

Current diagnosis and management of rare pediatric diseases in China

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SUMMARY This review categorizes and summarizes the rare pediatric diseases that have been included in the *First List of Rare Diseases* that was jointly published by the National Health Commission and four other government departments in China in 2018. In total, 58 diseases that develop during childhood are included. These diseases involve nine organ systems, including the musculoskeletal, respiratory, immune, endocrine and metabolic, nervous, cardiovascular, hematological, urinary, and integumentary systems. Affected children often have multiorgan involvement with various presentations. Severe diseases can cause acute symptoms starting in the neonatal period that lead to increased morbidity and mortality without prompt management. Early diagnosis and treatment can significantly change the course of a disease and improve its prognosis. This work systemically reviews the status of rare pediatric diseases with a relatively high incidence in the *First List of Rare Diseases*.

Keywords rare pediatric diseases, diagnosis, management, China

1. Introduction

Most rare pediatric diseases are genetic disorders. Missed diagnosis and misdiagnosis can cause children to miss the best treatment window. In addition, both in China and the rest of the world, most children with rare diseases frequently suffer from an awkward situation due to the poorly understood pathogenesis, diagnosis, and treatment of these diseases, as well as difficulties in managing and obtaining medications for affected children. In recent years, there have been great breakthroughs in clinical research on these rare diseases. The development of numerous targeted therapeutics has provided promising results for patients. The introduction of a series of policies in China, such as the development and publication of standard treatment protocols for rare diseases, the accelerated evaluation of medications for rare diseases, the revision of drug regulations, the prioritization of rare disease treatments in the annual adjustment of the National Drug Reimbursement List, and the establishment of special funds, have significantly improved the management and accessibility of medication for rare diseases.

The *First List of Rare Diseases* was jointly published by the National Health Commission and other four government departments in China in May 2018. This list

includes 121 diseases that require urgent clinical attention due to their serious disease burden and pressing social concern. All 121 of these rare diseases meet the following four conditions: *i*) low incidence and prevalence as indicated by domestic and international studies; *ii*) substantial impacts on patients and their families; *iii*) definitive diagnostic criteria; and *iv*) treatments or interventions that are affordable, or their potential management falls under national research projects even if there are no effective treatments or interventions yet (*1*). The release of the *First List of Rare Diseases* has filled a gap by defining rare diseases and ushering in a new era of using a catalogue to identify rare diseases in China. This may affect approximately 3 million patients in China (*2*). In February 2019, the Guidelines for the Diagnosis and Treatment of Rare Diseases (2019 edition) was published. It comprehensively describes the clinical management protocols for 121 rare diseases, which include disease definition, etiology, epidemiology, clinical presentations, auxiliary examinations, diagnosis and differential diagnosis, and treatment and management policies. The guidelines also propose a management process, which improves standardized diagnosis and treatment to facilitate early diagnosis and treatment of rare diseases in China (*3*). A total of 58 different rare pediatric diseases are included in the list,

and those diseases and their incidence are shown in Table 1.

2. Rare pediatric diseases of different systems

2.1. Rare pediatric diseases of the musculoskeletal system

The *First List of Rare Diseases* includes nine rare pediatric diseases that primarily involve the musculoskeletal system. They are congenital myasthenic syndrome, congenital myotonia syndrome, congenital scoliosis, hypophosphatemic rickets, osteogenesis imperfecta, Prader-Willi syndrome, progressive muscular dystrophy, severe myoclonic epilepsy in infancy, and Russell-Silver syndrome. Currently, there is no special treatment targeting the etiology of most of these rare musculoskeletal diseases. Their management usually requires multidisciplinary collaboration to treat the disease using different approaches. Management mainly includes symptomatic relief with medication and surgery, with a fundamental goal of slowing the disease progression and improving quality of life. In China, further epidemiological studies are required to better understand the prevalence of rare pediatric musculoskeletal diseases. The following is a review of several typical diseases of the musculoskeletal system, including HR and progressive muscular dystrophy, that are highly disabling and deforming.

2.1.1. Hypophosphatemic rickets

Hypophosphatemic rickets (HR) is a group of skeletal mineralization disorders characterized by hypophosphatemia due to various genetic or acquired causes. HR carries a high risk of disability and deformity. Its etiology includes gene mutations, such as the PHEX mutation, or other acquired causes that can increase the level of the phosphorus-regulating fibroblast growth factor 23 (FGF23) and result in a decreased renal phosphorus threshold and reduced intestinal absorption of calcium and phosphorus. These changes can ultimately lead to impaired bone mineralization. The disease begins in childhood and is known as rickets. Affected children often present with a square skull, a pigeon chest, beaded ribs, and bowed limbs (O- or X-shaped legs) when they start to bear weight at nearly age 1. Their symptoms can also include growth delay, multiple fractures, bone pain, and abnormal tooth development. Diagnosis of HR is based on clinical interviews, including questions about the use of anti-hepatitis B virus drugs (adefovir and tenofovir) and aminoglycosides, as well as a physical examination. Laboratory tests include blood phosphorus, calcium, parathyroid hormone, 25-hydroxyvitamin D, alkaline phosphatase, and the renal phosphorus threshold. Imaging studies can reveal skeletal deformities with a generalized reduction in bone density. Genetic tests

can also be performed to identify relevant mutations. In addition, family members of an affected child should be screened to rule out the possibility of HR in order to provide prompt diagnosis and treatment (4).

In children with acquired HR, the cause needs to be promptly identified and any potential drug or toxic exposure needs to be halted. If the cause of HR cannot be eliminated or it is hereditary HR, standardized treatments in children can promote growth and gradually correct leg deformities as well as improve tooth mineralization. Affected children can show signs of rickets during infancy. Standardized treatment initiated in infancy can achieve satisfactory outcomes (5). Previously, pharmaceutical therapies often included the administration of neutral phosphate and active vitamin D. However, their efficacy was inadequate due to poor compliance as a result of prolonged use of medication and adverse reactions. The role of growth hormone in the treatment of rickets is still controversial. Therefore, a new treatment approach with better efficacy needs to be formulated. Burosumab is a recombinant fully human monoclonal antibody targeting the FGF23 antigen. It can bind to and inhibit the activity of FGF23 to increase serum phosphorus. In January 2021, the China National Medical Products Administration (NMPA) conditionally approved burosumab, under the name Crysvida, for use in children with X-linked hypophosphatemic rickets (XLH). This is the world's first approved recombinant fully human-derived monoclonal IgG1 antibody targeting FGF23. It fills the gap in the clinical treatment of XLH in China. The successful approval of this therapy has brought optimism and new hope to children with this rare disease.

In children, premature surgery should generally be avoided as their epiphyseal plates are not closed (4). However, when affected children have severe skeletal deformities, obvious knee varus or valgus deformities, abnormal height or body appearance, or pathological fractures that affect daily life, surgery can be considered to improve quality of life. Currently, the best treatment outcome is obtained with surgery guided by a three-dimensional reconstruction (6).

