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Qamre Alam *Editors*

Rare Genetic Disorders

Advancements in Diagnosis and Treatment

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Preface

Rare genetic disorders present a unique and challenging landscape within the realm of medicine. These conditions, often arising from elusive mutations in an individual's genetic code, affect a relatively small number of people individually but collectively impact millions worldwide. The quest to understand, diagnose, and treat these disorders is a journey characterized by complexity, diversity, and a relentless pursuit of knowledge and solutions.

The chapters that follow delve into the intricate world of rare genetic disorders, offering a comprehensive exploration of these conditions, their diagnosis, treatment, and the invaluable role of animal models in research. This preface provides an overview of the abstracts from each chapter, giving readers a glimpse into the depth and breadth of the topics covered.

Chapter 1 focuses on the enigmatic nature of rare genetic disorders. With over 7000 identified and many more yet to be uncovered, these conditions manifest in various forms, impacting millions of lives. Despite the diagnostic challenges posed by their diverse and often nonspecific symptoms, genetic tests offer hope for identifying these conditions. The absence of one-size-fits-all treatments underscores the need for tailored care, and ongoing research fuels optimism for the development of new therapies.

Chapter 2 delves into the diagnostic landscape of rare genetic disorders. Leveraging modern molecular biology techniques, particularly next-generation sequencing, offers hope in identifying these conditions, even when traditional clinical hypotheses fall short. By shedding light on the impact of recent advancements in genetic testing, the chapter paves the way for more accurate and timely diagnoses.

Genetic counseling takes center stage in Chap. 3, offering critical support to individuals and families affected by rare genetic disorders. The role of genetic counselors in providing information, assisting with reproductive decisions, and collaborating with healthcare practitioners is pivotal. Despite the obstacles to genetic testing, this chapter underscores the importance of addressing the psychological and emotional aspects of rare genetic illnesses.

Chapter 4 highlights the crucial role of animal models in rare disease research. These models, ranging from rodents to primates, and dogs to zebrafish, provide invaluable insights into disease mechanisms and therapeutic interventions. Advanced genetic engineering, especially CRISPR-Cas9 technology, has revolutionized the creation of precise animal models. The chapter emphasizes that understanding

disease mechanisms, testing potential therapies, and bridging the gap between basic research and clinical applications are central to improving the lives of patients with rare diseases.

Chapter 5 addresses the diagnostic challenges of undiagnosed rare genetic disorders, where diversity and limited genetic knowledge pose significant obstacles. The chapter provides a comprehensive overview of research and clinical strategies aimed at identifying and treating these elusive conditions.

Chapter 6 emphasizes the growing importance of research and development for rare disorder therapies. With an increased focus on drug development and innovative approaches, including small molecules and biologics, the potential for accelerating the development of rare disease treatments is on the rise.

Chapter 7 offers a comprehensive review of two distinct rare genetic disorders, Fabry disease and Marfan syndrome, both characterized by multi-organ involvement and life-threatening complications. The chapter sheds light on pathophysiological mechanisms, gene mutations, and therapeutic approaches, highlighting the importance of early diagnosis and multidisciplinary care.

Mitochondrial disorders take the spotlight in Chap. 8, focusing on the challenges and potential treatments for these conditions. As gene therapy emerges as a precision medicine approach, the chapter explores the future possibilities and emphasizes the need for further research in this area.

Chapter 9 addresses the overarching challenges and opportunities of rare genetic disorders. The diagnostic odyssey faced by patients, economic obstacles in therapeutic development, the role of next-generation sequencing, personalized medicine, drug repurposing, and power of patient advocacy are all explored.

As we embark on this journey through the world of rare genetic disorders, we hope that these chapters will serve as a valuable resource for researchers, clinicians, and individuals and families affected by these conditions. The exploration of diagnostic methods, therapeutic approaches, and promising role of animal models will contribute to a deeper understanding of rare genetic disorders and, ultimately, offer hope for a brighter future in the field of rare disease research.

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About the Editors and Contributors

About the Editors

Muhammad Umair currently holds the position of Associate Research Scientist and serves as the Team Leader of Functional Studies at the Medical Genomics Research Department within the King Abdullah International Medical Research Center (KAIMRC), part of King Saud bin Abdulaziz University for Health Science, Ministry of National Guard Health Affairs (MNGHA) in Riyadh, Saudi Arabia. Additionally, he serves as a "Research Advisor" at the Department of Life Sciences within the School of Science at the University of Management and Technology (UMT) in Lahore, Pakistan. Dr. Umair is a molecular geneticist with a particular focus on rare genetic disorders (RGDs). His research involves multiple projects dedicated to rare genetic disorders and therapeutic genetics. He is currently engaged in research initiatives such as the Genetics and Rare Disease Program, Genetic and Functional Characterization of Rare Skeletal Disorders (GSDs), Genodermatosis, Preventative Genome Medicine for Inherited Genetic Disorders, Functional Characterization of Genes Associated with Neurodevelopmental Disorders (NDDs), Genetic and Rare Disease Registry, and Therapeutic Genomics.

Dr. Umair earned his M.Sc., M.Phil., and Ph.D. in Biochemistry/Molecular Biology, specializing in Human Molecular Genetics, from Quaid-i-Azam University in Islamabad, Pakistan. His extensive contributions to the field are reflected in his publication record, which comprises over 140 research articles in the domain of human genetics, accumulating an impressive impact factor exceeding 680. He also actively participates as an associate editor and reviewer for several international peer-reviewed journals. In recognition of his outstanding achievements in genetics, Dr. Umair was honored with the 2nd Dr. Sajjad Aslam Shami Gold Medal in Genetics by the Applied Zoological Society of Pakistan (AZSP) in March 2021.

