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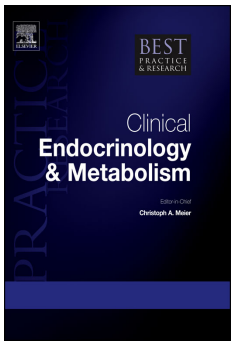

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Sclerosing bone dysplasias

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Abstract

The group of sclerosing bone dysplasia's is a clinically and genetically heterogeneous group of rare bone disorders which, according to the latest Nosology and classification of genetic skeletal disorders (2015), can be subdivided in three subgroups; the neonatal osteosclerotic dysplasias, the osteopetroses and related disorders and the other sclerosing bone disorders. Here, we give an overview of the most important radiographic and clinical symptoms, the underlying genetic defect and potential treatment options of the different sclerosing dysplasias included in these subgroups.

Keywords: osteopetrosis, hyperostosis, bone density, differential diagnosis, sclerosing bone disorders

Introduction

Bone mass is a quantitative trait that can most easily be assessed by bone mineral density (BMD) measurements using dual-energy X-ray absorptiometry or DXA scanning. Bone mass varies throughout life resulting in a peak bone mass around the age of 25 followed by a decline over time (1). In addition to that, there is a lot of inter-individual variation. The most common clinical condition associated with an abnormal bone mass is osteoporosis, diagnosed in an individual reaching a BMD level of more than 2.5 standard deviations below the median peak bone mass (2). The major risk factor for osteoporosis is age because of the decline in BMD in the elderly, but in addition to that a lot of environmental factors do have an effect. These include exercise, calcium and Vitamin D intake can have a positive effect, while others such as smoking, alcohol use and some medications result in a decline of BMD and consequently an increased risk for osteoporosis (3).

In addition to the environmental factors, it has become clear that also the genetic background of an individual has a major influence on BMD and the risk for osteoporotic fractures. Genome-wide genetic association studies in very extended cohorts identified currently already more than 300 common genetic variants in the human genome that influence BMD (4,5). However, the effect size of all these variants is very small as all together they explain only about 30% of the genetic variation in BMD (4).

A more dramatic effect of genetic variations is encountered in rare, monogenic diseases characterized by an abnormal bone mass. In these, one mutation in a specific gene explains almost completely the clinical and radiological observations of such a condition. In the context of BMD and osteoporosis, a lot of attention has gone into the group of so-called sclerosing bone dysplasias. This is a heterogeneous group of rare monogenic diseases characterized by a significantly increased bone mass resulting in a broad range of secondary clinical complications. Genetic research on these conditions resulted in the identification of a number of disease causing genes and a broad set of pathogenic mechanisms as illustrated in Figure 1.

In the latest report of the “Working group on the classification and nomenclature of skeletal dysplasias”, the diseases with an increased bone mass are subdivided in three categories. Group 22

includes neonatal osteosclerotic dysplasias, group 23 the osteopetroses and related disorders and finally group 24 representing the other sclerosing bone disorders (6).

In this review, we will discuss the genetic, clinical and radiological aspects of these conditions with special attention to potential treatments if available (Table 1-3).

Group 22: neonatal osteosclerotic dysplasias

The group of neonatal osteosclerotic dysplasias includes rare, severe disorders (Table 1) marked by hyperostosis or osteosclerosis accompanied by several other clinical features.

Blomstrand dysplasia

Blomstrand dysplasia is a rare lethal osteochondrodysplasia that was first described in 1985 by Blomstrand (7). The disorder is inherited in an autosomal recessive manner and is characterized by advanced skeletal maturation, osteosclerosis, short limbs, dwarfism and perinatal lethality. In 1999, Karperien et al. reported that the phenotype of type I PTH/PTH-related peptide (PTHrP) receptor (PTHR1)-ablated mice (8) highly resembles that of Blomstrand dysplasia patients. Subsequently, sequence analysis demonstrated that bi-allelic inactivating mutations in *PTHrP* result in accelerated chondrocyte differentiation which is the underlying mechanism underlying Blomstrand dysplasia (9). Complete loss of PTHR1 function results in severe type 1 Blomstrand dysplasia while partial loss of PTHR1 function results in the less severe type 2 Blomstrand dysplasia (10).

Caffey disease

Caffey disease or infantile cortical hyperostosis is a rare skeletal disorder that affects various skeletal bones as well as the adjacent tissues (11). The disorder can occur both in an infantile and a prenatal lethal form. The infantile form is usually self-limiting and of variable penetrance. It is reported that during adolescence, a relapse of cortical hyperostosis can occur (12). The cortical thickening (hyperostosis) can be found in single or multiple bones. Most often the asymmetric lesions are found in the mandible, clavicle, scapula, skull, ilium and long bones (11). Genetic studies have shown that

infantile Caffey disease is inherited in an autosomal dominant manner and caused by a specific heterozygous missense mutation (p.Argthe *COL1A1* gene which encodes the Collagen alpha-1(I) chain (COL1A1), an important building block of connective tissues and bone (13). Mutations in *COL1A1* were previously also shown to cause osteogenesis imperfecta, a monogenic bone dysplasia marked by skeletal deformities and increased bone fragility (14).

