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New diagnostic modalities and emerging treatments for neonatal bone disease.

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Review

Abstract
Bone disease in the neonatal period has often been regarded as an issue affecting premature infants, or a collection of rare and ultra-rare disorders that most neonatologists will see only once or twice each year, or possibly each decade. The emergence of targeted therapies for some of these rare disorders means that neonatologists may be faced with diagnostic dilemmas that need a rapid solution in order to access management options that did not previously exist.
The diagnostic modalities available to the neonatologist have not changed a great deal in recent years; blood tests and radiographs still form the mainstays with other techniques usually reserved for research studies, but rapid access to genomic testing is emergent. This paper provides an update around diagnosis and management of bone problems likely to present to the neonatologist.

Key words: fracture; alkaline phosphatase; dysplasia; osteogenesis imperfecta; mineralisation

Metabolic bone disease of prematurity

At birth, the transplacental supply of calcium and phosphate that has provided the mineral substrates for both hard tissue mineralisation and soft tissue growth ceases. Calcium falls rapidly, reaching a nadir around 24-48 hours of age,[1] provoking PTH production[2] with the physiological consequences listed below. In very sick infants, the fall in blood calcium levels can be greater and last for longer; maternal antenatal vitamin D deficiency may also be a factor in this situation.[3]

Renal phosphate excretion increases and fasting serum phosphate levels fall when PTH rises. Phosphate is required for the apoptosis of hypertrophic chondrocytes in the growth plate, as well as mineralisation of newly formed bone matrix.[4] Lack of phosphate leads both to persistence of hypertrophic chondrocytes and reduced ossification in the primary spongiosa, the new bone initially formed at the growth plate. Phosphate levels typically decline over the first two weeks of life but are hard to assess accurately due to the difficulty in obtaining fasting samples in orally-fed infants; non-fasting levels reflect recent phosphate intake.

The diagnosis of metabolic bone disease of prematurity, also known as osteopenia of prematurity, osteopathy of prematurity and preterm rickets, is often made on the basis of raised serum alkaline phosphatase. Alkaline phosphatase is present on the surface of bone-forming cells, osteoblasts, and on osteoblast-derived matrix vesicles found in areas of active new bone formation and mineralisation.[5] The role of alkaline phosphatase here is to remove the mineralisation inhibitor pyrophosphate (PPi) in order that newly formed mineral crystals that grow within and then rupture from matrix vesicles can seed into the calcium and phosphate-containing fluid that bathes the bone surface,[5] with further propagation of tissue mineralisation following. The level of alkaline phosphatase in the prematurely born infant may thus reflect the rate at which mineral crystals form, grow and disrupt the matrix vesicles releasing alkaline phosphatase into the circulation.

Rickets is characterised by the failure to mineralise newly formed bone. Alkaline phosphatase increases in every rachitic disorder with the exception of hypophosphatasia (see later). Thus in every rachitic disorder, the rate of mineral crystal release from matrix vesicles is increased, but without consequent increase in tissue mineralisation. Either the crystals are being destroyed, or there is insufficient mineral substrate available for the further propagation of bone matrix mineralisation.

In nutritional rickets in older children, lack of vitamin D results in reduced absorption of calcium from the gut. In response to falling serum calcium levels, parathyroid hormone (PTH) excretion increases and acts on osteoblasts to increase secretion of RANK-ligand, an activator of the cells that resorb bone, the osteoclasts.[6] Both calcium and phosphate are released from bone, with restoration of circulating calcium and avoidance of the neuromuscular consequences of hypocalcemia. PTH acts on the kidney to increase calcium resorption and also increases the conversion of 25-hydroxyvitamin D (the vitamin D metabolite that is measured when a “serum vitamin D” is requested)

to the active metabolite 1,25dihyroxyvitamin D that both increases gastrointestinal calcium (and probably phosphate) uptake and acts coordinately with RANK-ligand to promote osteoclastic activity. PTH also increases renal phosphate excretion, and PTH production is increased in response to prolonged phosphate exposure.

As serum phosphate falls after delivery, so the hypertrophic chondrocyte cell layer increases in depth, resulting in growth plate widening. This is difficult to see on plain radiographs in preterm infants, because secondary ossification centres only appear on distal femur radiographs ex utero at around 36 weeks gestation in some series[7] and later at other epiphyses. Other imaging modalities have not been employed to assess growth plate widening, although ultrasound has been used to assess the appearance of secondary ossification centres. Ossification centres in the distal femurs are reliably detected by prenatal ultrasound at 33 weeks[8].