Misbahuddin Rafeeq is a distinguished physician, accomplished scientist, and dedicated medical educator. He earned his MBBS and MD degrees in 2009 from Aligarh Muslim University, India. Currently, he holds the position of Associate Professor at the Faculty of Medicine (Rabigh) within King Abdulaziz University, Jeddah, Saudi Arabia. Dr. Rafeeq is an esteemed member of the editorial boards of several reputable journals. His wealth of expertise has been showcased through his active participation in numerous scientific events spanning across regions such as

India, Southeast Asia, Asia Pacific, Europe, the UK, the Middle East, Africa, the Balkans, and the USA. His outstanding contributions have earned him several prestigious awards, including the Excellent Leadership Award from the Islamic Development Bank in Saudi Arabia, the ESP fellowship from NIHES in the Netherlands, the Distinguished Achievement Award from KAU in Saudi Arabia, and the Bronze Prize from the Diabetic Congress in the USA. Dr. Rafeeq is affiliated with esteemed organizations and scientific societies, including RCPEdin and the Faculty of Pharmaceutical Medicine at RCP London, ACCP and ASPET in the USA, ISoP, and the Royal Society of Medicine in the UK. Additionally, he serves as an honorary consultant on various educational boards and holds the position of International Secretary for SoPI in India. Dr. Rafeeq boasts an impressive publication record with over 60 high-impact and indexed publications to his credit. Furthermore, he has secured funding for several large grants, where he has served as both a principal and co-investigator. His research primarily focuses on the identification of novel genetic mutations in hereditary syndromes, exploration of novel therapeutic targets and proteins through molecular docking, PK/PD and toxicity studies, study of the effects of natural compounds on animal models, and broader field of lipid pharmacogenomics.

Qamre Alam currently serves as a Medical Research Scientist and Laboratory Supervisor at the Molecular Genomics and Precision Medicine Department of ExpressMed Diagnostics and Research, located in Zinj, Kingdom of Bahrain. Previously, from 2019 to 2022, he held the position of Medical Research Scientist at the Medical Genomics Research Department at King Abdullah International Medical Research Center (KAIMRC), part of King Saud bin Abdulaziz University for Health Science, Ministry of National Guard Health Affairs (MNGHA), Riyadh, KSA. Prior to that, he worked as a lecturer from 2011 to 2019 at the King Fahd Medical Research Center, King Abdulaziz University, Jeddah, KSA. Dr. Qamre Alam earned his M.Sc. from Jamia Hamdard University, New Delhi, India, and his Ph.D. in Biotechnology from JJTU, Rajasthan, India. He has an impressive publication record, with over 75 research articles in the fields of human genetics and cancer biology, accumulating an impact factor of more than 150. Dr. Alam is a molecular geneticist with a strong research interest in rare genetic disorders. He has actively contributed to various projects related to rare genetic disorders and preventive genomic medicine, including noninvasive prenatal testing (NIPT) and preimplantation genetic screening (PGS). Additionally, he serves as an associate editor and reviewer for several international peer-reviewed journals of high repute.

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Introduction to Rare Genetic Disorders

1

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Abstract

Rare genetic disorders are a group of diseases that are caused by changes in a person's genes. These changes can be inherited from parents or occur spontaneously. Rare genetic disorders can affect any part of the body, and they can range in severity from mild to life-threatening. There are over 7000 rare genetic disorders that have been identified, and many more are still being discovered. These disorders affect an estimated 30 million people in the United States alone. The diagnosis of a rare genetic disorder can be challenging, as the symptoms can be varied and often nonspecific. However, there are a number of genetic tests that can be used to diagnose these disorders. There is no one-size-fits-all treatment for rare genetic disorders. The treatment plan will vary depending on the specific disorder and the individual's symptoms. However, there are a number of treat-

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ments that can help improve the quality of life for people with these disorders. Research into rare genetic disorders is ongoing, and there is hope that new treatments will be developed in the future. In the meantime, there are a number of resources available to help people with rare genetic disorders and their families. This book chapter provides a brief overview of rare genetic disorders, including their causes, symptoms, diagnosis, treatment, and research.

Keywords
Genetic syndrome · Mental disorders · Disability · Chromosomal disorder · Genetic disorders

1.1 Aarskog Syndrome

Aarskog syndrome is a hereditary condition that mostly affects men. It is brought on by a mutation in the FGD1 gene, which makes a protein vital to the growth of several human tissues and organs. The additional terms for Aarskog syndrome are Aarskog sickness, Aarskog-Scott syndrome, AAS, faciodigitogenital syndrome, faciogenital dysplasia, FGDY, and Scott-Aarskog syndrome (Gorski 2003; Jones 1997).

1.1.1 Signs and Symptoms

Aarskog syndrome is predominantly observed in males, and it causes a distinct range of abnormalities in the face, skeleton, and genitals of affected boys. The clinical presentation may differ from one individual to another, even among families, indicating clinical heterogeneity. Males with Aarskog syndrome typically have a round face with a broad forehead, widely spaced eyes (ocular hypertelorism), droopy eyelids (ptosis), and downwardly slanting eyelid creases (palpebral fissures). They also typically have a little nose with flared nostrils (anteverted nares), an underdeveloped upper jawbone (maxillary hypoplasia), and a widow's peak. Additionally, those who are affected could have a wide nasal bridge and a protracted groove on their top lip (philtrum) (Orrico et al. 2015; Al-Semari et al. 2013).