Raine dysplasia

Another rare neonatal osteosclerotic dysplasia is Raine dysplasia, an autosomal recessive disorder that in most cases is fatal within the first weeks of life. However, some patients are reported to survive into childhood or even adulthood. Raine syndrome is characterized by generalized osteosclerosis and typical facial features including midface hypoplasia, hypoplastic nose, exophthalmos and low set ears. In addition, amelogenesis imperfecta is recently reported to be an important clinical feature of non-lethal Raine dysplasia as well as mild hypophosphatemia (15,16). Amelogenesis imperfecta (AI) is a disorder affecting both the structure and the enamel of the teeth (17) and can occur independent or as part of a syndrome such as e.g. Raine dysplasia. Other syndromes marked by AI are tricho-dento-osseous syndrome (MIM 190320), Jalili syndrome (MIM 217080), Heimler syndrome (MIM 234580), Kohlschutter-Tonz syndrome (MIM 226750) and enamel-renal syndrome (MIM 204690). Elalaoui and colleagues recently described these syndromes as possible differential diagnosis for Raine dysplasia (15). Based on their findings they suggested to screen more patients with AI for loss-of-function mutations in *FAM20C*, alternatively called *dentin matrix protein 4*, the genetic cause for Raine dysplasia (15,18). In addition, Whyte and colleagues recently also identified bi-allelic mutations in *FAM20C* in a family diagnosed with sclerosing osteomalacia with cerebral calcification (MIM 259660) (19). Based on the clinical overlap between Raine syndrome and sclerosing osteomalacia with cerebral calcification it is most likely the same condition. *FAM20C* expression is most pronounced in odontoblasts, ameloblasts, cementoblasts, osteoblasts and osteocytes (20). It encodes a Golgi casein kinase that is involved in the phosphorylation of secretory calcium-binding phosphoprotein members such as for example, dentin

matrix protein 1 (DMP1), osteopontin (OPN), matrix extracellular phosphoglycoprotein (MEPE) and bone sialoprotein (BSP). The contribution of these proteins to mineralization is complex, however, it has been reported that abnormal phosphorylation of these proteins is involved in the aberrant mineralization observed in Raine syndrome (21-23).

Group 23: the osteopetroses and related disorders

The osteopetroses comprise a group of conditions that are clinically and radiologically very heterogeneous. However, they share a common pathogenic mechanism caused by impaired bone resorption by osteoclasts which are multinucleated cells of hematopoietic origin (24). They are classified based on inheritance, severity, age of onset, and secondary clinical features (25). The histological hallmark of these conditions are remnants of unresorbed cartilage in mature bone tissue. The latter also explains the reduced strength of bones resulting in an increased fracture rate (26). Recently, also the number of osteoclasts has become an important discriminator between different forms as the impaired bone resorption can be present for two different reasons. First, the differentiation from hematopoietic stem cells to fully differentiated, multinuclear osteoclasts can be disturbed, obviously resulting in an osteoclast-poor form of osteopetrosis. Secondly, in some forms the osteoclastogenesis is not defective but the functioning of the differentiated osteoclast is disturbed. In most cases, this relates to an impaired process of acidification of the extracellular compartment between the osteoclast and the bone tissue as an acidic environment with a pH of about 4 is essential for bone resorption (25,27,28).

Over the last decennium, a lot of genes have been identified underlying the osteopetroses both mice but also in humans. These novel insights contributed a lot to the current understandings of the mechanisms of bone resorption. Furthermore, it also makes it possible to identify the precise molecular genetic defect in a patient diagnosed with osteopetrosis which in many cases has a major impact both on the prognosis and on the treatment of the patient (25).

In table 2 the different forms of osteopetrosis and their causative genes are listed. Most of the osteopetroses are inherited in an autosomal recessive mode of inheritance (ARO) and in general these are the most severe cases. The disease is mostly diagnosed soon after birth and fractures are common due to brittle sclerotic bones (28-30). Impairment of haematopoiesis often leads to extramedullary haematopoiesis and hepatosplenomegaly. Furthermore, it is often associated with neurological impairment due to narrowing of the foramina of the skull base (31). If untreated, children usually die in their first decade due to recurrent infections (31). As mentioned, in some cases the differentiation of osteoclasts is disturbed resulting in osteoclast-poor osteopetrosis (7). In those, not unexpectedly, some genes involved in Nuclear factor-κ B (NFκB) signalling are mutated as this is a key pathway for osteoclast differentiation. (31) First, loss of function mutations in the *TNFSF11* gene encoding the receptor activator of nuclear factor-kappa B (RANK) ligand (RANKL) result in severe ARO (32). In other cases, mutations in the *TNFRSF11A* gene encoding its receptor RANK are described (33). In the latter, the mutations result in a loss of function of the receptor, in contrast to activating mutations in the same gene that were reported in conditions with increased bone turnover including familial expansile osteolysis and early onset Paget's disease of bone. Finally, an X-linked form of osteopetrosis was linked with hypomorphic mutations in the nuclear factor-κ B essential modulator (NEMO) (34), an upstream signalling protein of NFκB. In these patients, osteopetrosis is associated with ectodermal dysplasia and an immune defect.