Alkaline phosphatase (ALP) values are assay-specific and thus may vary considerably between centres. ALP typically rises in the three weeks following delivery before plateauing at a level approximately two to three times the maximum of the adult normal range.[9] ALP in combination with serum phosphate at two weeks age has been found to be predictive of later bone mineral density by dual energy x-ray absorptiometry(DXA)[10]. Others have found that PTH >180ng/l and phosphate <4.6mg/dl (<1.4mmol/l) at age 3 weeks, rather than raised ALP, was predictive of metabolic bone disease as shown by altered distal femoral appearance on plain radiographs at age 6 weeks.[11]

Bone mineralisation will be affected when substrate supply - i.e. calcium and phosphate - is reduced. The accumulation of mineralised bone mass may be influenced by other factors. In older individuals, both immobility and inflammation have been clearly demonstrated to adversely affect bone accrual. Sick preterm infants are often relatively immobile, and are subject to a range of inflammatory insults such as infection and necrotising enterocolitis. These factors in combination result in lower mineralised bone mass that in turn predisposes to fracture. Identifying and mitigating these risks before fracture occurs is clearly desirable.

Measurement of mineralised bone mass by DXA requires transportation to the scanner; values are not comparable between the different manufacturers. The commonly reported value of areal bone mineral density of the lumbar spine (LSaBMD) reflects bone size as well as mass; bone mineral apparent density (BMAD) is a calculated estimate of lumbar spine volumetric density based on an assumed cubic vertebral shape and is less affected by bone size.[12] Tibial ultrasound has been used to measure speed of sound (SoS) as a proxy for “bone quality”[13]; it is unclear what precisely is being measured, although studies in adults show a relationship of SoS with tibial cortical thickness. Neither measure appears to be discriminatory in identifying those at risk of fracture, and hence have not entered routine clinical practice.

Starting in the 1980s, the management of metabolic bone disease of prematurity focused on providing an increased amount of mineral substrate. The basis of this intervention is supported through a multitude of interventional supplementation studies, although the optimal level of supplementation for any given infant remains the subject of debate. It is clear, however, that no additional benefit accrues through the use of more than 400IU (10mcg) vitamin D daily.[14,15] Physicochemical constraints in respect of the solubility of inorganic calcium and phosphate salts in intravenous feeding solutions resulted in efforts to either supply additional oral supplements or avoid solubility issues through the use of organic phosphate salts.[16] Most multi-nutrient fortifiers for breast milk and preterm infant formulas contain large amounts of both calcium and phosphate. In some instances, additional phosphate alone is given, typically in doses of 1.0 - 1.5 mmol/kg/day. Phosphate can complex with calcium in the gut, so ideally additional phosphate should be given separately to the feeds, clearly an unrealistic proposition in those receiving continuous or hourly bolus feeds. Phosphate can be admixed with expressed breast milk; it is thought to enter the micelles, so if additional calcium is also to be administered, add the phosphate first, mix gently and leave for 30 minutes before adding the calcium.

Additional calcium may be required for some infants, typically those born very preterm, as they grow and develop. The key indicator here is PTH; if serum calcium is normal but PTH is raised, this suggests inadequate calcium supply. Further vitamin D supplementation, or the use of active vitamin D metabolites, will not help; additional calcium, and reducing additional phosphate intake, will.

Fractures are the "end stage" of metabolic bone disease; fractures occur more often in infants born weighing <1000g, who have chronic lung disease (presumably a marker for inflammation and immobility, as well as allowing more frequent radiological assessment), prolonged intravenous feeding/delayed enteral feeds, conjugated hyperbilirubinaemia, steroids and diuretics, and physiotherapy.[17] It is appropriate to give advice to both parents and staff regarding the increased risk of fractures and need for careful handling to try and reduce fracture risk both in hospital and after discharge home.