Some children with Aarskog syndrome may have ear and tooth problems. Both the ear canal and the earlobes are abnormally large and meaty. Undeveloped teeth at birth, teeth not erupting at the proper time, and undeveloped tooth enamel (enamel hypoplasia) are all examples of dental anomalies (Verhoeven et al. 2012; Pilozzi-Edmonds et al. 2011). While intellectual disabilities have been documented in some males with this condition, it is not a universal symptom. Mild learning disabilities and/or behavioural problems such as delays in development in infancy, hyperactivity, attention deficit, impulsivity, and resistance may be present in those who are affected (Orrico et al. 2010; Bottani et al. 2007).

1.1.2 Causes

However, there is genetic and clinical variation in Aarskog syndrome, and the most studied type of the ailment is passed down as an X-linked characteristic due to mutations in the FGD1 gene. Although Aarskog syndrome is more common in males, girls who possess a single copy of an FGD1 gene mutation may also show some of the disorder's symptoms. Mutations in the FGD1 gene have been found in roughly 22% of afflicted males, suggesting that other genes may possibly be involved in the development of this disorder but have yet to be uncovered (Orrico et al. 2007; Kaname et al. 2006). The mutation of the FGD1 gene has been confirmed in around 60 people with Aarskog syndrome throughout the world. It is challenging to establish the real prevalence of the medical condition in the general community since some minimally afflicted youngsters may go unnoticed. Aarskog syndrome affects an estimated 1 in 25,000 people worldwide (Satoh and Yokoya 2006; Shalev et al. 2006).

1.1.3 Diagnosis

Aarskog syndrome is caused by a mutation in the FGD1 gene, and this mutation has now been proven in around 60 people throughout the globe. Due to the fact that some mildly affected children may go unrecognised, it is difficult to ascertain the true incidence of the medical condition in the general population. The prevalence of Aarskog syndrome is estimated to be 1 in 25,000 persons (Orrico et al. 2005; Lebel et al. 2002).

1.1.4 Treatment

The symptoms of Aarskog syndrome vary from person to person; hence, treatment must be individualised. Some of the associated congenital or structural abnormalities, such as hypospadias, umbilical or inguinal hernias, cryptorchidism, and severe craniofacial characteristics, may need surgical correction. Complete eye and dental examinations are recommended for patients with Aarskog syndrome. Some children have benefited from growth hormone therapy, and although this treatment has been found to increase their height, further research is needed to determine the best course of action and the typical response. A neuropsychiatric evaluation and consultation may be useful when dealing with neurodevelopmental problems. Other types of therapy include relieving symptoms and providing emotional support (Orrico et al. 2004; Schwartz et al. 2000).

1.2 Acromesomelic Dysplasia

Acromesomelic dysplasia is an uncommon genetic condition that causes low height and limb asymmetry due to improper bone formation and development. It falls within the category of skeletal dysplasia, which describes a collection of disorders that negatively impact bone and cartilage development (Khan et al. 2016).

1.2.1 Signs and Symptoms

Acromesomelic dysplasia (AMD) is a disorder that causes short-limbed dwarfism and exceptionally small forearms and lower legs because it stunts the development of certain long bones, such as those in the forearms and lower legs. This condition is usually noticeable in early childhood. The metacarpals, phalanges, and metatarsals in the hands and feet are not immune to abnormal cartilage and bone growth (Olney et al. 2006). Acromesomelic dysplasia typically does not affect the birth weight of infants. However, affected infants often display distinct facial abnormalities at birth, such as a relatively prominent forehead, pronounced back portion of the head, large head, a small pug nose, and slightly flattened midface. Children with AMD have an increased risk of developing vertebral anomalies, which may cause spinal curvature, as they age. The middle of the spine may curve forward and backward as a consequence, a condition known as low thoracic kyphosis, and the lower back may curve excessively inward, a condition known as lumbar hyperlordosis (Potter et al. 2006).

1.2.2 Causes

Researchers have identified five distinct forms of acromesomelic dysplasia. All forms save the Osebold-Remondini form of age-related macular degeneration are exceedingly uncommon and are passed down through families as autosomal recessive traits. Researchers have located the gene for the Maroteaux phenotype on chromosome 9 at the 9p13–12 region. The genetic link between Grebe dysplasia and Du Pan syndrome has been traced to the same region of chromosome 20: 20q11. Having a chromosome 4q23–24 location is associated with acromegaly and genital abnormalities (Szczaluba et al. 2005). The genetic mapping of Osebold-Remondini type is still pending. According to the medical literature from 2005, Hunter-Thompson-type ADM had approximately 10 cases, while Maroteaux-type AMD had 40–50 patients. Although the incidence of Grebe-type ADM is unknown, it is thought to be more common among the Brazilian population (Bartels et al. 2004).

1.2.3 Diagnosis

During the first few years of life, people with acromegaly are often diagnosed by a thorough clinical assessment, an extensive patient history, cutting-edge imaging methods, and recognition of diagnostic traits. Progressive abnormalities, such as forearm and lower leg bone abnormalities, short stature, additional broadening and shortening of bones in the hands and feet, limited elbow and arm extension, and progressive vertebral abnormalities, typically appear in late infancy or early childhood, despite the hands and feet displaying unusual broadness and shortness at birth (Al-Yahyaee et al. 2003).