2.1.2. Progressive muscular dystrophy

Progressive muscular dystrophy (PMD) is a group of heterogeneous genetic defective disorders with increasing skeletal muscle weakness and atrophy as their main clinical presentation. Its incidence is estimated to be approximately 1 in 3,583 people, with approximately 70,000 patients in China at present. Currently, dozens of genes causing this disease have been identified. There are nine major types of PMD, with varying age at onset, rate of progression, range of involvement, and disease severity. Here, the diagnosis and treatment of a typical form, Duchenne/Becker muscular dystrophy, will be reviewed. Caused by the *DMD* gene, Duchenne muscular

Table 1. Rare pediatric diseases in the First List of Rare Diseases

System	Disease	Inheritance	Phenotype, MIM number	Pathogenic gene	Gene/Locus, MIM number	Incidence [#]	
Musculoskeletal system	*Hypophosphatemic rickets, HR	XLR, AD, AR, XLD	193100, 241520, 307800, 300554	FGF23, DMP1, PHEX, CLCN5	605380, 600980, 300550, 300008	3.9/100,000	
	Progressive muscular dystrophy, PMD	XLR, AD, AR	310200	DMD	300377	1/3,953	
	Congenital myasthenic syndrome, CMS	AR, AD	601462, 603034, 254210, 615120, 254300, 616326, 610542	CHRNA1, COLQ, CHAT, AGRN, DOK7, RAPSIN, GFPT1	100690, 603033, 118490, 103320, 610285, 601592, 138292	9.2/1,000,000	
	Congenital myotonia	AD	160800	CLCN1	118425	1/100,000	
	Congenital scoliosis, CS	AR	618578	PAX7	167410	0.5-1/1,000	
	Osteogenesis imperfecta, OI	AD	166200, 166210, 259420, 166220, 610967, 610682, 610915, 259440	COL1A1, COL1A2, IFITM5, CRTAP, P3H1, PPIB	120150, 120160, 614757, 605497, 610339, 123841	1/20,000-1/15,000	
	Prader-willi syndrome, PWS	AD	176270	NDN, SNRPN	602117, 182279	1/30,000-1/10,000	
	Dravet syndrome, DS	AD	607208	SCN1A	182389	1/40,000-1/20,000	
	Silver-Russell syndrome, SRS	AD	180860, 618905, 616489, 618907, 618908	ICR1, IGF2, PLAG1, HMGA2	616186, 147470, 603026, 600698	1/100,000-1/30,000	
	Respiratory system	*Cystic fibrosis, CF	AR	219700	CFTR, FCGR2A, TGFB1	602421, 146790, 190180	1/25,000-1/1,800
		Primary combined immunodeficiency, CID	AR	/	IL2RG	308380	1/100,000-1/75,000
	Immune system	Severe congenital neutropenia, SCN	AD, AR, XLR	202700, 613107, 610738, 612541, 615285, 616022, 617014, 618752, 300299	ELANE, GFI1, HAX1, G6PC3, VPS45, JAGN1, CSF3R, SRP54, WAS	130130, 600871, 605998, 611045, 610035, 616012, 138971, 604857, 300392	1/250,000
X-linked agammaglobulinemia, XLA		XLR	300755	BTK	300300	1/379,000	
Endocrine and metabolic system	*Wiskott-Aldrich syndrome, WAS	XLR, AR	301000, 614493	WAS, WIPF1	300392, 602357	1/100,000	
	β-ketothiolase deficiency, BKD	AR	203750	ACAT1	607809	1/960,600	
	Biotinidase deficiency, BTDD	AR	253260	BTD	609019	1/60,000	
	Congenital hyperinsulinemic hypoglycemia, CHI	AD, AR	256450, 601820, 602485, 609975, 609968, 606762, 610021	ABCC8, KCNJ11, GCK, HADHSC, INSR, GLUD1, SLC16A1	600509, 600937, 138079, 601609, 147670, 138130, 600682	1/50,000-1/30,000	
	Adrenal hypoplasia congenita, AHC	XLR	300200	NR0B1	300473	1/12,500	
	*Gaucher disease, GD	AR	230800, 230900, 231000, 231005, 608013	GBA	606463	1/80,844	
	Glycogen storage disease, GSD (I, II)	AR	232200, 232240, 232300	G6PC, SLC37A4, GAA	613742, 602671, 606800	1/100,000-1/20,000, 1/100,000-1/14,000	
	Hepatolenticular degeneration	AR	277900	ATP7B	606882	1/30,000	
	Hereditary fructose intolerance, HFI	AR	229600	ALDOB	612724	1/20,000	
	Hereditary hypomagnesemia	AR, AD	602014, 154020, 248250, 611718, 248190, 613882	TRPM6, FXYD2, CLDN16, EGF, CLDN19, CNNM2	607009, 601814, 603959, 131530, 610036, 607803	1-10/40,000	
	Holocarboxylase synthetase deficiency, HLCS	AR	253270	HLCS	609018	/	
	Homocysteinemia	XLR	309541	CBS, HCF1	300019	1/300,000-1/200,000	
Hypophenylalaninemia, HPA	AR	261640, 233910, 261630, 264070, 261600	PTS, GCHI, QDPR, PCB1, PAH	612719, 600225, 612676, 126090, 612349	1/10,397		
Inborn errors of bile acid synthesis, IEBAS	AR	607765, 235555, 613812, 214950, 616278, 617308	HSD3B7, AKR1D1, CYP7B1, AMACR, ABCD3, ACOX2	607764, 604741, 603711, 604489, 170995, 601641	1/70,000		
Laron syndrome	AR	262500	GHR	600946	/		
Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency, LCHADD	AR	609016	HADHA	600890	1/250,000		
Lysinuric protein intolerance, LPI	AR	222700	SLC7A7	603593	/		
Lysosomal acid lipase deficiency, LALD	AR	278000	LIPA	613497	1/300,000-1/40,000		
Maple syrup urine disease, MSUD	AR	248600	BCKDHA, BCKDHB, DBT	608348, 248611, 248610	1/139,000		
Medium chain acyl-CoA dehydrogenase deficiency, MCADD	AR	201450	ACADM	607008	0.66/100,000		
Methylmalonic acidemia, MMA	AR	251000, 277400	MMUT, MMACHC, PRDX1	609058, 609831, 176763	1/28,000		

[#]Incidence figures are from the Guidelines for Diagnosis and Treatment of Rare Diseases (2019 Edition); *Diseases that were mentioned in this review.

Table 1. Rare pediatric diseases in the First List of Rare Diseases (continued)

