out national continuing education classes, international academic exchanges, remote medical center consultations, and cultivating local specialty teams at the grassroots level; (3) Continuous strengthening of

regional medical cooperation: deepening and implementing the medical service requirements of the "Beijing-Tianjin-Hebei System Development Outline", doing a good job of free clinic and referral for pediatric rheumatic diseases, and helping other regions to establish pediatric rheumatic specialty or sub-specialty according to the "one city, one department, one center" discipline development direction[5].

In order to expedite the reform of medical education and promote innovation in disciplines, the Ministry of Education and the National Development and Reform Commission established the "National Life Science and Technology Talent Cultivation Base" at Capital Medical University in July 2002. To this end, Capital Medical University proposed the goal of integrating the advantages of its various clinical colleges and constructing an academic discipline development platform in the form of specialized colleges and departments. On December 11, 2009, after being reviewed by the Office Meeting of the President of Capital Medical University, the Department of Rheumatology of Capital Medical University was approved to be established. It includes 15 medical and scientific research units under the jurisdiction of Beijing, with more than 250 beds, 23 attending physicians (professors), 28 associate attending physicians (associate professors), and 46 resident physicians; among them, there are 22 doctors and 50 masters. In 2021, Professor Li Caifeng served as the director of the Department of Rheumatology of Capital Medical University, leading the construction of the rheumatology discipline of Capital Medical University and reserving talents for the rheumatology cause.

2.3 Problems and Challenges

As the rheumatology discipline in our country is booming, it also faces many problems and challenges.

(1) The number of specialist doctors is insufficient, and the regional distribution is uneven.

The Rheumatology Branch of the Chinese Medical Association conducted a survey across the country from July 2014 to March 2015. As of March 2015, a total of 1364 hospitals were surveyed, of which 717 (40%) had established rheumatology departments, and 7197 rheumatology specialists were included, of which 6016 (83.6%) were employed in tertiary hospitals and 779 in secondary hospitals. There were 4410 main attending physicians, of which 4386 (99.4%) were engaged in clinical work and 185 (4.2%) in laboratory work. Most of them were young doctors, and there were few high-seniority specialists; most of the specialists were concentrated in tertiary hospitals or above in first-tier and economically developed cities. As of September 2018, the number of rheumatology practitioners had increased to 12289, belonging to 3372 departments of 2017 hospitals; the number of rheumatology specialists had increased by 1.7 times, but it was still far from enough compared with the more than 200 million rheumatology patients [6,7].

(2) There is a dearth of independent pediatric rheumatology departments, and the scale needs to be increased.

Although rheumatology and related disciplines have developed rapidly in the past two decades, compared to other disciplines, pediatric rheumatology is still a weak discipline. By the end of 2022, there are only more than 50 medical institutions in China that offer pediatric rheumatology specialty, and the number of departments and professional personnel scale need to be improved.

(3) The international influence of pediatric rheumatology remains to be improved.

There are multiple rheumatic disease research collaborations such as the International League Against Rheumatism (ILAR), the European League Against Rheumatism (EULAR), and the American College of Rheumatology (ACR) that have played a positive role in the formulation of consensus guidelines, promoting international cooperation in research and discipline development. The Pediatric Rheumatology Collaborative Study Group (PRCSG) and the International Pediatric Rheumatology Research Organization (PRINTO) have also made great contributions to the pediatric rheumatology diagnosis and treatment guidelines and standards. Although a domestic academic organization for pediatric rheumatology has been established, it has yet to produce results with international influence, and further strengthening of international cooperation and exchanges are needed to enhance international discourse power and influence.

(4) The public's understanding of pediatric rheumatology is inadequate.

With the increasing recognition of pediatric rheumatology among domestic doctors, the diagnosis and remission rate of such diseases have obviously improved. However, the status of rheumatology as a niche department and "peripheral discipline" has not been significantly improved, which is closely related to the low social attention and public awareness. Therefore, it is very crucial to increase the efforts of popularizing specialty diseases, strengthen dialogue and communication with the government, and increase social support.