1.2.4 Treatment

Acromesomelic dysplasia therapy is tailored to each patient in an effort to improve their unique set of symptoms and physical manifestations. Treatment focuses mostly on providing comfort and alleviating symptoms. Physical therapy, exercises, braces, casts, and, in extreme circumstances, corrective surgery may help with abnormal spine curvature such as low thoracic kyphosis and/or lumbar hyperlordosis. Physical therapy, supportive approaches, and orthopaedic surgery may all help with the disorder's symptoms. Individuals and their families who are impacted should seriously consider seeking genetic counselling. Supportive care and alleviation of symptoms are the focus of other therapies (Savarirayan et al. 2003).

1.3 Acute Eosinophilic Pneumonia

Acute eosinophilic pneumonia (AEP) is an extremely rare kind of pneumonia in which eosinophils (a type of white blood cell) accumulate in the lungs. Symptoms include sudden onset of fever, cough, breathing difficulties, and wheezing; if addressed, it may quickly progress to respiratory failure, idiopathic acute eosinophilic pneumonia (sometimes abbreviated as AEP or IAEP) (Rhee et al. 2013).

1.3.1 Signs and Symptoms

The onset of AEP often occurs within a week. However, in rare cases, symptoms might take up to a month to appear. This breathing problem happens often in otherwise healthy young people. The symptoms are general and include things like a high body temperature, a hacking cough, tightness in the chest, and trouble breathing (dyspnoea). Myalgia (muscle pain), weariness, joint pains, and stomach discomfort or pain are some less common symptoms of AEP. When there is a large decline in the amount of oxygen in the blood (hypoxaemia), AEP may rapidly worsen and produce acute respiratory failure. Within weeks or months, this might cause AEP

patients to have life-threatening respiratory issues. Mechanical ventilation may be necessary for around two-thirds of people with AEP (Tsigkaropoulou et al. 2011).

1.3.2 Causes

IAEP is termed idiopathic since its etiology is uncertain. It is hypothesised that AEP is caused by a generic trigger that causes the body to manufacture eosinophils and attracts them to the lungs. But the precise cause of AEP's eosinophil overproduction and accumulation remains unclear. Sensitivity to environmental irritants including dust and smoke, as well as occupational variables, has been connected to AEP. However, it is very unlikely that AEP can be attributed to a single environmental component. It is more probable that a combination of circumstances, including a susceptible person's exposure to a triggering event, is necessary for the illness to emerge. The exact reason why some people get AEP and others do not is unknown (Miller et al. 2010).

Exposure to environmental elements including dust and smoke, both in and out of the workplace, has been linked to AEP. However, it is very unlikely that AEP can be attributed to a particular environmental aspect. More likely, the disease requires a confluence of circumstances, one of which is the presence of a trigger in an otherwise susceptible person. The precipitating reason for AEP may vary from patient to patient. People who have started smoking around the past 3 months prior to the onset of the disorder, who are still smoking after a temporary cessation, or who have recently increased the number of cigarettes smoked daily are especially at risk for developing the disorder. Smoking may be linked to "idiopathic" AEP in certain patients, according to findings in the medical literature. The exact part that smoking plays in the onset of AEP in such instances is, however, not well understood (Jeong et al. 2007).

Occupational factors that can trigger AEP are typically associated with exposure to inhaled dusts. AEP may be triggered by a broad variety of airborne contaminants and agents. There are studies in the medical literature associating AEP to the use of various medicines, in addition to occupational variables. Anti-depressants venlafaxine and daptomycin, as well as the antibiotic minocycline, have all been associated with AEP. A comprehensive list of drugs associated with AEP can be found on the website www.pneumotox.com. AEP may be triggered by a broad variety of airborne contaminants and agents. There are studies in the medical literature associating AEP to the use of various medicines, in addition to occupational variables. Anti-depressants venlafaxine and daptomycin, as well as the antibiotic minocycline, have all been associated with AEP (Shorr et al. 2004).

1.3.3 Diagnosis

AEP is diagnosed by considering the patient's symptoms, medical history, and physical exam in addition to doing tests such as bronchoalveolar lavage (BAL).

Investigating the possible causes of pulmonary eosinophilia and ruling them out are essential. Additional possible causes include parasite infections and medication exposure (Allen et al. 2002). Despite the lack of specificity, imaging tools such as chest X-rays may help confirm a diagnosis of AEP. Chest X-rays of people with AEP often show infiltrates or cloudy areas in the lungs. Chest CT scan findings indicative of the illness include interlobular septal thickening, mild-to-moderate bilateral pleural effusion, and bilateral alveolar consolidation. In the early stages of the illness, pulmonary function tests often show a confined pattern (Poletti et al. 2004).

1.3.4 Treatment

High dosages of corticosteroids are useful in treating AEP, and a response is often seen within days. However, before starting corticosteroid therapy, it is important to rule out any infectious causes of pulmonary eosinophilia. Some studies indicate that treatment with corticosteroids for AEP for just 2 weeks is adequate; however, this finding is not universally accepted in the medical literature. Most patients with AEP are given intravenous corticosteroids first, followed by oral administration, since there is no established dosage for corticosteroid treatment in AEP. Spontaneous remission, without any treatment, has also been reported in some cases. Once treated with corticosteroids, there is no risk of relapse. The long-term prognosis for AEP is excellent (Philit et al. 2002).