Osteogenesis imperfecta/inherited bone fragility

The last two decades has been transformative in terms of our understanding of the genetic origins of bone fragility (although this remains incomplete), less so in terms of therapeutic interventions – until recently.
Osteogenesis imperfecta (OI) has been used as an umbrella term for inherited bone fragility conditions; over time, there has been a growing acceptance that the original use of the common name "brittle bone disease" is a useful way to identify and differentiate OI from bone fragility as the dominant material property of OI bone is its brittleness, likely a combination of increased amounts of mineral platelets in relation to the proteinaceous matrix, with additional stiffening of the matrix through excessive non-enzymatic cross-linking.[18]
The genetic origins of inherited bone fragility are listed in Table 1. The list is ever-expanding but useful in terms of providing advice to families as inheritance patterns vary, although dominant inheritance remains the most common. Many of the genes are involved in the production, processing or export of type I

collagen from osteoblasts, the bone-forming cells. There are no specific treatments for any of the different forms as yet, although one might anticipate that an enterprising biotech company will eventually produce the replacement protein for type VI.

Along with many other "short limb" syndromes, moderate and severe OI may be identified on antenatal scans. At birth, bones look lucent as well as short and may be bowed or fractured. Characteristic features that can help distinguish type V OI at birth are metaphyseal changes suggesting rickets or dysplasia,[19] and a wedge-shaped inclusion in the anterior wall of the vertebrae seen on lateral spine radiographs. Infants with fragile bones and contractures may have Bruck Syndrome,[20-22] resulting from defects in *FKBP10* or *PLOD2*; those with craniosynostosis may have Cole-Carpenter syndrome, caused by defects in *P4HB* or *SEC24D*.[23-25] In those where there are concerns about neurodevelopment, Wnt1 mutations should be considered.[26,27]

Insert Table 1 here:

Table 1. Inherited bone fragility syndromes

Gene	Sillence type/ syndrome name	Severity	Protein	Additional phenotypic details
Collagen molecule				
COL1A1	I-IV	Mild-lethal	Type 1 collagen α1 chain	High bone mass in C-propeptide cleavage site defects – gracile "shattered" bones[28] Caffey disease with defect at p.Arg1014Cys[29]
COL1A2	I-IV	Mild-lethal	Type 1 collagen α2 chain	High bone mass in C-propeptide cleavage site defects
Collagen folding				
CRTAP	III	Severe-lethal	Cartilage associated protein	Cole-Carpenter features reported in one case.[30]
LEPRE1	III	Severe-lethal	Prolyl-3-hydroxylase	
PPIB	III	Moderate-lethal	Cyclophilin B	
Collagen stability				
FKBP10	III	Moderate-severe	FKBP65; 65kD FK506-binding protein	Bruck syndrome (OI with contractures)[20,22]; Kuskokwim syndrome (contractures alone)[31]
PLOD2	Bruck syndrome	Moderate-severe	Lysyl hydroxylase 2	Contractures
SERPINH1	III	Severe	Heat Shock Protein 47	Pyloric stenosis, skin bullae,

				renal stones[32]
SPARC	III	Moderate -severe	Secreted protein, acidic, cysteine-rich; osteonectin	Notable sarcopenia[33]
Collagen processing/cleavage				
BMP1	III	Mild-moderate	Bone morphogenetic protein 1; tolloid	High bone mass, similar to C-propeptide cleavage defects, hyperosteoidosis, cardiac defects[34-37]
Wnt-signalling pathway				
WNT1	III	Mild-severe	Wingless-type MMTV integration site family, member 1	Homozygous – severe OI; some have brain malformation; autism, learning difficulties in some.[26,27] Heterozygous – early onset osteoporosis, normal growth
Mineralisation regulation				
IFITM5/ BRIL	V	Moderate - severe	Interferon-induced transmembrane protein 5, or, bone-restricted IFITM5-like	Metaphyseal dysplasia and sclerosis, hypertrophic callus, interosseous membrane calcification. [38-41]
SERPINF1	III	Moderate -severe	Pigment epithelium derived factor	Slowly progressively worsening OI; osteoid mineralization defect (no endochondral defect)[42]
Osteoblast lineage				
SP7/OSX	III	Severe	Specificity Protein 7; Osterix	Typical OI features[43]
Developmental/patterning				
TAPT1	III	Lethal	Transmembrane anterior posterior transformation-1 protein	Complex osteochondrodysplasia with multiple fractures; also have brain, cardiorespiratory and renal defects [44]
ER-related				
P4HB	III	Moderate -severe	Prolyl 4-hydroxylase; protein disulfide isomerase	Cole-Carpenter syndrome; craniosynostosis, ocular proptosis, hydrocephalus[23,25,45]
TMEM38B	III	Moderate -severe	Trimeric Intracellular Cation Channel Type B; TRIC-B	Severe osteopenia and limb fractures without vertebral fractures [46,47]
CREB3L1	III	Severe	Old Astrocyte	Severe OI; cardiac failure [48]