In other forms a normal or even increased number of osteoclasts is present. This suggests that the differentiation is not disturbed but rather the resorption capacity of differentiated osteoclasts. Several of the genes identified do play a role in the intracellular generation of protons and their transport over the plasma membrane into the extracellular compartment where bone resorption takes place. It starts with loss of function mutations in the carbonic anhydrase II (*CAII*) gene (35) underlying a severe, autosomal recessive osteopetrosis associated with renal tubular acidosis and cerebral calcifications (36). This enzyme is essential in generating protons within the osteoclast. About half of the patients have a loss of function mutation in the *TCIRG1* gene encoding a subunit of

the vacuolar H^+-ATPase (V-ATPase) proton pump essential for translocating protons into the resorption lacuna (37). More recently, mutations in the *Sortin Nexin 10* (*SNX10*) gene were identified in ARO patients showing hepatosplenomegaly, failure to thrive macrocephaly, but with normal neurocognitive development (38). These include cases of "Västerbottenian osteopetrosis," as a high incidence of this disease was found in this Swedish Province (39). SNX10 co-immunoprecipitates with V-ATPase and regulates its intracellular trafficking suggesting a shared pathogenic mechanism (40).

By transporting protons over the membrane, a potential is generated which should be compensated for. Electro neutrality is maintained by the chloride channel ClCN7. Loss of function in the gene encoding this protein also result in severe recessive forms of osteopetrosis. Linked to that, deficiency in OSTM1, an essential β-subunit for ClCN7 result in a similar, very severe form of recessive osteopetrosis. (41-44). In contrast to mutations in *TCIRG1*, mutations in *CLCN7* or *OSTM1* results also in retinal atrophy and neurodegeneration (31).

Autosomal dominant osteopetrosis (ADO) or Albers-Schönberg disease has a prevalence of 5,5:100 000 (45). Radiologically, the patients display a generalized osteosclerosis, mainly at the vertebral endplates resulting in a so-called Rugger-Jersey spine. Also the skull base and the iliac wings are sclerotic and bone-in-bone structures can be seen radiologically (46). Patients with ADO have also an increased fracture risk of the femur, the long tubular bones and the arches of the vertebrae (47). Other clinical features are cranial nerve involvement, osteomyelitis of the mandible and anaemia with extramedullary haematopoiesis while neurological signs are not common (47). Interestingly, this form of osteopetrosis is also caused by mutations in the *ClCN7* gene, more precisely some specific heterozygous missense mutations that result in a dominant negative effect on the homodimeric CLCN7 protein (42,48,49).

Finally, some rare forms of intermediate autosomal recessive osteopetrosis (IARO) are reported. They are in general associated with short stature, dental problems, osteomyelitis, and high fracture risk (25). In some cases, missense *ClCN7* mutations are reported that only mildly reduce Cl^-

conductance (50). In a few others, mutations in the *PLEKHM1* gene were shown to underlie this type of osteopetrosis (51). The clinical outcome in the reported family was mild with the oldest patient showing Erlenmeyer flask deformities of the distal femora and chondrolysis of a hip. Her younger brother does not have clinical features. The function of the PLEKHM1 protein has been suggested to be in osteoclast vesicular transport and autophagy (51,52).

Especially for the severe forms of ARO treatment is recommended trying to avoid early death. For these, hematopoietic stem cell transplantation (HSCT) represents a possible cure despite the fact that this remains a risky procedure. Furthermore, this can only be helpful in case the defect is intrinsic to the osteoclast, being of hematopoietic origin. Furthermore, it can only rescue the osteoclast related problems but not the neurological problems as seen in some forms of ARO.

Recently, an Osteoporosis Working Group was established (53) to write some consensus guidelines for the diagnosis and management of the different forms of osteopetrosis and these can be summarized as follows:

- The diagnosis of osteopetrosis should be based on a skeletal radiographic survey.
- In order to confirm the precise form of osteopetrosis, genetic testing should be performed. This implies either the use of a gene panel including the different genes causative for osteopetrosis or screening of the complete exome. In the latter, uncomplete coverage for some genes might prevent the identification of the causative mutation.
- Hematopoietic stem cell transplantation (HSCT) is a recommended treatment but only for a subset of the most severe forms of osteopetrosis. Patients with RANKL deficiency will not benefit as this protein is not produced by osteoclast but by cells of mesenchymal origin. Mutations in *OSTM1* result in patients with severe involvement of the central nervous system causing early death. Therefore, only solving the bone problem by HSCT will not implicate enough benefit to consider HCT. Along the same lines, some mutations in *CLCN7* also have a pleiotropic effect which can only be partially rescued by HSCT.

- In the absence of an effective treatment for cases where HSCT is not recommended, supportive treatment of symptoms should be offered.

Currently efforts are ongoing to develop novel approaches including gene and cell therapies or small interfering RNA's (54). They could be very important for those forms for which currently no specific treatments are available or for others to avoid the dangerous procedures of HSCT.

Pycnodysostosis

This autosomal recessive condition is also caused by an impaired bone resorption but, in contrast to the osteopetroses, it is not due to a disturbed acidification of the microenvironment of the resorption area but rather an impaired degradation of the organic matrix of bone. (55) It is caused by a deficiency for Cathepsin K (CTSK), a lysosomal cysteine protease essential for the degradation of collagen type 1 fibres at a low pH(56,57) (58-61). The osteoclasts are able to demineralise the matrix underneath the ruffled border (62) but collagen degradation does not occur, resulting in short stature, clavicular dysplasia, short terminal phalanges, dolichocephaly, delayed closure of the anterior fontanel, obtuse angle of mandible, and general increased bone density and fragility (63). No specific treatment is available.