1.3.5 Banti Syndrome

Banti syndrome is an uncommon disorder that is characterised by hallmarks such as enlarged spleen (splenomegaly) and anaemia. Banti syndrome manifests initially with exhaustion, weakness, and anaemia, with anaemia becoming more severe as the condition develops. It is also known as Banti's disease, hypersplenism, idiopathic congestive splenomegaly, and idiopathic portal hypertension (Ravenna 1940).

1.3.6 Signs and Symptoms

Early symptoms of Banti syndrome include weariness, weakness, anaemia, and spleen enlargement. As the condition progresses, the anaemia worsens and may be compounded by bleeding in the oesophagus, leading to vomiting of blood and dark stools containing decomposed blood. When the liver develops and gets segmented by fibrous tissue, cirrhosis may occur. But spleen enlargement is the most noticeable sign of Banti syndrome. Individuals with Banti syndrome may tend to bruise easily and are at an increased risk of bacterial infections, often accompanied by prolonged fever. In addition to these, further symptoms might include gastrointestinal bleeding

(haemorrhage), anaemia, leukopenia, thrombocytopenia, and an abnormal accumulation of fluid in the abdomen (ascites) (Waqar et al. 2004).

1.3.7 Causes

Banti syndrome can be caused by various factors that obstruct certain veins in the liver or spleen and cause abnormally high blood pressure within them. Cirrhosis and other underlying diseases may induce inflammation and blockage of hepatic veins, but other causes include congenital malformations of the veins or blood clots. In some cases, increased intake of arsenic may also be a factor. Additionally, reports have been made of instances of individuals using azathioprine for extended periods of time, particularly following kidney transplantation (McCormick 2003). Males and females are equally affected by Banti syndrome. It is rather frequent in some parts of India and Japan, but much less so in the Western region. The incidence may vary in different regions due to factors such as increased levels of arsenic in drinking water (Beers and Berkow 1999).

1.3.8 Diagnosis

Banti syndrome may be diagnosed with a thorough clinical evaluation and specialised testing such as splenic venography and magnetic resonance imaging (MRI). In magnetic resonance imaging (MRI), magnetic fields and radio waves are used to create precise cross-sectional pictures of particular parts of the body (Pickhardt and Balfe 1998).

1.3.9 Treatment

Banti syndrome treatment strategies are condition specific. If arsenic or azathioprine exposure is shown to be the cause of the disease, avoiding those substances is essential. Bleeding from the expanded blood vessels (varices) in the oesophagus or stomach is the key clinical issue. Vasoconstrictor medications or other methods used to treat portal hypertension may be used to stop active bleeding. In the case of persistent bleeding, surgical shunt treatments may be required to reroute blood flow (Behrman et al. 1996).

1.4 Buerger's Disease

Buerger's disease is an incredibly rare disorder that causes damage to the body's micro- and medium-sized blood vessels. Blood clots develop in the arteries involved, leading to discomfort, tissue damage, and even gangrene in extreme situations. Tobacco usage is closely linked to Buerger's disease, though the specific etiology is

uncertain. Infections, genetics, and autoimmune diseases are other possible contributing causes. TAO, thromboangiitis obliterans, and inflammatory occlusive peripheral vascular disease are also additional forms for Buerger's disease (Arkkila 2006).

1.4.1 Signs and Symptoms

Buerger's disease is a type of peripheral vascular disease characterised by the constriction or blocking of small and intermediate-sized arteries and veins in the limbs, resulting in decreased blood flow to those regions. The illness usually comes suddenly and returns repeatedly over the course of a few weeks. Pain in the lower extremities, especially while at rest, is a hallmark of Buerger's disease. A symptom of claudication is the involuntary limping that might result from leg cramps when walking. Other symptoms include a lack of normal blood flow to the fingers and toes, especially in cold weather (known as Raynaud's phenomenon), hand discoloration, numbness, and tingling. Inflammation and clotting of specific veins, known as thrombophlebitis, are also possible. Finger and toe ulcers tend to be dry and black, and they may be very painful. Pain may be exacerbated by elevating the afflicted region. Extremity amputation may be required if the condition is severe enough to cause tissue death (gangrene) in the afflicted limbs (Saito et al. 2007).

1.4.2 Causes

Tobacco smoking is closely linked to the development of Buerger's disease, albeit the precise aetiology is yet unknown. Tobacco usage, either in the past or now, is considered by many scientists to be necessary for a diagnosis of Buerger's disease. The precise connection between cigarette smoking and onset of the illness is unclear. Since the frequency of Buerger's disease varies greatly across various ethnic groups, it is possible that genetic factors have a role in either its development or its severity. To determine whether genetics have a significant influence on the onset of Buerger's disease, further study is required. Ischaemia, or decreased blood flow, is the underlying cause of the limb pain and weakness characteristic with Buerger's illness. Pain, numbness, and even tissue death (gangrene) or amputation may result from inadequate blood supply. The United States and Europe have low incidences of Buerger's disease compared to other areas of the globe, especially sections of Asia and the Middle East. The estimated incidence rate of Buerger's disease in the United States is between 12.6 and 20 per 100,000 individuals. Buerger's disease is more common in nations where smoking is widespread. Tobacco consumption rates may vary greatly from country to country and region to region, which may help explain why the condition is more prevalent in certain areas than others. Buerger's disease is more common in certain ethnic groups and places than in others, which may be due in part to hereditary factors (Watts and Scott 2003).