System	Disease	Inheritance	Phenotype, MIM number	Pathogenic gene	Gene/Locus, MIM number	Incidence*
Nervous system	Mucopolysaccharidosis, MPS	AR, XLR	607016, 309900, 252900, 252920, 252930, 252940, 253000, 253010, 253200, 601492	IDUA, IDS, SGSH, NAGLU, HGSNAT, GNS, GALNS, GLB1, ARSB, HYAL1	252800, 300823, 605270, 609701, 610453, 607664, 612222, 611458, 611542, 607071	1/100,000
	Multiple acyl-CoA dehydrogenase deficiency, ADD	AR	231680	ETFDH, ETFB, ETFB	231675, 608053, 130410	/
	N-acetylglutamate synthase deficiency, NAGSD	AR	237310	NAGS	608300	/
	Neonatal diabetes mellitus, NDM	AD, AR	601410, 610374, 610582, 606176, 618856, 618857	ABCC8, KCNJ11, GCK	600509, 600937, 138079	1/500,000-1/400,000
	Omithine transcarbamylase deficiency, OTCD	XL	311250	OTC	300461	7.1/100,000
	Phenylketonuria, PKU	AR	261600	PAH	612349	1/11,800
	Primary carnitine deficiency, PCD	AR	212140	SLC22A5	603377	0.8-2.5/100,000
	Progressive familial intrahepatic cholestasis, PFIC	AR	211600, 601847, 602347, 615878, 617049, 619484	ATP8B1, ABCB11, ABCB4, TJP2, NR1H4, SLC51A	602397, 603201, 171060, 607709, 603826, 612084	1/100,000-1/50,000
	Tetrahydrobiopterin deficiency, BH4D	AR	261640, 233910, 261630, 264070	PTS, GCHI, QDPR, PCBD1	612719, 600225, 612676, 126090	/
	Tyrosinemia	AR	276700, 276600, 276710	FAH, TAT, HPD	613871, 613018, 609695	1/120,000-1/100,000
Very long chain acyl-CoA dehydrogenase deficiency, VLCADD	AR	201475	ACADVL	609575	1/100,000-1/30,000	
X-linked adrenoleukodystrophy, ALD	XLR	300100	ABCD1	300371	1/21,000-1/15,500	
Cardiovascular system	*Spinal muscular atrophy, SMA	AR, XLR	253550, 253400, 271150, 604320, 313200, 301830, 158600	SMN1, SMN2, IGHMBP2, AR, UBA1, DYNC1H1	600354, 601627, 600502, 313700, 314370, 600112	1/10,000-1/6,000
	*Cardiac ion channelopathies, CICP *Noonan syndrome	AD AD, AR	192500, 609621, 601144, 604772 163950, 605275, 609942, 610733, 613224, 615355, 618499	KCNQ1, SCN5A PTPN11, LZTR1, KRAS, SOS1, NRAS, RIT1, MRAS	607542, 600163 176876, 600574, 190070, 182550, 164790, 609591, 608435	1/2,500 1/2,500-1/1,000
Hematologic system	*Diamond-Blackfan anemia, DBA	AD	105650, 612527, 612561, 612562, 612563, 613308, 617408, 617409, 618312	RPS19, RPS17, RPL5, RPL11, RPS7, RPS10, RPL27, RPS27, RPL35	603474, 180472, 603634, 604175, 603658, 603632, 607526, 603702, 618315	1.5-5.0/100,000
	Severe congenital neutropenia, SCN	AD, AR, XLR	202700, 613107, 610738, 612541, 615285, 616022, 617014, 618752, 300299	ELANE, GFI1, HAX1, G6PC3, VPS45, JAGNI, CSF3R, SRP54, WAS	130130, 600871, 605998, 611045, 610035, 616012, 138971, 604857, 300392	1/250,000
Urinary system	Fanconi anemia, FA	AR, XLR	227650, 300514, 227645, 605724, 227646, 603467, 609054	FANCA, FANCB, FANCC, BRCA2, FANCD2, FANCF, BRIP1	607139, 300515, 613899, 600185, 613984, 613897, 605882	1/160,000
	Isovaleric acidemia, IVA *Propionic acidemia, PA	AR AR	243500 606054	IVD PCCA, PCCB	607036 232000, 232050	1/160,000 0.6-0.7/100,000
Integumentary system	*Alport syndrome	XL, AD, AR, AD	301050, 203780, 104200	COL4A5, COL4A3, COL4A4	303630, 120070, 120131	/
	*Hereditary epidermolysis bullosa	AR, AD	226700, 131750, 226600	LAMC2, LAMB3, LAMA3, COL7A1, MMP1	150292, 150310, 600805, 120120, 120353	/
	*Langerhans cell histiocytosis, LCH	Sporadic nonhereditary disorder	604856	BRAF V600E, MAP2K1	164757, 176872	0.5-5.4/100,000

*Incidence figures are from the Guidelines for Diagnosis and Treatment of Rare Diseases (2019 Edition); *Diseases that were mentioned in this review.

dystrophy (DMD) begins in childhood. China is one of the countries with the largest number of patients with this disorder, which has an incidence of about 1/3,853 (7,8).

The natural course of DMD usually starts with mildly delayed motor development in early childhood and progresses into motor activity decline, abnormal gait, Achilles tendon contracture, and lumbar lordosis during childhood (5 to 6 years old). Affected children can lose the ability to walk at around age 10 and can die due to cardiopulmonary failure at around age 20. Diagnosis of DMD is mainly based on serology, electromyography, muscle magnetic resonance imaging, muscle biopsy, and genetic tests. DMD can be clinically diagnosed when a child displayed obvious bilateral gastrocnemius pseudohypertrophy, combined with serology results indicating a significantly elevated blood muscle enzyme profile, and myogenic damage according to electromyography.

Although there is no cure for DMD, there have been breakthroughs in research and clinical trials on its treatment in recent years. Specifically, treatment with corticosteroids (prednisone or fluticasone) has been found to delay disease progression and extend patients' lifespans (9). In affected children who are older than 3, standard oral steroid treatment should be initiated before their motor functions start to decline (7). The development of DMD is a process of multiorgan system involvement. A series of pathological changes caused by a protein deficiency means that DMD requires a joint, multidisciplinary effort for its diagnosis and treatment. Management should target osteoporosis, muscle atrophy, and declining cardiopulmonary function. Pharmaceutical treatments, including bisphosphonates and medications for heart failure, should be given as adjuvant medications. Appropriate specialties should be consulted for any nutritional, digestive, or psychological issues. In addition, with the development of gene editing technology, gene therapy and stem cell therapy can play an important role in the relief of symptoms by increasing the expression of dystrophin. These therapies have yielded promising results, although some potential adverse effects are still under investigation (8).

Orthopedic surgery can be performed in children with severe skeletal deformities to maximize motor and respiratory functions. At each stage of the disease, affected children can benefit from rehabilitation, including lifelong routine physiotherapy evaluation, dietary counseling for patients on corticosteroids, pulmonary care (manual or mechanical cough assistance or noninvasive or invasive ventilation), and cardiac recovery (an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker). Standardized pharmacological treatment and rehabilitation, along with regular follow-ups to assess and treat relevant systemic symptoms, can significantly delay disease progression, prolong the patient's lifespan, and improve the patient's quality of life.

2.2. Rare pediatric diseases of the respiratory system

Cystic fibrosis (CF) is the only rare pediatric pulmonary disease included in the *First List of Rare Diseases*. CF is a multi-system disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It is one of the most common genetic diseases in the Caucasian population. Due to the small number of CF patients reported in China, we are still in the preliminary stage of understanding this disease. More epidemiological studies are required to investigate this disease since the number of patients diagnosed with CF is rapidly increasing in China.

CFTR mutations cause abnormal production, structures, and functions of proteins, which result in chloride channel dysfunction. Decreased secretion of chloride ions and water can lead to mucus accumulation, with subsequent blockage of the lumen of the exocrine glands in the respiratory tract and pancreas. This can further cause bacterial growth and produce recurrent infections and inflammatory reactions (7). The skin can taste salty due to increased chloride in sweat. Patients with CF often have chronic bacterial infections and pathogen colonization of the respiratory tract. Once an infection occurs, it can rapidly result in diffuse bronchiectasis, which often begins in early childhood. More than 90% of pediatric patients with CF have recurrent chronic upper and lower respiratory tract infections (10). Gastrointestinal disorders also start in the neonatal period, with excessive viscous secretions that can cause meconium intestinal obstruction and peritonitis. Pediatric patients with CF may have salt crystals on the skin. More than 95% of male patients are infertile, which is most often a result of the absence of the vas deferens due to the incomplete development of the Wolffian tube. In general, the diagnosis of CF requires six different types of tests and studies, including laboratory tests, pulmonary function tests, imaging studies, respiratory pathogen tests, reproductive system tests, and genetic tests. Determination of the chloride ion concentration in sweat is considered to be the gold standard diagnostic test for CF (11). The diagnosis can usually be confirmed when typical presentations of CF are present, such as dyspnea and other pulmonary diseases, with at least one of the following abnormal results of a cystic fibrosis transmembrane conductance regulator (CFTR) test, *i*) sweat chloride ≥ 60 mmol/L or sweat chloride ≥ 40 mmol/L according to a single test; *ii*) two CFTR pathogenic mutations in the allele; and *iii*) an abnormal nasal potential difference (12). In addition, the presence of two CFTR pathogenic mutations on the allele or an abnormal nasal potential difference can also confirm the diagnosis of CF (7).