Osteopoikilosis and Buschke–Ollendorff syndrome

Osteopoikilosis has a very specific and easy recognisable radiographic picture as it is characterized by spots with increased bone density within the skeleton. Because of that it is also known as spotted bone disease or osteopathia condensans disseminate. It presents with an autosomal dominant mode of inheritance. In most cases it is asymptomatic and diagnosed after radiography. However, a small subset of patients (15-20%) suffer from joint pain and effusion (64-66). In some other cases, the bone phenotype is accompanied by connective tissue nevi and on these occasions it is called Buschke–Ollendorff syndrome (BOS) (67). The molecular defect underlying osteopoikilosis and BOS has been identified, being, heterozygous loss of function mutations in the *LEM domain-containing protein 3*

(*LEMD3*) gene. LEMD3 is a nuclear membrane protein that was shown to inhibit the TGFβ and BMP signalling pathways by binding to SMAD proteins (66,68).

Melorheostosis

The name Melorheostosis, Greek for "drippling candle wax" is used for a very rare bone dysplasia characterized by unilateral lesions of the long bones character. It involves hyperostosis of the cortical bone and sclerosis of the adjacent soft tissue. This might result in chronic pain, contractures, limb deformities and joint stiffness. Treatment to relief pain is often needed and exceptionally amputation of affected limbs is performed. Although it seems to have a somewhat increased prevalence in families with osteopoikilosis, in most cases it is sporadic. Partially based on the asymmetric presentation, it was suggested to be caused by a somatic mutation (69). Whyte et al suggested that melorheostosis in a 14 year old boy, who also has osteopoikilosis due to a mutation in *LEMD3*, was caused by postzygotic mosaicism for a mutated KRAS proto-oncogene GTPase (KRAS) (70). However, this was not confirmed in other cases and most recently somatic mutations in affected bone tissue of 8 of the 15 patients were found in the *MAP2K1* gene (71). MAP2K1 produces the protein MEK1 and has previously been linked to some types of cancerous growths as well as to conditions characterized by abnormal blood vessel formation in the head, face or neck. Further studies are needed to confirm these findings and to unravel the molecular defect in cases where no mutation was found (71).

Osteopathia striata with cranial sclerosis

Osteopathia striata with cranial sclerosis (OSCS) is characterised by dense linear striations in the diaphysis and metaphysis of the long bones and pelvis and is also accompanied by cranial sclerosis (72,73). Furthermore, macrocephaly, broad nasal bridge, frontal bossing, ocular hypertelorism, hearing loss and palate abnormalities are often reported. In a subset of patients, cardiac malformation and mental retardation are described (74-76). Loss-of-function mutations in *FAM123B* or complete deletion of *FAM123B* have been identified as the cause of the disease. As this gene, also known as *AMER1* (APC Membrane Recruitment Protein 1), is located on the X-chromosome is

segregates in an X-linked dominant. Furthermore, it is often lethal in affected males due to severe heart defects and/or gastrointestinal malformations. *FAM123B*, encodes for WTX (Wilms tumor on the X chromosome) a repressor of the canonical WNT signalling activity by increasing ubiquitination and degradation of β-catenin, the downstream mediator of canonical WNT signalling activity (75,77). As canonical WNT signalling was shown to be an essential pathway for bone formation, the loss-of-function mutations in WTX and consequently β-catenin accumulation in the cytoplasm and translocates to the nucleus explains the striations due to excessive bone formation (78).

Dysosteosclerosis

Dysosteosclerosis (DOS) is an autosomal recessive bone disease characterized by irregular osteosclerosis and platyspondyly. Patients are in general short with increased risk to fracture. The calvaria and skull base are sclerotic resulting in secondary effects by cranial nerve compression. *Solute carrier family 29, member 3* (*SLC29A3*) mutations have been reported as being causal in two DOS families (79). Recently, another patient showed a bi-allelic mutation in the splice donor site of intron 6 of *TNFRSF11A* encoding the RANK receptor suggesting genetic heterogeneity for this condition (80).

Group 24: other sclerosing bone disorders

The group of other sclerosing bone disorders includes several rare sclerosing bone dysplasias caused by increased bone formation or altered bone remodelling. In this group, several disorders (sclerosteosis, Van Buchem disease, Pyle disease and craniodiaphyseal dysplasia) are included that are caused by mutation in genes of the WNT signalling pathway, indicating that this pathway is important for bone formation. In addition, in several disorders osteosclerosis is affecting the skull as well as the tubular bone bones.

Sclerosteosis and Van Buchem disease

Sclerosteosis and Van Buchem disease (VBCH) are two very similar, rare, and progressive sclerosing bone disorders marked by hyperostosis most severely affecting the skull, mandible and tubular bones (81,82). The increased bone mass of the skull often results in cranial nerve compression which leads to hearing loss and facial palsy and in increased intracranial pressure which causes severe headaches, eventually accompanied by visual impairment, dizziness or even sudden death. In general, sclerosteosis patients are more severely affected compared to VBCH patients and in addition to the above described symptoms, they also often display syndactyly and tall stature (81,82).