3. OVERVIEW OF THE DIAGNOSIS AND TREATMENT OF RHEUMATIC DISEASE IN CHINA

Children's rheumatic diseases include arthritic conditions, systemic connective tissue diseases, vasculitis, autoimmune diseases, and other disorders. Common systemic connective tissue diseases include systemic lupus erythematosus, juvenile idiopathic arthritis, overlap syndrome, mixed connective tissue disease, neonatal lupus, scleroderma, etc. Common vasculitis includes Kawasaki disease, allergic purpura, polyarteritis nodosa, Behcet's disease, ANCA-associated vasculitis, etc. Common autoimmune diseases include familial Mediterranean fever, BLAU syndrome, CAPS, familial cold autoinflammatory syndrome, DADA2, and interferonopathies. Other rare diseases include progressive osseous heteroplasia, chronic recurrent multifocal osteomyelitis, Ig4-related diseases, etc. The exact incidence, prevalence, mortality, etc. of the above diseases in children in China are lacking.

Children with rheumatic diseases are treated with glucocorticoids, non-steroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, biologics, and small molecule targeted drugs. Commonly used disease-modifying antirheumatic drugs in China include methotrexate, leflunomide, cyclosporine, mycophenolate mofetil, leflunomide, cyclophosphamide, salazosulfapyridine, and tacrolimus. Methotrexate is the most commonly used disease-modifying antirheumatic drug, which can be used for juvenile idiopathic arthritis, systemic lupus erythematosus, juvenile dermatomyositis, vasculitis, and other autoimmune diseases; leflunomide is mainly used for juvenile idiopathic arthritis. Cyclosporine is used for systemic lupus erythematosus with involvement of the blood system, juvenile dermatomyositis with involvement of the lung, and other rheumatic diseases with involvement of the lung. Mycophenolate mofetil is mainly used for the treatment of lupus nephritis. Cyclophosphamide is mainly used for rheumatic diseases with involvement of the lung, kidney, and nervous system. Salazosulfapyridine is used for the treatment of systemic juvenile idiopathic arthritis, juvenile dermatomyositis, and other autoimmune diseases. Biologics are numerous, including tumor necrosis factor- α (TNF- α) antagonists, interleukin (IL)-1 receptor antagonists, IL-6 receptor antagonists, IL-17 antagonists, T-cell co-stimulatory factor blockers, belimumab, CD20 monoclonal antibodies, etc.; small molecule targeted drugs mainly refer to Janus kinase (JAK) signal pathway inhibitors [9]. IL-1 receptor antagonists have not yet entered the domestic market.

In recent years, in order to standardize the diagnosis and treatment of rheumatic diseases in China, our hospital has also taken the lead in publishing a series of expert consensus and guidelines. Chinese pediatric rheumatologists have overcome the difficulties of few doctors, few drugs, and many patients in the past decades, and have significantly improved the prognosis of pediatric rheumatic diseases, among which the mortality rate of systemic lupus erythematosus has significantly decreased, some children have reached the state of steroid remission, and successfully transitioned to adulthood; the disability rate of arthritis-related diseases has also decreased significantly. The pediatric rheumatology discipline has also entered a period of rapid development.

4. PLAN AND FORECAST

Although Chinese pediatric rheumatology is facing various challenges, after decades of unremitting efforts, it has entered a period of rapid development. We will seize the historical opportunity to develop the pediatric rheumatology with high quality, and work from the following aspects as a starting point.

4.1 Discipline Construction

In order to strengthen discipline capacity building, scientific research cooperation among various disciplines should be increased, and multi-center research and results transformation should be promoted. More young scholars should be encouraged to carry out scientific and technological innovation projects. At the same time, peer experts can be actively organized to write professional books, including diagnosis and treatment guidelines, to promote the development of juvenile rheumatology [10].

The construction of teaching staff should be intensified, and the construction of ethics and ethics should be adhered to. In terms of curriculum setting, the curriculum of juvenile rheumatology should be optimized, and the teaching management and reform should be strengthened. It is meaningful to optimize the teaching materials for undergraduate, graduate and international students, and optimize the courses and processes of teaching and internship. Optimizing teachers' team, reforming and broadening teaching forms are breakthroughs in popularizing juvenile rheumatology knowledge and improving students' comprehensive quality [11].

4.2 Clinical Exploration

We should establish a noninvasive method to predict and diagnose early, accurately evaluate the progression of rheumatic disease, judge the therapeutic effect and prognosis of children as soon as possible [12]. It is important to develop new serum markers that can be observed continuously and dynamically [13].

To establish mandatory and incentive policies for children's drug clinical trials, we can draw on the experience of the United States, Europe, Japan and other countries to formulate relevant policies. For example, a drug clinical trial research protocol could be submitted before the drug is marketed. The patent protection system of children's drugs shall be established, and corresponding support shall be given to enterprises conducting clinical trials of children's drugs, so as to improve the development of clinical trials of children's drugs [14].