The life expectancy of children with CF does not usually exceed 10 years if appropriate interventional therapy is not provided. In clinical settings, CFTR modulators can be used as targeted therapy for CF. With

advances in research on the *CFTR* gene, clinical therapy has attempted to target *CFTR* gene defects. Ivacaftor is a typical *CFTR* modulator that was approved by the US Food and Drug Administration (FDA) in 2012 as the first medication to treat the underlying cause of CF (13). It can improve *CFTR*-mediated chloride secretion by restoring the function of the mutated *CFTR* channel and improving the function of the defective *CFTR* protein. In October 2019, the FDA approved Trikafta, a triple combination therapy that is effective for most CF patients. It can increase the lung capacity by 10-15% and delay the development of CF complications by correcting the most common mutations in CF. This treatment was a milestone achievement in the genetic therapy for CF because it transformed CF from a progressive disease to a chronic manageable disease (14). In addition, multidisciplinary comprehensive treatment is an essential approach to managing CF, which includes medications such as inhaled DNase I (α -streptokinase) to improve the clearance of airway secretions, antibiotics for at least 10-14 days to treat pulmonary infections, bronchodilators such as β -agonists and glucocorticoids to relieve asthma symptoms, and 14- or 15-membered ring macrolides to promote respiratory function and reduce the incidence of acute exacerbations. Patients with end-stage CF should receive double-lung transplantation (15).

At the end of the 20th century, many clinics started to use preimplantation genetic screening to facilitate the management of CF. In recent years, preimplantation genetic screening has been used to prevent the transmission of rare hereditary diseases.

2.3. Rare pediatric diseases of the immune system

Immunodeficiency diseases refer to a group of clinical syndromes in which the immune response is absent, reduced, or imbalanced due to defects in immune cells or immune molecules, which can result in reduced immune capacity against infections or immune dysfunction in the body. The *First List of Rare Diseases* includes four immune system diseases that develop during childhood: primary combined immunodeficiency disease, severe congenital neutropenia, X-linked agammaglobulinemia, and eczema-thrombocytopenia-immunodeficiency syndrome. Infection is the most common presentation and consequence of immunodeficiency diseases. It is usually serious or even fatal. Prompt prevention and aggressive control of infection are important treatment principles for immunodeficiency diseases. In addition, treatment approaches depend on whether the patient has single-organ, single-system, or multiple-system involvement. Alternative or immune reconstitution therapies can be given based on the type of immunodeficiency. General treatment can be guided by endocrine test results. Intravenous immunoglobulin infusion can be given as replacement therapy.

Eczema-thrombocytopenia-immunodeficiency

syndrome (Wiskott-Aldrich syndrome, or WAS) is an X-linked recessive disease characterized by a triad of bleeding diathesis, eczema, and recurrent infections, as well as a high risk of autoimmune diseases and lymphoma. The *WAS* gene encodes the Wiskott-Aldrich Syndrome protein (WASp), which is an intracellular signaling molecule and skeletal protein specifically expressed in hematopoietic cells. It plays an important role in actin polymerization and cytoskeletal remodeling (16,17). Mutations in *WAS* can lead to self-activation of WASp, with subsequent morphological and functional platelet and lymphocyte abnormalities that cause different types of disease. Depending on the mutation, WAS is classified into four types in clinical settings, with the most common being the classic type. WAS almost exclusively affects males. Without a hematopoietic stem cell transplantation, the average lifespan of patients not expressing WASp is only about 15 years (7). Clinical diagnosis is based on a patient's medical history, physical examination, and laboratory tests (routine blood test, humoral immunity, cellular immunity, WASp expression, and genetic analysis). WASp flow cytometry and *WAS* genetic analysis are effective as confirmatory diagnostic tests (16). The classic type of WAS should be ruled out in boys with thrombocytopenia, isolated or concomitant eczema, recurrent respiratory infections, autoimmunity, and/or cancer. Further examination of a deficiency in or a reduced level of WASp expression and *WAS* gene mutations can confirm the diagnosis (17).

Mutations in the *WAS* gene and the degree of WASp deficiency are closely related to the clinical presentations and severity of WAS and determine the treatment options (18). Most affected children start to show signs of bleeding diathesis and immunodeficiency in the neonatal period, and those signs worsen as they grow. Other clinical complications, such as eczema, autoimmunity, and malignancies, can occur with different presentations and different levels of severity. Only about one quarter of patients have the classic triad of clinical presentations simultaneously. Children with typical WAS who do not receive radical therapy will eventually die from complications such as infections, bleeding, or malignancies. Thanks to breakthroughs over the past 20 years, hematopoietic stem cell transplantation therapy is currently the only curative treatment for WAS. The optimal age for transplantation is 1-2 years, with an overall survival rate greater than 90% (16). Some genetic therapies for WAS are currently undergoing clinical trials and have been found to cure WAS by genetic correction of autologous stem cells through viral vectors. Once its safety is improved, genetic therapy is expected to be the treatment of choice for pediatric patients with WAS who lack appropriate donors. In addition, pediatric patients with WAS also require aggressive and comprehensive treatments, such as supportive therapy with inactivated vaccines, improved nutritional, and targeted antibiotics. Affected children can receive an intravenous

immunoglobulin infusion to extend their lifespan as they wait for a hematopoietic stem cell transplantation. Immunosuppressive therapy should also be administered if there are signs of autoimmune complications.

2.4. Rare pediatric diseases of the endocrine and metabolic system

Hereditary metabolic diseases are caused by genetic mutations that result in disorders of enzyme or protein synthesis, defective receptors, or dysfunctional cell membranes. These can lead to the accumulation of substrates and their derivatives in the body and the development of metabolic disorders. There are about 169 rare endocrine and metabolic diseases involving various endocrine organs. The *First List of Rare Diseases* includes 32 endocrine and metabolic diseases with an age of onset in infancy or early childhood: β -ketothiolase deficiency (incidence of 1/960,600), biotinidase deficiency, primary carnitine deficiency (incidence of 2.4/100,000 in Shanghai and 3.1/100,000 in Zhejiang, China), congenital adrenal hypoplasia, Gaucher disease, glycogen accumulation disease (type I and II), hereditary fructose intolerance, hereditary hypomagnesemia, holocarboxylase synthetase deficiency, hyperhomocysteinemia (incidence of 27.5%), hyperphenylalaninemia (incidence of 1:10,397), congenital bile acid synthesis defect, Laron syndrome, long chain-3-hydroxyacyl-CoA dehydrogenase deficiency (incidence 1:250,000), lysinuric protein intolerance, lysosomal acid lipase deficiency, maple syrup urine disease (incidence of 1/139,000), medium-chain acyl-CoA dehydrogenase deficiency (incidence of 0.66/100,000), mucopolysaccharidosis, multiple acyl-CoA dehydrogenase deficiency, N-acetylglutamate synthase deficiency, neonatal diabetes mellitus, ornithine transcarbamylase deficiency, phenylketonuria (incidence of 1/11,800), progressive familial intrahepatic cholestasis, tetrahydrobiopterin deficiency, tyrosinemia, very long-chain acyl-CoA dehydrogenase deficiency, X-linked adrenoleukodystrophy, methylmalonic acidemia, congenital hyperinsulinemic hypoglycemia, and hepatolenticular degeneration. Most of these diseases still require more epidemiological studies in China (7). Management of these endocrine and metabolic diseases mainly includes symptomatic support, pharmacological treatments, and replacement therapies. The treatment principles are to correct metabolic disorders, alleviate symptoms, reduce or delay the occurrence of serious complications, and maintain normal or close-to-normal quality of life in patients.