Both disorders are inherited in an autosomal recessive manner and we and others demonstrated that sclerostin deficiency underlies the development of the disease. In patients with sclerosteosis, loss-of-function mutations in *SOST*, encoding sclerostin, are found, while VBCH disease is caused by a 52 kb deletion, 35 kb downstream of *SOST* (83-85). The deletion contains an enhancer region that is important for the expression of sclerostin in bone and deletion of this region results in severely reduced expression of sclerostin (82,83,86). Sclerostin is a secreted glycoprotein that can inhibit the canonical WNT signalling pathway by binding to the LRP5/6 co-receptor and in this way preventing WNT ligands from activating the LRP5/6 receptor which ultimately results in decreased bone formation (87). Besides LRP5/6, sclerostin can also bind to the LRP4 receptors and recently, we and others demonstrated that this interaction is important for the inhibitory action of sclerostin (88,89). Furthermore, we demonstrated that hypomorphic mutations in LRP4 can also cause sclerosteosis. So far, we identified three mutations that are all located in the third β-propeller domain of LRP4 and result in an impaired LRP4-sclerostin binding (88,89). The patients with mutations in LRP4 have similar radiological, biochemical and clinical features as patients with loss-of-function mutations in *SOST*, except for the elevated serum sclerostin levels which indicate that sclerostin and LRP4 interact to keep sclerostin in the bone tissue hereby regulating bone formation (88).

Due to the almost limited expression of sclerostin by osteocytes, targeting sclerostin with antibodies is considered an important mechanism for the treatment of osteoporosis (90-92). In contrast, no therapy is currently available for Sclerosteosis or VBCH disease patients. Based on the pathogenic mechanism described above, treatment with sclerostin is a potential therapeutic strategy to inhibit the bone formation in patients with sclerosteosis or VBCH disease caused by sclerostin deficiency. Before sclerostin administration can be used as a therapeutic strategy, additional studies are needed to investigate the ability of administrated sclerostin to reach the bone cells and regulate bone formation. However, the fact that VBCH disease patients have a very low sclerostin expression and a milder phenotype compared to Sclerosteosis patients, strengthens the hypothesis that sclerostin administration can slow down the bone formation in these patients. Although sclerostin administration seems to be a valuable strategy for treatment of patients with sclerostin deficiency, it cannot be used for patients with genetic defects in *LRP4*. For these patients, other therapeutic strategies need to be searched for. To do this, the role of LRP4 in the regulation of bone formation needs to be further elucidated.

Craniodiaphyseal dysplasia

Craniodiaphyseal dysplasia (CDD) is a very rare autosomal dominant inherited disorder marked by hyperostosis of the cranial and facial bones. As a result of the progressive overgrowth of the cranial and facial bones, patients have severe facial distortions also referred to as “leontiasis ossea” and choanal stenosis (93). Furthermore, similar as reported for sclerosteosis and VBCH disease hyperostosis of the skull often results in facial palsy, deafness and visual impairment. In contrast to the hyperostosis of the cranial and facial bones, the cortex of the long bones is rather thin and the bones are expanded. Genetic studies have shown that a heterozygous mutation in the signal peptide of sclerostin is underlying the phenotype in at least two patients with CDD. The mutations result in a decreased expression of sclerostin in these patients, possibly via a negative feedback mechanism (94). Similar as reported for sclerosteosis and VBCH disease, administration of recombinant sclerostin is a possible therapeutic strategy for the treatment of CDD that deserves some further investigation.

Pyle disease

Pyle disease is a rare metaphyseal dysplasia that is inherited in an autosomal recessive manner and was first described in 1931. The long bones show thinning of the cortical bone and wide and expanded trabecular metaphysis (Erlenmeyer flask appearance) which result in increased bone fragility. In addition, patients with Pyle disease have platyspondyly and widened ribs and collarbones (95,96). Recently, homozygous loss-of-function mutations in the gene encoding secreted *Frizzled related protein 4 (sFRP4)* were shown to be disease causing in patients with Pyle's disease (97,98). sFRP4 is an extracellular modulator of the WNT signalling pathway which can modulate the pathway by binding to WNT ligands. In this way sFRP4 not only modulates the canonical WNT signalling activity but also the non-canonical WNT signalling activity (87). Additional evidence that loss-of-function mutations in sFRP4 are the underlying cause of Pyle's disease is provided by a mouse model lacking *sfrp4*. These mice have an increased trabecular bone mass as well as thin cortical bone, similar as seen in patients with Pyle disease (99). A possible differential diagnosis for Pyle disease is metaphyseal dysplasia, Braun-Tinschert type as it is also marked by long bones with an Erlenmeyer flask deformity, however, it is inherited in an autosomal dominant manner and has a varus deformity of the distal part of the radii (100). So far the genetic cause of the latter condition remains to be elucidated.