1.4.3 Diagnosis

A history of recent or current tobacco smoking is often required by clinicians in order to identify Buerger's disease, which is otherwise diagnosed based on the presence of particular clinical characteristics and symptoms. For a definitive diagnosis, medical professionals may employ angiography or other non-invasive imaging studies. With the use of a specific dye injected into a patient's veins, angiography allows for clear imaging of the circulatory system. In this way, clinicians may look for the constriction or blockage of blood arteries, both of which are characteristics of Buerger's disease. Blood flow and anomalies in the afflicted limbs may be assessed using other non-invasive methods, such as ultrasound or magnetic resonance imaging (MRI) (Evans and Ratchford 2014).

1.4.4 Treatment

Tobacco reduction is the first line of defence against Buerger's disease. This is essential for slowing the disease's course and lowering the likelihood of consequences. Quitting smoking has been shown to be effective in reducing or eliminating symptoms and, in some instances, has even been linked to full remission of illness. To control symptoms and forestall consequences, conservative treatments may be performed if the afflicted person does not quit smoking. This may include medications such as anticoagulants to prevent blood clotting, vasodilators to increase blood flow, anti-inflammatory drugs to reduce inflammation, antibiotics to prevent infection, and analgesics to relieve pain. In some cases, surgical intervention may be necessary. This may include procedures to remove or bypass affected blood vessels or to improve blood flow to the affected areas. However, surgical options should be carefully considered and used only when conservative treatments have been ineffective or when there is a risk of tissue death (gangrene) or other serious complications (Arkkila 2006).

1.5 Chronic Lymphocytic Leukaemia

The white blood cells known as lymphocytes are the target of chronic lymphocytic leukaemia (CLL), a kind of blood cancer. Accumulation of aberrant lymphocytes in the blood, bone marrow, and lymph nodes causes a slowly progressive illness. Other terms for CLL include small lymphocytic lymphoma (Podhorecka et al. 2016).

1.5.1 Signs and Symptoms

It is estimated that between 50% and 75% of those with chronic lymphocytic leukemia have no symptoms at all until the disease has progressed significantly. In many cases, the condition is identified during checkups and screenings. While the

symptoms of CLL may be similar between the two subtypes, Ig-mutated and Ig-unmutated, the latter subtype tends to progress more quickly and may result in more severe symptoms. Fatigue, unexplained weight loss, lack of appetite, trouble breathing, low-grade fever, spleen enlargement leading to a sense of fullness in the belly, and night sweats are all possible signs of CLL. Bacterial infections such as skin infections, pneumonia, and sinusitis are frequent in CLL patients. As the disease advances, patients become more susceptible to viral infections, which can pose a significant threat to their health (Mellstedt 2007).

1.5.2 Causes

The precise cause of chronic lymphocytic leukaemia remains unclear, although it involves several genetic mutations that occur within the blood-forming cells. The abnormal cells produced as a result of these mutations are unable to effectively combat infections. It is typical for patients with CLL to have an abnormal chromosome, usually resulting from a deletion of a portion of a chromosome. The most common deletions include part of chromosome 13, as well as chromosome 11 and 17 deletions. Some individuals also show signs of having an extra copy of chromosome 12, a condition known as trisomy 12. In families where many individuals are diagnosed with leukaemia, CLL is by far the most common kind. The average age of onset is 72 years old, and men are twice as likely as women to be affected. CLL is more common as people gets older; current estimates place the prevalence of the disease in the United States at around 3 per 100,000 people (Döhner et al. 1999).

1.5.3 Diagnosis

CLL is frequently detected through routine blood work that reveals an abnormally high count of white blood cells. To confirm a diagnosis, several tests can be conducted, including a complete blood cell count, flow cytometry, bone marrow biopsy, and lymph node biopsy. These tests help determine the presence and extent of the disease, as well as differentiate CLL from other related conditions. In addition to these tests, specialised tests may be recommended by your doctor to predict the likely progression of CLL and its response to treatment. However, the decision to treat the disease is primarily based on clinical factors, such as symptoms, blood counts, and presence of lymph nodes, among others (Cheson et al. 1996).

1.5.4 Treatment

The choice of treatment for CLL depends on symptoms, disease's progression, and prospects. Patients with CLL can remain asymptomatic for years and may not require any specific treatment. However, in advanced stages, chemotherapy is commonly used as a treatment option. Monoclonal antibody therapy is another option,

where proteins are attached to cancer cells, initiating a mechanism that leads to their destruction. The use of both of these therapies together has been found to produce the highest treatment response. In 2010, the FDA approved the use of the anti-cancer drug Rituxan (rituximab) in combination with the chemotherapy drugs Fludara (fludarabine) and Cytoxan (cyclophosphamide) for first-line treatment of CLL. Another FDA-approved drug, Treanda (bendamustine hydrochloride), has shown effectiveness in treating CLL when administered once every 4 weeks, like other chemotherapies (Wu et al. 2012).

1.6 Cicatricial Alopecias

Cicatricial alopecias, also known as scarring alopecia, alopecia cicatrisata, and scarring hair loss, are a type of hair loss disease characterised by hair follicle destruction and replacement with scar tissue. This results in permanent hair loss and the inability of hair to regrow in affected areas (Price and Mirmirani 2011).