2.4.1. Gaucher disease

Gaucher disease (GD) is a relatively common autosomal recessive lysosomal storage disease. GD is caused by a defective gene that results in a deficiency of

β -glucocerebrosidase (GBA). Affected children are unable to hydrolyze glucocerebrosides, which leads to their accumulation in the mononuclear macrophages in the liver, spleen, bone, and the central nervous system, where they form typical storage cells, or Gaucher cells. These can ultimately cause lesions in the tissues and organs (19). Depending on the level of neurological involvement, GD is mainly classified into type I (non-neuropathic, adult GD), type II (acute neuropathic, infantile GD), and type III (chronic or subacute neuropathic, juvenile GD). Type I is the most common type of GD and can occur in patients in all age groups, with approximately two-thirds of patients developing the disease in childhood (20). Currently, the best estimate of the incidence of GD in China is from a study in Shanghai, China. That study tested the glucose brain glyoxalase activity in dried blood spots from neonates and found an incidence of 1:80,844 (7). A more comprehensive epidemiological survey is still required in mainland China.

The clinical characteristics of GD are progressive and involve multiple organs. All three types of disease involve hepatosplenomegaly, especially splenomegaly, as well as thrombocytopenia and anemia. In addition, pediatric patients with type I GD often have bone conditions, such as osteoporosis and long bone metaphyseal deformities, that can cause delayed growth or even disability. Pediatric patients with type II GD often have acute neurological involvement, such as medullary paralysis and seizures, that starts after birth or in infancy. Type II GD has a high mortality rate. Affected children often die before the age of 2 to 4 years. Pediatric patients with type III GD often develop the disease in childhood. Neurological involvement progresses slowly, and affected children can have a relatively long life expectancy (7). The diagnosis of GD requires a comprehensive examination. The main clinical sign is splenomegaly, which can be up to five times a normal-sized spleen and which is found in 87% of affected children. Children with significant splenomegaly should undergo a bone marrow examination to identify characteristic Gaucher cells *via* an enzyme activity assay. Measuring glucocerebrosidase enzyme activity is the most effective method to confirm the diagnosis of GD (20).

In the past, the treatment of GD was mainly symptomatic support. Since α -glucuronidase was first used in clinical settings in 1989, enzyme replacement therapy (ERT) has gradually become the treatment of choice for GD. ERT is currently the most effective and widely used approach to managing GD. ERT can specifically reverse an enzyme deficiency, reduce glucose ceruloplasmin accumulation, correct anemia and thrombocytopenia, decrease the size of the liver and spleen, and relieve bone pain, which can significantly improve quality of life for patients (21). The only glucocerebrosidase enzyme currently approved in China

is imiglucerase, as it has adequate evidence-based support and obvious efficacy in the treatment of bone involvement in GD (20). In addition, therapy with a glucosylceramide synthase inhibitor, such as miglustat, is used in other countries, but is not a treatment option in children with GD and has not been approved in China. Other therapies include hematopoietic stem cell transplantation, which carries the risk of implantation failure and graft-related complications, and gene therapy, which requires more study before extensive clinical use.

2.4.2. Phenylketonuria

Phenylketonuria (PKU) is an autosomal recessive disorder caused by the lack of or insufficient activity of phenylalanine hydroxylase (PAH) or tetrahydrobiopterin (BH4). These conditions can result in abnormal metabolism of phenylalanine (Phe), which cannot be converted to tyrosine (Tyr). The accumulated Phe can cause a high concentration of phenylpyruvate, which can cause a series of clinical symptoms. PKU is the main type of hyperphenylalaninemia (HPA). PKU is classified differently based on different measurements (22). The average incidence of PKU is 1/11,800 in China (23).

An earlier diagnosis of PKU can result in a better treatment outcome. PKU has become one of the mandatory screening tests for newborns. It is performed by checking the level of Phe in the blood. Further analysis of a PAH deficiency or BH4 deficiency is required in newborns with confirmed PKU. Urine pterin analysis is currently an important method to diagnose a BH4 deficiency in China. In addition, the BH4 loading test, BH4-responsive PKU/HPA determination, and the blood dihydrobiopterin reductase (DHP) activity assay can also be used as auxiliary methods of diagnosing a BH4 deficiency (24). Affected neonates often have no clinical symptoms. The typical symptoms gradually appear 3-4 months after birth and become obvious at age 1. Clinical signs, such as yellow hair, white skin, mousy smelling urine, and delayed psychomotor development, can provide clues to diagnose PKU. Vomits and eczema are often seen in infancy (7).

Currently, Phe-restricted diet therapy is the main treatment approach for PKU. The principle of management is to provide the appropriate amount of Phe, with frequent adjustments based on the signs and symptoms of the disease, to facilitate a child's normal development (25). Although this treatment approach with a low-Phe diet can reduce the Phe concentration, it cannot stop the continued progression of neurological symptoms, which requires supplementation of BH4 and other medications. BH4 is effective in reducing the Phe concentration in patients with PKU. Sapropterin, a synthetic BH4, has a long-lasting effect in reducing the Phe concentration by 62% in patients with PKU. Pegvaliase-pqpz is the first recombinant phenylalanine

ammonia enzyme (PAL) (developed by BioMarin Pharmaceuticals, USA). It can replace phenylalanine hydroxylase to convert Phe into ammonia and trans-cinnamic acid, which are eventually metabolized in the liver and excreted in the urine. Treatments with pegvaliase-pqpz can decrease the level of Phe and alleviate clinical symptoms in patients with PKU (26).

2.5. Rare pediatric diseases of the nervous system

Nervous system diseases are disorders of the nervous system caused by various pathological processes, such as infections, metabolic disorders, tumors, and congenital developmental abnormalities. In clinical settings, affected patients can have impaired motor, sensory, and higher nervous activity and autonomic dysfunction. Due to the highly specialized functions of the nervous system and its limited capacity for repair, the diagnosis and treatment of nervous system diseases are often difficult. Nervous system diseases account for more than one quarter of all diseases in the *First List of Rare Diseases*. Spinal muscular atrophy (SMA) is one such rare disease starting in childhood.

SMA is an autosomal recessive disorder and is the most common fatal neurogenetic disorder in infancy and childhood. SMA is caused by survival motor neuron gene 1 (*SMN1*), which encodes the survival motor neuron (SMN) protein. Mutations in *SMN1* can cause functional defects in the SMN protein (27). An increasing number of studies have indicated that SMA is a disorder that involves multiple organs and systems, including the cardiovascular system. About 1 in 42 people carry the *SMN1* mutation. SMA is the main genetic cause of infant mortality (28). Epidemiological data on SMA are required in China.

The clinical presentations of SMA in children vary significantly and mainly include muscle weakness and atrophy due to the degeneration and loss of motor neurons in the anterior horn of the spinal cord. SMA can be classified into four types based on the age of onset (prenatal or intrauterine onset), acquired motor function, and rate of disease progression. Children with type I SMA develop symptoms within 6 months of age (1 month after birth on average), with the main presentations being reduced fetal movements and severe hypotonia. Children with type II SMA can develop the disease from childhood to adolescence but usually show symptoms within the first 18 months of life, with the main presentations being progressively worsening generalized muscle weakness and hypotonia to varying degrees. Children with type IV SMA tend to develop symptoms between 30 and 60 years of age; the disease progresses slowly without affecting life expectancy (28). Children with different types of SMA can have various clinical symptoms. Its diagnosis is often based on electromyography. Laboratory tests, such as serum creatine kinase or genetic tests, can be performed to

corroborate the diagnosis of SMA (7).