Craniometaphyseal dysplasia

In group 24 of the nosology of skeletal dysplasias, two different forms of craniometaphyseal dysplasia (CMD) are described, an autosomal dominantly and an autosomal recessivly inherited type (6). CMD is a rare progressive sclerosing bone disorder characterized by hyperostosis of the cranial and facial bones and metaphyseal widening of the long bones. Similar as previously reported, hyperostosis of the skull can cause facial palsy, deafness and blindness as a result of facial nerve compression. In addition, CMD patients have a wide nasal bridge and hypertelorism (101,102).

The autosomal dominantly inherited type of CMD is caused by mutations in the *ANKH Inorganic Pyrophosphate Transport Regulator (ANKH)* gene that encodes for a pyrophosphate (PPi) transporter that channels intracellular PPi into the extracellular matrix (103,104). *In vitro* and *in vivo* studies have shown that mutations and ANKH affect mineralization (105), osteoblastogenesis and osteoclastogenesis (106,107). The autosomal recessive form (MIM 218400) is caused by bi-allelic loss-of-function mutation in the gene encoding the gap junction protein connexin 43 (*GJA1*), the most abundantly expressed connexin. Connexins are important for the intracellular communication as they form gap junctions and hemichannels. Mice lacking functional connexin 43 in the osteoblasts display cortical thinning and increased bone marrow cavity area which is caused by abnormal osteoblast differentiation and an imbalanced bone remodelling (108-111). The phenotype of the mouse models highly resembles that of the human CMD phenotype. Currently, treatment of CMD patients is focussed on treatment of the symptoms and not on the underlying pathogenic mechanism. However recently, Chen and colleagues suggested based on their study using peripheral blood of CMD patients, that the use of isogenic human induced pluripotent stem cells (hiPSCs) has great potential in the treatment of bone dysplasias with osteoclast defects (106). Of course additional studies are needed to investigate the feasibility, efficacy and safety of such treatment.

Oculo-dento-osseous dysplasia

Oculo-dento-osseous dysplasia (ODOD) also referred to as oculodentodigital dysplasia is a rare dysplasia that can be inherited both in an autosomal dominant (MIM 164200) and recessive (MIM 257850) manner. The recessive form of ODOD is rarer and more severe (6). Patients with ODOD can show craniofacial bone defects around the eyes and the nose, microphthalmia, microcornea, syndactyly of the digits, skin disorders and loss of enamel. In addition there is a wide spectrum of other symptoms that is only reported in a subset of the patients such as conductive hearing loss, muscle weakness and other neurological manifestations (112,113). In both types of ODOD, mutations in the *GJA1* gene are the underlying genetic cause (114). So far, over 80 mutations in *GJA1* are reported and the majority of these are autosomal dominant missense mutations (113). As mentioned

previously, bi-allelic mutations in GJA1 are also found in patients with CMD. However, these patients do not display the characteristics tooth defects, syndactyly or ocular involvement which is normally found in ODOD patients (115). In contrast to the CMD causing mutation in *GJA1* which is located at the C-terminus of the protein that is important for the interaction with microtubuli and signalling molecules, mutations causing ODOD are located upstream of the C-terminus and are reported to affect channel functioning (116).

Diaphyseal dysplasia

Diaphyseal dysplasia or alternatively called Camurati-Engelmann disease (CED) is a progressive disorder characterized by generalized sclerosis, hyperostosis of the skull base and the thickening of the cortex of the tubular bones. In addition, patients suffer from bone pain and muscle weakness (117,118). More than 15 years ago, heterozygous gain-of-function mutations in the latency-associated protein (LAP) domain of the *transforming growth factor beta 1* (*TGFβ1*) gene were demonstrated to cause CED. TGFβ1 is a ligand of the TGFβ signalling pathway which is a known regulator of bone turnover (117,119). The LAP domain is important to keep TGFβ1 inactive in the bone matrix. As a result of the mutations, the release of active TGFβ1 from the bone during bone resorption is increased which results in abnormal bone remodelling and increased bone turnover (120).

Treatment of the patients is symptom based using corticosteroids and more recently also the effect of an angiotensin II type 1 receptor antagonist, losartan, was shown to have some positive effects on treating bone pain in CED patients (121). Losartan is reported to decrease the synthesis of TGFβ-1 and is used for the treatment of hypertension and Marfan syndrome (121). As CED is caused gain-of-function mutations in TGFβ-1, losartan is a promising therapeutic agent for the treatment of CED. However some conflicting results are published which indicates that additional research into the safety and efficacy of the treatment is needed (121-123).

Another type of diaphyseal dysplasia is Ghosal hematodiaphyseal dysplasia (GHDD) that in contrast to CED is inherited in an autosomal recessive manner (124). Furthermore, compared to CED whereby only the diaphysis are affected, the metaphysis are also affected in patients with GHDD. In addition to the skeletal phenotype, GHDD patients suffer from anaemia, leukopenia and thrombocytopenia (124,125). Genetic analysis demonstrated that GHDD is caused by bi-allelic loss-of-function mutations in the gene encoding thromboxane synthase (TXAS), namely *TBXAS1*. Furthermore *in vitro* studies have shown that TXAS can modulate the expression of *TNFSF11* and *TNFRSF11B* (encoding RANKL and osteoprotegerin (OPG), respectively) two important modulators of osteoclastogenesis which could explain the skeletal phenotype observed in the patients (126).