In view of the current situation of the pediatric rheumatic medicine industry in China, it is necessary to apply for relevant industrial policies to encourage the optimization of marketed drugs suitable for the characteristics of Chinese children, and to adopt internationally recognized clinical study design principles, implementation and management norms. By paying attention to the research of health economics and strengthening the cost-effectiveness analysis of various drugs and therapies, medical resources can be more reasonably and effectively allocated and utilized, and the health economic burden can also be reduced [15].

4.3 Talent development

At present, the lack of medical personnel and specialized physicians in the field of pediatric rheumatic diseases remains unresolved. It is therefore essential to set scientific and reasonable objectives, leverage professional training bases and clinical teaching staff, and improve the system of medical personnel training in China to cultivate a large number of medical personnel proficient in pediatric rheumatic diseases.

To this end, the cultivation of undergraduates, postgraduates, overseas students, continuing education students and interns should be strengthened to popularize the knowledge and skills of pediatric rheumatic diseases. Teams of backbone personnel should be sent to foreign high-level hospitals for visits, learning and degree upgrading, and high-level clinical and scientific personnel in pediatric rheumatic diseases should be introduced through both outbound and inbound initiatives. Furthermore, extensive domestic and international academic exchanges, academic conferences, academic salons and forums should be held to promote the long-term

development of pediatric rheumatic diseases and facilitate personnel training. A guest professor system should be established to attract foreign professionals in pediatric rheumatic diseases to work in China, and a sound training program and assessment indicators and access mechanism for practitioners and special technical personnel should be established, as well as a standardized training system for pediatric rheumatic disease specialists, to help the country cultivate more highly specialized personnel in this field [16].

In addition, the concept and clinical practice model of evidence-based medicine should be promoted and popularized, and clinical diagnosis and treatment behaviors should be standardized to improve the overall clinical diagnosis and treatment level of pediatric rheumatic diseases at the grassroots level. Training methods should be tailored to different types of medical professionals at different levels, and specialized training on different topics should be provided to different types of medical technical personnel to improve the recognition rate of pediatric rheumatic diseases among clinical disciplines [17].

4.4 International cooperation and exchange

Inviting renowned international scholars to China to introduce the latest developments and directions in the relevant international fields through various forms such as the International Forum on Pediatric Rheumatic Diseases, with equal emphasis on exchange and training, and continuing education activities and skill training for professionals at all levels. Providing opportunities for young doctors and students to share achievements and showcase their talents. Actively contributing to and participating in global pediatric rheumatic disease conferences such as the World Pediatric Congress, the American Pediatric Rheumatic Disease Annual Meeting, the European Rheumatic Annual Meeting, and the Asia-Pacific Rheumatic Annual Meeting, to make China's voice heard in the world[18]. Actively conducting and participating in global pediatric rheumatic drug clinical research, strengthening cooperation among researchers, and overall improving the level and capability of the domestic research team to ensure the balanced development of the research team and research level.

4.5 The Flaming Torch Plan

The health of children is of paramount importance to the happiness of families and the development of our nation's future, providing a blue sky for their wellbeing. Leveraging the Fu Tang Children's Medical Development Research Center for the dissemination of rheumatology knowledge, the Rheumatology and Immunology Professional Committee of the Fu Tang Children's Medical Development Research Center was established in 2018, and currently has 53 hospitals as members. The construction of the "China Children's Medical Health" service platform is dedicated to promoting the development of Chinese pediatric medicine to meet international standards; realizing expert sharing, medical sharing, research sharing, teaching sharing, prevention sharing and management sharing [19]. Taking the responsibility of pediatric medical research, promotion of new pediatric diagnosis and treatment technologies, training of pediatric personnel, and health education for children, the Center is constantly improving the level of pediatric medical care and service

capabilities [20]. Through various forms of training, hundreds of medical personnel with certain business levels have been trained in grassroots medical institutions to meet the local medical and health needs [21]. After returning, the students can drive more grassroots doctors to take the lead in local pediatric rheumatology construction with what they have learned, and work together for the better.

In conclusion, with the development opportunities for pediatric rheumatology in China, we should strengthen the discipline construction, enhance personnel training, improve clinical skills, enhance medical humanities literacy, expand the specialty team, and promote the long-term development of the pediatric rheumatology in China.

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