			Specifically Induced Substrate - OASIS	
SEC24D	III	Moderate -severe	Component of COPII complex	Cole-Carpenter syndrome; craniosynostosis, ocular proptosis, hydrocephalus[24]
MBTPS2	III	Moderate -severe	Site-2 metalloproteinase S2P	regulated intramembrane proteolysis of transcription factors such as OASIS x-linked[49]
Nucleotidyltransferase fold protein				
FAM46A	III	Severe	Family with sequence similarity 46A	Stüve-Wiedemann – like features, blue sclerae[50]
Linker enzyme deficiency				
XYLT2	III	Moderate -severe	Xylosyltransferase II	Vertebral fractures, cataracts, heart defects [51]
Bone fragility, not clearly OI				
LRP5/6	N/A	Mild-severe	Lipoprotein receptor-related protein 5/6	Homozygous – osteoporosis pseudoglioma syndrome; Heterozygous – osteoporosis and/or vitreoretinopathy [52-55]
NBAS	N/A	Moderate -severe	Neuroblastoma Amplified Sequence	Early onset osteoporosis, recurrent acute liver failure, developmental delay[56,57]
LIFR	Stüve-Wiedemann syndrome	Moderate -severe	Leukaemia inhibitory factor receptor	Long bone bowing, camptodactyly, hyperpyrexia, fractures later[58]
Osteocyte dysfunction				
PLS3	N/A	N/A	Plastin 3	X-linked early onset severe osteoporosis without other OI features[59,60]

Next generation sequencing (NGS) allows high performance sequencing of whole genomes or can be limited to a smaller number of genes of interest. The original Sangar method of sequencing DNA was a time consuming and expensive process sequencing one DNA fragment at a time. NGS allows the parallel sequencing of millions of DNA fragments simultaneously. These can then be compared to large online databases cataloguing genetic variability to identify a causative gene. It may also be possible to identify a causative gene through comparison of a very small number of individuals but this may also identify non-causative variants. NGS can be performed at relatively low cost (around £200/sample); specific panels are available for bone fragility and skeletal dysplasia that allow the identification of mutations in "known genes"; whole exome or whole genome sequencing can be undertaken when the "panels" fail to identify potential candidate mutations, but may still fail to identify mutations that lie outside of coding or regulatory regions.

Management, as with most skeletal disorders, is multidisciplinary.[61] Whilst the neonatologist's skills in terms of respiratory support may be required for a time, the on-going management of the musculoskeletal system requires physiotherapy, occupational therapy and nursing involvement from the outset, especially in respect of moving and handling, and input from a psychologist and social worker in due course. Bisphosphonates are given intravenously in this age group; in the UK, this is usually pamidronate, but zoledronic acid has been given in some North American centres. Indications for starting bisphosphonates in infants with OI are the presence of multiple fractures, and the need for pain relief; bisphosphonates are widely reported by older children to reduce musculoskeletal pain and improve endurance and fatigue.

New treatments are emerging. Denosumab, an anti-RANK-ligand antibody licenced for the treatment of post-menopausal osteoporosis,[62] has been used in some children with type VI OI[63] and is currently being trialled in a phase 3 study of older children with commoner forms of OI. RANK-ligand is the principal factor that both attracts and activates mononuclear cells to fuse to become osteoclasts, and then promotes their activity in resorbing bone.

Anti-sclerostin antibody treatment is being evaluated in adults with OI,[64] and will start paediatric trials in 2019. Sclerostin, produced by osteocytes, both inhibits bone formation and increases bone resorption.[65] Anti-sclerostin antibody thus increases bone mass, and does so on both modelling (addition or removal of bone without prior resorption) and remodelling (removal of bone with replacement at the same site) surfaces, a potential advantage over the purely antiresorptive agents that inhibit bone formation at remodelling sites.

A study of a human anti-TGFb antibody, fresolimumab, is underway in adults with OI in North America. Preclinical work suggests substantial restoration of bone mass in mouse models of OI using the mouse 1D11 anti-TGFb antibody.[66] In addition, the use of 1D11 was associated with an improvement in lung tissue morphology, increasing alveolar number. None of the proposed studies include infants, but once safety and efficacy have been shown in the older age groups we may reasonably expect that there will be a "trickle down" to infants and eventually neonates.