The main therapeutic strategy for SMA is to increase the level of expression of the full-length SMN protein (29). In addition, small molecule compounds, antisense oligonucleotide gene supplementation, and stem-cell transplantation therapy can also be used in an attempt to improve nerve cells with SMA (30). Nusinersen (brand name: Spinraza) is a modified antisense oligonucleotide that can upregulate the level of expression of the full-length SMN protein. However, its safety and long-term tolerability still need to be investigated further because it can only be injected intrathecally, and patients require close postoperative monitoring. Nusinersen was approved by the China Food and Drug Administration (CFDA) in February 2019, making it the first medication to treat SMA in China (27). The clinical performance of small molecule compounds (such as novel pyridazine analogs) that regulate the splicing of exon 7 in the *SMN* gene still need to be studied further. Other approaches, such as gene supplementation therapy by introducing normal *SMN* cDNA, have achieved promising preliminary results in clinical trials. At present, SMA should be diagnosed as early as possible. Affected children can be treated with a novel medication if it is affordable. Appropriate rehabilitation exercises can be added to control clinical symptoms and slow disease progression (31).

2.6. Rare pediatric diseases of the cardiovascular system

The cardiovascular system is an essential system to maintain normal activity, homeostasis of the body, and metabolism. Cardiovascular diseases are currently the leading cause of death in the general population. Rare pediatric cardiovascular diseases include cardiac ion channelopathies and Noonan syndrome. Both diseases often have an early age of onset, which is usually in childhood or infancy. Like other rare pediatric diseases, rare cardiovascular diseases are often caused by genetic mutations. Attention should be paid to early prevention, timely diagnosis, and prompt treatment when managing these diseases. Pharmaceutical therapy is the most important treatment approach. At present, there are no accurate epidemiological data on this type of disease in China.

2.6.1. Cardiac ion channelopathies

Cardiac ion channelopathies (CICPs) are a large group of diseases that are caused by defective ion channels in cardiac myocytes. Arrhythmias are clearly associated with abnormal expression of the ion channel genes, which can affect protein transport and interactions directly or indirectly by interfering with the structures and functions of cardiac ion channel proteins. All of these changes can ultimately lead to the development of gene-related CICP. Mutations in multiple ion channel

genes can cause various arrhythmias (32,33). CICP can be classified into two types, hereditary and acquired. This review will focus on the hereditary type for brevity. Hereditary CICP includes long QT syndrome (LQTS, the first CICP identified clinically), short QT syndrome (SQTS), Brugada syndrome (BRS), and catecholaminergic polymorphic ventricular tachycardia (CPVT). CPVT is a serious hereditary arrhythmia.

Clinical studies have found that patients with hereditary CICP often have sudden death or cardiac arrest as the first clinical presentation. Electrocardiographic screening can reveal abnormal QT intervals. LQTS can have torsade de pointes arrhythmia, which can cause syncope or sudden death. The terminal ventricular arrhythmia in SQTS typically presents as ventricular fibrillation (34). LQTS is often seen in females at a young age, whereas patients with SQTS can exhibit their first symptom as early as 1 year of age. CPVT is more common in children and adolescents without organic heart disease (7). The diagnosis of LQTS is currently based on the Schwartz scoring system, which includes three components (an electrocardiogram, clinical interview, and family history). The history of LQTS plays an important role in the diagnosis and determination of its subtype. Exercise and invasive electrophysiological tests have a limited role. The process of diagnosing SQTS is similar to that of diagnosing LQTS (34).

The treatment principles for CICP mainly include pharmaceutical therapy, lifestyle modifications, and assistive devices. Risk stratification and assessment of the disease can help clinicians make the right clinical decisions. All patients with LQTS should avoid medications that can prolong the QT interval or lower the potassium level. β -blockers remain the treatment of choice for LQTS. Clinical studies have indicated that propranolol can significantly shorten the QTc more than nadolol and metoprolol. In patients with CPVT who still experience ventricular arrhythmias or syncope despite treatment with β -blockers, verapamil may be considered, with or without a β -blocker. For pediatric patients with BRS who are not candidates for an implantable cardioverter defibrillator (ICD), treatment with quinidine should be considered (7). Although antiarrhythmic medications are still the preferred treatment option for CICP, non-pharmaceutical treatments have become standard care, as antiarrhythmic medications alone usually have poor outcomes or cause additional arrhythmias. ICD implantation is the only effective treatment to prevent sudden death in children with SQTS or BRS. In addition, radiofrequency catheter ablation and left stellate ganglionectomy are also important options in the clinical management of these rare pediatric diseases (35).

2.6.2. Noonan syndrome

Noonan syndrome (NS) is a group of autosomal dominant

disorders with similar clinical presentations caused by mutations in multiple genes. The RAS/mitogen-activated protein kinase (RAS-MAPK) signaling pathway can alter gene transcription, regulate the activity of cytoplasmic targets, and induce appropriate short- and long-term cellular responses to stimuli. Extracellular ligands (such as certain growth factors, cytokines, and hormones) can stimulate cell proliferation, differentiation, survival, and metabolism *via* the RAS-MAPK pathway. Mutations in this pathway can cause NS (36). Approximately 50% of patients with NS have a mutation in the *PTPN11* gene, which is a non-receptor protein tyrosine phosphatase SHP-2 that participates in a variety of intracellular signaling cascades downstream of growth factors, cytokines, and hormone receptors and which is required for normal growth and development. *PTPN11* encodes SHP-2. Mutations in *PTPN11* can lead to over-activation of SHP-2 (37).

Children with NS usually present with short stature (gradually occurring after 1 year of age), a characteristic facial appearance (such as wide eye spacing, ptosis, epicanthus, a low ear position, a high palatal arch, a full forehead, a low posterior hairline, a short nose, and thick lips), congenital heart defects (50–80% of patients have congenital heart disease), delayed psychomotor development, a webbed neck, an abnormal thorax (a sunken or protruding chest), and cryptorchidism (7). The clinical symptoms can vary significantly, with hematological disorders being the most common initial symptoms (37). The diagnosis of NS mainly depends on clinical presentations, although a characteristic facial appearance can change with aging, which can cause a missed diagnosis. Genetic testing is not used as the preferred diagnostic option. A clinical diagnostic scoring system can facilitate the diagnosis of NS (38). There is currently no targeted treatment for NS. The main goal of treatment is to maximize the child's growth so that he or she reaches normal height. The presence of congenital defects in other systems requires a multidisciplinary approach and symptomatic support to improve the patient's quality of life. Long-term growth hormone therapy can help most children reach normal adult height (39). However, children receiving growth hormone therapy should be monitored closely to rule out the incidence of tumors. Clinical trials are still examining use of a target therapy on the RAS/MAPK pathway in NS. Whether medications that inhibit the RAS/MAPK pathway can be safely used in children with NS needs to be studied further (40).

2.7. Rare pediatric diseases of the hematologic system

In the hematological system, there are six rare diseases that start in childhood and infancy: congenital pure red blood cell aplastic anemia, severe congenital neutropenia, Fanconi anemia, isovaleric acidemia, propionic acidemia, and sickle cell anemia (common in Africans and African

Americans). Fanconi anemia is a multisystemic disease. If there is no cure for a hematologic disorder, then the main goal of clinical management is to ensure the growth, development, and daily activity of the affected child. The acute phase usually requires promoting anabolic metabolism while the remission phase generally involves diet therapy and medications. Typical diseases are reviewed here, including congenital pure red blood cell aplastic anemia and propionic acidemia.