Juvenile Paget's disease of bone

In general, Paget's disease of bone is a focal, late onset disease caused by an initial increased of bone resorption followed by a compensatory increased bone formation, thus resulting in increased bone turnover. Disorganized bone tissue is formed with increased risks for fractures and deformities. The Juvenile form of this condition is more severe with an early onset and affecting the whole skeleton (127). Loss of function mutations are identified in the *TNFRSF11B* gene encoding osteoprotegerin (OPG), a decoy receptor for RANKL (128,129). As the latter is an essential protein for osteoclastogenesis and bone resorption, the loss of function mutations in *TNFRSF11B* resulting in a deficiency for OPG are characterized by increased bone resorption and turnover. Treatment with recombinant OPG resulted in suppression of bone resorption and radiographical improvement (130).

Trichodentoosseous syndrome

Trichodentoosseous (TDO) syndrome is a rare uncommon form of ectodermal dysplasia (131). TDO is inherited in an autosomal dominant manner and primarily affects the hair ("tricho"), teeth ("dento") and bone ("osseous"). Patients with TDO have kinky or curly hair and poorly developed tooth enamel and taurodontism. The skeletal phenotype of the patients shows increased density of the cranial, mandibular and/or long bones. Furthermore, some patients may also have abnormal thin, brittle

nails and craniosynostosis (132). The great phenotypic heterogeneity between patients makes the diagnosis of TDO somewhat difficult. The most reliable sign of TDO are the distinct dental defects which in combination with all other symptoms and genetic analysis are important for the diagnosis (131). Studies have shown that heterozygous mutations in the *Distal less homeobox 3 (DLX3)* gene are the cause of TDO (132-135). DLX3 is a member of the DLX/distalless family of homeobox genes which can regulate the transcription of target genes by binding to related DNA sequences. In mice, *Dlx3* expression was reported the surface ectoderm (including dental epithelium and hair follicles) as well as in craniofacial mesenchyme and osteogenic condensates (132). In addition, studies have demonstrated that due to the mutations in *DLX3,* there is delayed cellular senescence of bone mesenchymal stem cells (BMSCs) which results in increased bone formation explaining the increased bone mass observed in the patients (136). Currently, no specific treatment for patients with TDO is available.

Lenz-Majewski hyperostotic dysplasia

Lenz-Majewski hyperostotic dysplasia (LMD) is a very rare syndrome characterized by dwarfism, generalized osteosclerosis, failure to thrive, mental retardation, loose, wrinkled or atrophic skin, cutaneous syndactyly, and a craniofacial dysmorphism with large anterior fontanel, prominent forehead, hypertelorism, prominent mandible and large ears (137-140). Using whole exome sequencing, Sousa and colleagues identified in 2014, heterozygous missense mutations in *PTDSS1* in several patients diagnosed with LMD (Table 1) (139). The *PTDSS1* gene encodes for phosphatidylserine synthase 1 (PSS1) which is one of the two enzymes that is responsible for phosphatidylserine (PTDS) synthesis. Following studies have shown that phosphatidylserine synthesis was markedly increased in patient's fibroblast (139). In addition, in one of the patients hyperphosphoserinuria was reported (141). These findings indicate that LMS is caused by gain-of-function mutations in *PTDSS1* which result in increased PTDS biosynthesis (139,141). Furthermore, it is also shown that PTDS can stimulation the osteogenic differentiation of mesenchymal stem cells and consequently bone formation explaining the finding of osteosclerosis in LMD patients (142).

Conclusions

The group of sclerosing bone disorders are a heterogeneous group of rare skeletal dysplasias with overlapping phenotypical and radiographical characteristics. Consequently, making a diagnosis is often difficult. However, the correct diagnosis is important for patient care as it can give an indication on the prognosis and possible treatments. During the last decade, next generation sequencing is implement in both research and diagnostics labs which resulted in a significant progress in identifying the genetic cause underlying these disorders. In this way, identification of the underlying genetic cause largely contributes to the diagnostic process as well as to the development of suitable therapeutic strategies. Increased knowledge on the pathogenic mechanism and the function of the mutated genes in the regulation of bone metabolism is necessary for the development of suitable therapeutic agents as demonstrated in this review for osteopetrosis and Camurati-Engelmann disease for which innovative cellular therapies and losartan treatment, respectively, are currently studied. However, for most of the discussed sclerosing bone disorders, the treatment is so far limited to symptomatic treatments (Table 1-3).

Practice Points.

- Because of overlapping clinical and radiographic characteristics of sclerosing bone dysplasias, molecular analysis, by means of e.g. whole exome sequencing, is essential to confirm the diagnosis. Furthermore, in some cases the identification of the underlying gene defect has important implications for treatment and prognosis.

Research agenda.

- Identification of the novel genetic disease causing genes in patients with sclerosing bone disorders due to an unknown aetiology

- Additional functional studies elucidating the role of disease causing genes in bone metabolism
- Identification of novel drug targets for rare diseases based on the underlying genetic defect.