As yet, no intervention has emerged that alters the material quality of bone; one potential approach to this issue would be the removal of mutant protein prior to its export from the cell, a process called autophagy. Autophagy enhancement could be used, but it is unclear as yet whether the degree of enhancement that can be achieved is sufficient to keep up with the production of mutant type I collagen molecules.[67] Another approach would be to replace the mesenchymal stem cells (MSCs) that give rise to osteoblasts. Bone marrow transplantation was tried in the late 1990's[68] but low levels of engraftment and lack of evidence of the production of normal type I collagen from transplanted cells, as well as safety concerns, led to suspension of the work. A recently proposed approach is that of using fetal MSCs administered both in utero and during infancy. The acid test will again be whether the investigators can demonstrate the production of type I collagen from the transplanted cells, or their daughter cells.

Hypophosphatasia

Hypophosphatasia (HPP) occurs when alkaline phosphatase (ALP) activity is insufficient to remove the mineralisation inhibitor pyrophosphate from

mineralising bone surfaces. ALP also removes the phosphate from pyridoxal 5-phosphate (PLP); pyridoxal then crosses the blood-brain barrier and is re-phosphorylated. PLP is a co-factor in multiple enzymatic processes, including those that result in the synthesis of some neurotransmitters.[69] The phenotype of infants presenting around the time of birth is one of severe demineralisation, rachitic changes at the metaphyses with very gracile ribs, elevated serum calcium and phosphate, nephrocalcinosis, and in some cases pyridoxine-dependent convulsions.[70]

Prior to the advent of enzyme replacement therapy with asfotase alfa, over 90% of perinatally-presenting cases and 55% of cases presenting later in infancy died. The published results from the initial and subsequent cohorts[70,71] of infants treated with asfotase alfa show an overall reduction in mortality to around 12%. Longer term follow-up suggests improvements in growth, motor and cognitive development in parallel with resolution of radiological changes.

The improvement in bone mineralisation can take months to become apparent radiologically; continued respiratory support is usually required until ribs mineralise and become broader and are able to sustain normal respiratory activity. Pneumonia may be more common in HPP than would be expected and should certainly be considered in any infant with worsening respiratory function. Worsening radiological appearance is a red flag and should provoke consideration of whether drug is being absorbed. It is unclear whether autoantibodies, present in at least 50%, affect efficacy. The more severely affected infants, and those with radiological worsening of bone disease may require more than the licenced starting dose of 6mg/kg/week subcutanously.

Hypercalcaemia requires institution of a low calcium diet initially; there can be a sudden change as increased bone mineralisation begins to place, so monitoring of serum calcium over the initial weeks is needed until the infant is established on asfotase alfa with a normal calcium intake.

Convulsions may occur within the first week of life; pyridoxine (ideally pyridoxal) can help, and affected infants should usually be responsive to enzyme replacement therapy. Craniosynostosis occurs in at least 25% of cases; although unlikely to be present at birth, it can develop over the first 6-12 months of life and result in raised intracranial pressure; regular monitoring of head circumference and ophthalmological examination is required.

Neonatal severe hyperparathyroidism

Infants typically present within days of delivery with severe hypercalcemia, high circulating parathyroid hormone (PTH) and characteristic radiological changes including bone demineralisation, rachitic-shaped chest, fractures and periosteal elevation/double cortices.[72] Affected infants have inactivating mutations of the calcium sensing receptor gene,[73] so that PTH continues to be produced despite the hypercalcaemia. Rehydration is required urgently, and the administration of an intravenous bisphosphonate, usually pamidronate will both contribute to reducing serum calcium levels. A small dose of pamidronate is usually given (0.5mg/kg over 4 hours), and may need repeating 24-48 hours later; administering larger doses can result in hypocalcaemia. Definitive treatment is surgical removal of the parathyroid glands; post-operatively hypocalcaemia will likely occur and may be problematic.