2.7.1. Congenital pure red blood cell aplastic anemia

Congenital pure red blood cell aplastic anemia, an autosomal genetic disorder also known as Diamond-Blackfan anemia (DBA), is a hereditary bone marrow failure syndrome caused by mutations in the genes encoding ribosomal proteins. Mutations or deletions in the ribosomal protein genes cause haploinsufficiency, which leads to selective poor erythropoiesis in patients with DBA (41). In addition, impaired ribosome synthesis can affect the stability and activity of the tumor suppressor pathway involving the tumor protein p53 (TP53), which contributes to the clinical presentations of the disease, including altered erythropoiesis and increased tumor susceptibility (7).

Approximately 93% of affected children develop the disease within 1 year of age and can present with pallor, depression, and feeding difficulties (42). The main clinical characteristics include bone marrow failure (macrocytic anemia and significantly reduced bone marrow erythroid cells, which occur in 35% of children at birth), congenital developmental abnormalities (mainly involving the head, upper limbs, heart, and genitourinary system), and increased susceptibility to cancer and early onset of tumors. The clinical diagnosis of DBA is usually based on the following four criteria, *i*) the onset of disease is within 1 year of age; *ii*) macrocytic (or normocytic) anemia, with a normal or slightly decreased white blood cell count, and a normal or slightly increased platelet count; *iii*) significantly reduced reticulocytes; and *iv*) active myeloproliferation with low erythroid precursor cells.

The main treatments for DBA are corticosteroids and blood transfusions, which should be started promptly, as earlier treatments with glucocorticoid can achieve better outcomes. Glucocorticoids are used to maintain a stable hemoglobin level to meet the requirements of physical and cognitive development. The treatment usually increases the percentage of reticulocytes in 1-2 weeks (43). If there is no significant increase in reticulocytes in 4 weeks, corticosteroids should be stopped immediately. More testing should be performed to rule out bone marrow failure. Steroid treatment in children younger than 6-12 months of age can have serious adverse effects and should be replaced by blood transfusion to maintain a hemoglobin level above 80 g/L to ensure growth and development, as well as daily

activity (7). A blood transfusion is also a main treatment for children unresponsive to corticosteroids or for whom corticosteroids are contraindicated. When both types of treatments are ineffective, hematopoietic stem cell transplantation can be considered. In addition, gene therapy to treat defective genes to encode ribosomal protein 19 (RPS19) in patients with DBA is in clinical trials.

2.7.2. Propionic acidemia

Propionic acidemia (PA) is an autosomal recessive disorder with abnormal propionic acid catabolism caused by mutations in the gene coding for propionyl-CoA carboxylase (PCC) or methylmalonyl-CoA mutase (MUT). PA is characterized by the abnormal accumulation of the catabolic products of branched-chain amino acids (3-hydroxypropionic acid, methylcitric acid, and/or methylmalonic acid) in the plasma, urine, and other body fluids, which results in organic acidemia and a series of biochemical, neurological, and other organ system dysfunctions (44). The prevalence of PA is reported to be 0.6/100,000 to 0.7/100,000 in China (7).

PA usually starts after birth or infancy. Most neonates with PA have acute and critical disease, with a high morbidity and mortality. Early identification and treatment of these children is crucial to saving their lives and improving their outcomes (45). The clinical presentations of PA are not specific and can include severe and persistent metabolic acidosis, ketosis, an elevated anion gap, and hyperammonemia. In a neonate with PA, typical symptoms can begin as early as the second day of life. When there is a dramatic deterioration in the overall clinical condition of a neonate, such as vomiting, weight loss, labile body temperature, neurological involvement with hypo- or hypertonic tone, irritability, lethargy, and progression to coma or seizures, the diagnosis of PA should be ruled out. Other possible conditions, such as sepsis, should also be excluded. Blood amino acid and acylcarnitine profile tests, as well as urinary organic acid analysis, can be performed in these symptomatic children. If elevated levels of glycine, C3/C2, 3-hydroxypropionic acid, and methylcitric acid are present, the diagnosis of PA can be confirmed. In addition, genetic testing is also important in confirming the diagnosis of PA (44).

Children in the acute phase of PA require aggressive treatment, including removing accumulated toxic organic acids, minimizing endogenous protein catabolism, and promoting anabolism. Continuous hemofiltration has been used to rapidly remove toxins and allow the administration of a large amount of fluid without the risk of overhydration. L-carnitine can be infused during the acute phase, since it can bind to the organic acids to form water-soluble metabolites to be excreted in the urine. A long-term management plan also includes nutritional support. Adequate protein and energy intake

should be ensured, but natural protein diets should be restricted. L-carnitine, betaine, and vitamin H should be supplemented. Vitamin H-containing biotin therapy can promote the catabolism of fat and carbohydrates and accelerate energy conversion. Liver transplantation may be considered in a small number of pediatric patients with PA who have frequent severe metabolic decompensation despite strict dietary control, death of siblings, or cardiomyopathy. Currently, there is no effective genetic therapy for PA (46-48).

2.8. Rare pediatric diseases of the urinary system

In the *First List of Rare Diseases*, the only rare pediatric-onset disease of the urinary system is Alport syndrome (AS), a hereditary basement membrane disorder. The molecular mechanism of its pathology involves three genetic mutations that alter type IV collagen, one of the major structural components of the basement membrane framework. This can result in structural and functional abnormalities of the α -3, α -4, or α -5 chains in this protein, which in turn lead to abnormal collagen structures in organs. Structural and functional impairments of type IV collagen in the glomerular, ocular, and cochlear basement membranes can result in AS (49).

AS can start during early childhood. It most often involves the kidneys, with glomerular hematuria being the first symptom. It can also affect the eyes and ears, causing sensorineural hearing loss and anterior lenticonus. Early diagnosis of AS is important because treatment to slow the progression of the disease depends on the stage in which treatment is initiated. The age when pediatric patients with AS transition from microalbuminuria to proteinuria is an important prognostic marker. An earlier transition indicates a worse prognosis. The diagnosis of AS relies on five components: laboratory tests (urinary analysis and routine blood and renal function tests), an ear examination (electric audiometry), an ophthalmologic examination (three lesions with diagnostic significance, anterior lenticonus, posterior polymorphous corneal dystrophy, and retinal flecks), a histopathologic biopsy (kidney, skin), and a genetic test. A genetic test is the gold diagnostic standard; it can reveal defects in the *COL4A3*, *COL4A4*, or *COL4A5* genes. Family history should be carefully reviewed since AS is a genetic disease, and affected children often have a significant family history (49).

Currently, there is no curative therapy for AS. Treatment aims to control urinary protein, maintain normal function, and delay the onset of renal failure. Management is mostly supportive care and renal replacement therapy. Treatment decisions should consider the patient's gender, disease stage, mutation type, and family history (especially the age of the patient's relatives at the time of end-stage renal disease).

The first line of pharmaceutical management is with angiotensin-converting enzyme inhibitors (ACEIs). Second-line treatments include angiotensin receptor blockers (ARBs) and aldosterone inhibitors. A number of studies have confirmed the safety and efficacy of ACEIs and ARBs in the treatment of chronic kidney disease in pediatric patients with AS. ACEI should be initiated in at least the 2nd stage of AS (proteinuria > 300 mg/day). It can inhibit the activation of the renin-angiotensin-aldosterone system (RAAS), adjust glomerular feedback, and decrease glomerular hyperfiltration to reduce proteinuria, delay glomerulosclerosis, and slow the progression to end-stage renal disease. During treatment, blood potassium and renal function should be monitored for possible adverse reactions. In addition to the urinary system, AS can also affect other organ systems. AS can be managed by an integrated multidisciplinary approach. Currently, studies involving animal models have identified many potential new therapies for AS, such as podocyte-targeting anti-inflammatory therapies or therapies with bone morphogenetic protein-7-like molecules, protease inhibitors, or collagen receptor antagonists, and cellular therapies targeting podocytes. Advances in basic and clinical research have advanced the treatments for children with AS (7,49-51).