1.6.1 Signs and Symptoms

The scalp may display symptoms such as redness, scaling, altered pigmentation, pustules, or draining sinuses in areas affected by cicatricial alopecia. However, some cases may exhibit minimal signs of inflammation. The underlying cause of the condition is inflammation, which kills the hair follicle and leaves the scalp completely hairless and devoid of the regular pore marks (Beers et al. 2006). In the active stage of the disease, follicle destruction is predominantly caused by inflammatory cells, and this information is used to classify the cicatricial alopecias. In lichen planopilaris, frontofacial fibrosing alopecia, central centrifugal alopecia, pseudopelade (Brocq), and lymphocytic inflammation predominate. Tufted folliculitis and folliculitis decalvans are both caused by neutrophilic inflammation. Changes from a neutrophilic to a lymphocytic inflammatory response may occur. Mixed inflammatory infiltrates are seen in cicatricial alopecias such as dissecting cellulitis and folliculitis keloidalis (Bergfeld and Elston 2003).

1.6.2 Causes

Unfortunately, it has yet to be determined what causes the various forms of cicatricial alopecia. However, the inflammation responsible for cicatricial alopecia always manifests itself at the hair follicle's apex, just where the stem cells and sebaceous gland reside. Damage to the hair follicle's stem cells and sebaceous gland by inflammation precludes any possibility of regrowth. Alopecia caused by scarring is not communicable, so do not worry about spreading it (Wu et al. 2008). Primary cicatricial alopecia is rare in youngsters, although it may afflict healthy men and women of any age. These alopecias are seen all over, although there is no data regarding

their prevalence from epidemiological investigations. The scarring hair loss caused by scar tissue is severe. Few families have been found to have more than one member affected by cicatricial alopecia; however, this is not the case for the vast majority of sufferers. Central centrifugal alopecia is most common in women of African heritage, and it may afflict many members of the same family (Blackwell and Rawnsley 2008).

1.6.3 Diagnosis

Cicatricial alopecia is first identified by a biopsy of the scalp. The diagnosis, evaluation, and treatment of cicatricial alopecia depend on the results of a scalp biopsy, which may provide information about the kind of inflammation, its location and severity, and other alterations to the scalp. After numbing the region, a biopsy punch is used to extract a tiny piece of skin (about the size of a rubber) for analysis. After horizontal and vertical sectioning of the skin samples, a biopsy or two are typically collected for analysis (Ochoa et al. 2008). In addition to the biopsy, a thorough clinical examination of the scalp is required. Inflammation is often characterised by the appearance of symptoms like itching, burning, pain, or soreness. Redness, scaling, and pustules on the scalp are all symptoms of inflammation. However, in certain situations, inflammation is still present while showing little outward symptoms or indications, and this is only revealed by a scalp biopsy. In addition to the results of the biopsy, the dermatologist considers the pattern and severity of hair loss in order to identify the exact kind of cicatricial alopecia that is present (Whiting 2001).

1.6.4 Treatment

Neutrophilic cicatricial alopecias, such as folliculitis decalvans and tufted folliculitis, are treated with antibiotics such as clindamycin, rifampicin, and doxycycline. If the patient does not respond to antibiotics, isotretinoin or oral prednisone may be used. It is important to note that cicatricial alopecias are chronic diseases and treatment is not always effective. It is essential for patients to maintain ongoing communication with their dermatologist and to follow the treatment plan as directed. In some cases, a combination of treatments may be necessary to achieve the best results. Early diagnosis and treatment can help prevent further hair loss and potentially improve hair regrowth (Olsen 2005).

1.7 Encephalocele

The birth defect encephalocele causes brain tissue to protrude through a skull defect. Birth defects of the brain and spinal cord result from an improper closure of the neural tube during embryonic development. As a result, the brain tissue protrudes

out of the skull and is covered by a sac-like membrane. Other names are cephalocele, craniocele, and cranium bifidum (Al-Tubaikh and Reiser 2009).

1.7.1 Signs and Symptoms

The symptoms of encephalocele, a birth defect in which brain tissue protrudes through a hole in the skull, vary according to a number of circumstances. When considering clinical implications for therapy and prognosis, the location of the encephalocele is a key consideration. Because they do not include brain tissue, anterior encephaloceles have a better prognosis than their posterior counterparts, which are often linked to neurological issues. Therefore, the location of the encephalocele is essential in assessing the severity of the condition and determining appropriate treatment. Most encephaloceles originate in the top part of the skull and expand back towards the occipital bone from the front of the head. The base of the skull, the sinuses, the forehead, and the nose are all potential sites for encephaloceles. The location of the encephalocele can impact the severity of symptoms and treatment options, so it is important to identify the location of the encephalocele for proper diagnosis and management (Mahapatra 2007).

1.7.2 Causes

The majority of cases of encephalocele arise for basically no reason in particular. Genetic and environmental variables are both speculated to have a role in the onset of encephalocele. There is a genetic susceptibility for encephalocele among people who have a history of other neural tube disorders, such as spina bifida or anencephaly, in their families. Carrying one or more disease-causing genes does not always indicate that the condition will manifest in a person. Therefore, encephalocele may arise as a result of a combination of hereditary and environmental causes. Researchers have shown that the prevalence of encephaloceles varies by gender and geographical area. Encephaloceles are more common in females than men, and they tend to occur in the occipital region of the skull in females but the front of the head in males. In addition, encephaloceles are often seen in the occipital area of the skull in Western people but the front of the head in Southeast Asian groups. The necessity of taking demographic parameters into account while analysing encephalocele cases is highlighted by these discrepancies, which may be attributable to genetic, environmental, or other reasons (Moore et al. 1997).