Tables

Table 1: Overview of conditions from group 22 including the neonatal osteosclerotic dysplasias

Disease	**Inheritance**	**Gene**	**Treatment in addition to symptomatic treatment**	**Clinical aspects**
Blomstrand dysplasia	AR	*PTHR1*		Perinatal lethality
Caffey disease	AD	*COL1A1*	Infantile form is self-limiting.	Infantile and prenatal lethal form
Raine dysplasia	AR	*FAM20C*		In most cases fatal within first weeks of life

Table 2: Overview of conditions from group 23 including the osteopetroses and related disorders

Disease	**Inheritance**	**Gene**	**Treatment in addition to symptomatic treatment**	**Clinical aspects**
Severe infantile form	AR	*TCIRG1*	HSCT	Represent 50% of infantile cases
Severe infantile form	AR	*ClCN7*	HSCT	primary neurodegeneration possible
Severe infantile form	AR	*OSTM1*		Includes primary neurodegeneration
Severe infantile form	AR	*SNX10*	HSCT	Also known as "Västerbottenian osteopetrosis"
Severe infantile form, osteoclast-poor	AR	*TNFSF11*	Recombinant RANKL administration is suggested as a possible treatment	
Severe infantile form, osteoclast-poor	AR	*TNFSF11A*	HSCT	
Osteopetrosis with renal tubular acidosis and cerebral calcifications	AR	*CAII*	HSCT	Neuronal involvement possible
Osteopetrosis with ectodermal dysplasia and immune defect	XR	*IKBKG (NEMO)*	HSCT	
Adult osteopetrosis	AD	*ClCN7*		Late onset, increased fracture rate

Intermediate osteopetrosis	AR	*ClCN7*		Depending on type of ClCN7 mutations a severe or milder phenotype is observed
Intermediate osteopetrosis	AR	*Plekhm1*		Chondrolysis at the hip has been reported
Pycnodysostosis	AR	*CTSK*		Clavicular dysplasia, open fontanel, short terminal phalanges
Osteopoikilosis/Buschke-Ollendorff syndrome	AD	*LEMD3*		Often asymptomatic
Melorheostosis	Somatic mutation	*MAP2K1*	In some cases amputation of affected limb has been performed	Asymmetric lesions, increased prevalence in osteopoikilosis families
Osteopathia striata with cranial sclerosis	XD	*FAM123B (WTX)*		Often foetal or neonatal lethality in males
Dysosteosclerosis	AR	*SLC29A3*		Expanded ends of the tubular bones and platyspondyly

Table 3: Overview of conditions from group 243 including the other sclerosing bone disorders

Disease	Inheritance	Gene	Treatment in addition to symptomatic treatment	Clinical aspects
Sclerosteosis	AR	*SOST* *LRP4*	Surgery aiming to reduce the severity of complications (craniectomy and nerve decompression). Recombinant sclerostin administration is suggested as a possible treatment for patients with *SOST* mutations	Progressive hyperostosis of the skull can result in headaches, facial palsy, deafness, blindness and sudden dead. Stabilization of the disease after the 3th decade, however, a substantial number of patients die before the age of 30 years (81).
Van Buchem disease	AR	*SOST*	Surgery aiming to reduce the severity of complications (craniectomy and nerve decompression). Recombinant sclerostin administration is suggested as a possible treatment	Progressive hyperostosis of the skull can result in headaches, facial palsy, deafness and blindness. Stabilization of the disease in adulthood (81).
Craniodiaphyseal dysplasia	AD	*SOST*	Surgery aiming to reduce the severity of complications (choanal dilatation, craniectomy and nerve decompression). Recombinant sclerostin administration is suggested as a possible treatment to slow down the progression of the disease	Progressive hyperostosis of the skull can result in facial deformities, headaches, facial palsy, deafness and blindness. Choanal stenosis can result in breathing difficulties. Early disease onset and oldest reported patient died at 16 years of age (94)
Pyle disease	AR	*sFRP4*		Increased fracture risk Benign course

Craniometaphyseal dysplasia	AD and AR	*ANKH* *GJA1*	Experimental treatment focussed on calcium homeostasis using calcitriol and low calcium diet is reported to improve facial paralysis and reduce the density of the skull in infancy (101)	Progressive hyperostosis of the skull can result in facial palsy, deafness and blindness. AR CMD is more severe and can be lethal due to an increase in intracranial pressure as a result of foramen magnum narrowing (143)
Oculo-dento-osseous dysplasia	AD	*GJA1*		
Camurati-Engelmann disease	AD	*TGFβ1*	Losartan (angiotensin II type 1 receptor antagonist) treatment under investigation to reduce pain.	Progressive hyperostosis of the skull can result in headaches, facial palsy, deafness and visual impairment
Ghosal hematodiaphyseal dysplasia	AR	*TBXAS1*		Anaemia, leukopenia and thrombocytopenia in combination with the skeletal phenotype
Juvenile Paget's	AR	*TNFRSF11B*	Treatment with recombinant OPG improved the observed phenotype (130)	Increased fracture risk and bone deformities Early onset, more severe compared to Paget's disease of bone
Trichodentoosseous syndrome	AD	*DLX3*		
Lenz-Majewski hyperostotic dysplasia	AD	*PTDSS1*		Most reported patients do not survive adulthood (144)

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Conflict of Interest

Eveline Boudin, and Wim Van Hul declare no conflict of interest

Legend of Figure

Figure 1: Graphical illustration of the function of some of the osteoclastic and osteoblastic proteins that are involved in sclerosing bone dysplasias.

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