2.9. Rare pediatric diseases of the integumentary system

Rare skin diseases can be classified into rare metabolic skin diseases, rare genetic skin diseases, and rare skin tumors. Rare genetic skin diseases are mostly caused by pathogenic genes affecting the expression of related proteins and the activities of enzymes. Epidermolysis bullosa is a rare genetic skin disease. Rare skin tumors often stem from unknown causes or fusion gene mutations. Langerhans cell histiocytosis is a rare skin tumor. It involves not only the skin mucosa but also multiple organ systems.

2.9.1. Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) is a type of dendritic cell myeloma that is currently considered to be an inflammatory myeloid neoplasm originating from the bone marrow monocyte-macrophage system. LCH is characterized by granulomatous lesions consisting of clonal pathological histiocytes. The disease is most often seen in children with a peak age of 1-4 years (52), and it has an estimated annual incidence of 0.5/100,000 to 5.4/100,000 (7). Although the exact mechanism of LCH's pathogenesis has yet to be elucidated, activation of the MAPK pathway is present in almost all patients with LCH and is a critical driver of carcinogenesis. The oncogene *BRAF* is the gene that is most often mutated in the MAPK pathway. The *BRAF* V600E mutation has been found in 50% of patients with LCH (53). It is statistically correlated with an age of onset younger

than 3, multisystem involvement, severe disease, permanent sequelae, resistance to first-line systemic therapy, and a high 5-year rate of recurrence. LCH is a neoplastic disease because it involves the activation and uncontrolled proliferation of pathological Langerhans cells (LC) due to the MAP kinase pathway activated by a functional *BRAF* V600E mutation (54).

Children with LCH can have various clinical presentations with different levels of severity, easily resulting in misdiagnosis and missed diagnosis. Affected children can have a fever, rash, central diabetes insipidus, an abnormal hematopoietic system, and bone damage, with a rash and bone damage being the most common presentations. Skin lesions most often appear in children under 2 years of age. Proptosis due to orbital bone lesions is a typical characteristic in pediatric patients (7). Approximately 75% of patients have bone lesions. A pathological examination is the gold standard to diagnose LCH. A typical pathological finding is the proliferation of well-differentiated histiocytes under a light microscope. In addition, clinical presentations, histology, and immunohistochemistry findings can be used to aid in diagnosis. LCH should be differentiated from other histiocytic diseases (55).

Determination of the management strategy in patients with LCH should comprehensively consider the clinical presentation, response to treatment, and risk of death. Partial local treatment is effective for patients with LCH and single-organ or single-system disease, whereas systemic treatment is the main therapy for patients with LCH and multisystem involvement. Patients with extensive skin lesions should receive glucocorticoids or nitrogen mustards. Patients with local bone lesions can undergo simple curettage. The first-line treatment for patients with multifocal monosystemic or multisystemic LCH is the LCH-III regimen, which was developed by the International Histiocyte Society. This treatment regimen consists of 1-2 courses of initial therapy and subsequent maintenance therapy. Daily oral steroids and weekly vincristine are given for a period of 6-12 weeks, with subsequent boluses of steroids/vincristine every 3 weeks, for a total treatment period of 12 months. In addition, 6-mercaptopurine should be included in subsequent maintenance therapy in patients with lesions involving the liver, spleen, or hematologic system (56). The Ras-ERK inhibitor vemurafenib can be used to treat patients who fail to respond to conventional therapies, but adverse reactions to vemurafenib should be monitored (7). Medications such as cytarabine and etoposide, which target myeloid tumors, and hematopoietic stem cell transplantation, have gradually become the second-line or salvage treatment options for LCH, and especially for patients with refractory LCH who have multisystem involvement but who fail to respond to first-line treatment. Patients with major organ involvement can also receive second-line treatment. However, further research should focus on drug toxicity,

the high rate of reactivation (30-50%), and sequelae. The prognosis for LCH varies widely. Children under 2 years of age without multiorgan involvement have a better prognosis than children with multisystem involvement. The latter have a higher mortality rate.

2.9.2. Congenital epidermolysis bullosa

Congenital epidermolysis bullosa (CEB) is a group of medical conditions with large blisters of the skin and mucous membranes. CEB is caused by dominant mutations in one or more genes that result in defects in the epidermal keratin or intradermal anchoring proteins with abnormal structure or function of the skin basement membrane. Patients with CEB have increased skin fragility. Minor mechanical injury can separate the epidermis from the dermis to cause blisters (57). CEB can be classified into three major types based on the location of blister formation: epidermolysis bullosa simplex (EBS, lesions within the epidermis), junctional epidermolysis bullosa (JEB, lesions in the center of the lamina lucida of the basement membrane zone), and dystrophic epidermolysis bullosa (DEB, lesions in the sub-lamina densa). The diagnosis of CEB requires a personal and family medical history, as well as lesion histopathology (intra- or subepidermal blisters without inflammatory cell infiltration), a skin immunofluorescence assay (negative results), and a salt-split test (fluorescent deposits on dermal sides) for further verification (7).

Children with CEB can have signs of skin lesions starting at birth. The severity of lesions depends on the type of disease. The clinical characteristics of CEB include increased skin fragility to mechanical forces and blister formations after trauma. Histopathology reveals intra- or subepidermal blisters without inflammatory cell infiltration. Children with CEB and critical lesions can die during infancy. There is currently no cure for CEB. Multidisciplinary comprehensive treatments are the main approach to treating CEB, with the major therapies being symptomatic support, injury prevention, infection control, and promotion of wound healing. The skin wound needs to be adequately assessed, including the area of the lesion and its morphology (intact blisters versus erosions, chronic versus acute, and exudative versus non-exudative), in order to implement a wound care plan (58). Specific skin management includes wound care, pain management, and treatment of pruritus. Non-adhesive foam, modified absorbent pads, lipido-colloid dressings, and contact covers can be used to protect non-exudative wounds. Exudative wounds can be managed with aqueous fibers, calcium alginate, and topical antimicrobials (*e.g.*, antibiotics, silver-containing dressings, and medical-grade honey). Sedatives, such as phenobarbital or chloral hydrate, can be given to children with irritability due to pain. The most commonly used medications for pruritus are antihistamines. Gabapentin, an antiepileptic medication, has also been found to

reduce pruritus in children with chronic kidney disease or a burn. All of these can be used for analgesia in children. Genetic and cell-based studies on molecular therapies have yielded promising results and have provided a new approach to managing CEB. However, their reliability, practicality, and safety need to be studied further. If secondary squamous cell carcinoma is suspected, a skin biopsy should be performed. If confirmed, surgical excision is required (7,57-59).

3. Conclusion

Due to the extremely low incidence of rare pediatric diseases, there is generally no precedent for their treatment. As medicine has advanced, however, clinical treatments and drugs for some rare pediatric diseases have become available. For many rare diseases, early treatment can significantly improve its prognosis and the patient's quality of life. Dietary treatment in infancy can help children with PKU to develop normally, while significant delays in treatment can lead to severe mental and physical disabilities. Neonatal screening will improve viability and effectively prevent death and disability. Determining the novel molecular mechanisms that cause hereditary rare diseases can also help to treat common diseases. Research on rare pediatric diseases is an important aspect of rare diseases and is expected to develop into a systematic and substantive discipline. At present, some rare diseases have been covered by medical insurance in some regions or in the Chinese population, but there is no policy directly targeting rare pediatric diseases. As diagnosis and treatment of rare diseases in China advances further, diagnosis and treatment of rare pediatric diseases should also advance further.

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