1.7.3 Diagnosis

Encephaloceles are typically diagnosed either during a routine prenatal ultrasound or immediately after birth. However, small encephaloceles near the nose or forehead may not be detected at first. Encephaloceles can be identified as cysts on prenatal

ultrasound scans because reflected sound waves are used to construct pictures of the growing fetus. Prenatal detection of an encephalocele may prompt evaluation for other abnormalities. In order to further assess the encephalocele and any related problems, prenatal care providers often employ magnetic resonance imaging (MRI) (Stoll et al. 2011).

1.7.4 Treatment

Children with encephalocele typically require surgical intervention, which is usually performed within the first 4 months of life, depending on factors such as the size and location of the encephalocele, any associated complications, and whether the encephalocele is covered by a thin layer of skin. Assuming that a protective skin layer is already in place, surgery may be delayed for several months. However, if the encephalocele is not protected by a layer of skin, surgery may be necessary shortly after birth (De Wals et al. 2007). During surgery, the protruding brain tissue is carefully placed back inside the skull. This is achieved through a craniotomy, in which a portion of the skull is cut and removed to allow contact with the brain. The neurosurgeon next makes an incision into the dura mater, the brain's protective outer barrier, to reach the encephalocele and correct any underlying problems. Encephalocele therapy must be individualised based on the patient's unique set of symptoms and anomalies. Surgical correction may be required in situations of craniofacial or other cranial anomalies. In addition, a shunt may be surgically implanted to treat hydrocephalus, a disorder characterised by an abnormal buildup of cerebrospinal fluid in the brain. This allows for the excess fluid to be drained and redirected to another part of the body, typically the abdominal cavity, where it can be reabsorbed by the body. The specific treatment approach will vary based on the individual case and the nature and severity of the associated conditions (Siffel et al. 2003).

1.7.4.1 Adrenoleukodystrophy

This is a rare hereditary condition affecting the adrenal glands and nerve system, sometimes known as adrenoleukodystrophy (ALD). Very-long-chain fatty acids (VLCFAs) build up in the body due to a mutation in the ABCD1 gene. Although both sexes are equally susceptible to ALD, men are disproportionately affected. Age of start and illness severity both have a role in how ALD manifests itself. The most severe type occurs in males between the ages of 4 and 10 and is called childhood cerebral form. Cognitive impairment, behavioural abnormalities, and loss of muscular control are all possible outcomes of this variant of the disease's fast progression. Although there is presently no cure for ALD, there are therapies that can alleviate its symptoms. Haematopoietic stem cell transplantation (HSCT) is an effective therapy that, when performed early on, can prevent the course of the illness (Moser and Raymond 2007).

Research into the pathogenesis and treatment of ALD is ongoing. The impact of very-long-chain fatty acids (VLCFAs) on disease progression has been the subject

of recent research and on the use of gene therapy as a potential treatment option. One study, published in the journal *Neurotherapeutics*, investigated the use of gene therapy to correct the genetic defect responsible for ALD. The study used a viral vector to deliver a corrected version of the ABCD1 gene to cells from patients with ALD. The results showed that the corrected gene was able to produce functional proteins and reduce the accumulation of VLCFAs in the cells. The researchers concluded that gene therapy could be a promising treatment option for ALD in the future (Eichler and Aubourg 2006).

Another study, published in the journal *Brain*, investigated the use of a drug called Lorenzo's oil. In Lorenzo's oil, a combination of two fatty acids is used in the treatment of ALD that has been shown to reduce the levels of VLCFAs in the blood. In children with the cerebral type of ALD, Lorenzo's oil was shown to stabilise the illness, according to the study, but it did not reverse the neurological damage that had already occurred. In conclusion, ALD is a rare genetic disorder that can cause severe neurological symptoms. However, there are medicines that can alleviate symptoms and reduce the disease's course, so it is not hopeless just yet. Ongoing research into pathogenesis and treatment of ALD is providing new insights into the disease and offering hope for future treatments (Cartier and Aubourg 2018; Engelen et al. 2012).

1.7.4.2 Ehlers-Danlos Syndrome

Hypermobility of the joints, skin that is both flexible and brittle, and easy bruising are just some of the symptoms of Ehlers-Danlos syndrome (EDS), a collection of hereditary illnesses that affect the connective tissues in the body. There are currently 13 subtypes of EDS, each resulting from a unique set of gene mutations that alter collagen synthesis and structure. In recent years, there has been growing interest in EDS among medical researchers, as advances in genetics have allowed for a better understanding of the underlying causes of the disorder. This has led to improved diagnostic criteria and development of new treatments and therapies for patients with EDS.

One of the key challenges in studying EDS is the wide range of symptoms that can occur, which can make diagnosis difficult. In addition, there is often overlap between different subtypes of the disorder, which can further complicate diagnosis and treatment. Despite these challenges, significant progress has been made in understanding the molecular and genetic basis of EDS, which has led to the development of new diagnostic tools and potential treatments. For example, recent research has focused on the role of specific collagen genes in EDS and identified potential targets for drug therapies that could help alleviate symptoms and improve quality of life for patients. As research on EDS continues to advance, it is likely that new insights into the disorder will emerge, leading to further improvements in diagnosis and treatment. With increased awareness and understanding of the disorder, patients with EDS can receive better care and support and ultimately live healthier, more fulfilling lives (Malfait et al. 2017).