FGFR3 disorders

Fibroblast growth factor receptor 3 (FGFR3)-dependent signalling regulates bone growth by affecting growth plate chondrocyte proliferation through STAT1 and maturation through the MAPKs ERK1 and 2[74].
Mutations in the *FGFR3* gene that lead to it being functionally overactive result in a spectrum of conditions causing dwarfism from the lethal thanatophoric dysplasia to the milder hypochondroplasia. The most common, achondroplasia, is often diagnosed at birth and is characterised by short long bones, shortening of the proximal skeleton and limited elbow extension. Effects on the skull include macrocephaly, mid face hypoplasia, frontal bossing and a small foramen magnum.[75] Thanatophoric dysplasia is a severe form of dwarfism and is usually lethal with infants stillborn or dying soon after birth due to respiratory failure. Affected infants have short limbs, a narrow thorax, macrocephaly and temporal lobe enlargement. Patients with hypochondroplasia share a similar phenotype with achondroplasia but in a milder form and will often be diagnosed later in childhood[75].

Achondroplasia may be diagnosed antenatally on USS. In neonates, a wrist radiograph shows delayed bone age; catch-up to chronological age occurs in adolescence. MRI may demonstrate cervicomedullary compression at the foramen magnum; problems in infancy are unusual but do occasionally occur. Thanatophoric dysplasia has two types with a similar phenotype; type II has a tri-lobar skull with a clover-leaf appearance.

Two mutations in the *FGFR3* gene account for nearly all cases of achondroplasia with both mutations creating the same change to the FGFR3 protein, resulting in constitutive activation[76]. 80% of affected individuals have new mutations but when inherited it follows an autosomal dominant pattern with homozygous individuals stillborn or dying soon after birth. More than 10 mutations of the *FGFR3* gene have been identified in cases of thanatophoric dysplasia; all result in ligand-independent activation of the FGFR3 protein[77,78].

Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) is a very rare skeletal dysplasia accompanied by seizures, profound developmental delay and additional skin folds on the limbs. In each of these lethal conditions individuals have only one affected gene due to the gain-of-function nature of the affected protein. Hypochondroplasia, as with achondroplasia, mostly arises from *de novo* mutations with 8 separate mutations identified to date.[75]

Currently, treatment is supportive only, but identification of the activating mutations in the *FGFR3* gene, and better understanding of the downstream consequences, have allowed the development of targeted treatments, with clinical trials now in progress.
Vosoritide, a “stabilised” C-naturetic peptide based drug administered as a daily subcutaneous injection, has entered phase 3 clinical trials in children

(https://clinicaltrials.gov/ct2/show/NCT02055157). Vosoritide binds to a specific receptor (natriuretic peptide receptor 2) whose downstream signalling inhibits the downstream FGFR3 signalling pathway[79]. Separately, a phase 1 trial commenced this year to assess TA-46, a soluble FGFR3 that sequesters FGFR3 ligands and prevents the receptor from dimerising and signalling.

Drugs used for no skeletal disorders are showing potential for their actions in bone. Meclozine, an H1 antagonist used for motion sickness, promoted chondrocyte proliferation and differentiation for long bone growth in mice but with no effects on the axial skeleton[80,81]. Its effects on bone have not been evaluated in humans. PTH regulates bone metabolism and is used in adults to treat osteoporosis by promoting new bone formation. Mouse pups with thanatophoric dysplasia born to mothers treated with subcutaneous PTH injections remained viable[82]. Again, there are no human studies examining the effect on skeletal dysplasias and PTH is currently "black boxed" for paediatric use due to concerns regarding the possibility of causing osteosarcomas.

Fibrodysplasias ossificans progressiva

Fibrodysplasia ossificans progressiva (FOP) is an extremely rare autosomal dominant disorder characterised by the extra skeletal development of bone tissue through the ossification of skeletal muscle, ligaments and tendons. The proximal, axial and cranial regions of the body are most commonly affected early which then progresses to more distal regions. Trauma, surgery and viral illnesses trigger flare up that begin with soft tissue swellings and lead to mature bone formation. A characteristic feature present at birth is a broad shortened deformed great toe. Formal diagnosis relies on genetic testing which reveals an identical mutation in all affected patients for the *ALK2/ACVR1* gene encoding the bone morphogenetic protein (BMP) type 1 receptor[83]. Whilst it may be inherited, the majority of cases are new mutations. The disease is characterised by flare-ups and there may be long periods of no disease activity. Flare-ups are managed with high dose steroids and this has led to the suggestion that an underlying immunological component driving them[84]. The retinoic acid receptor pathway (RAR) is known to be important in the process of bone formation. Preclinical studies of RAR inhibition have shown reduction of injury-induced bone formation and spontaneous bone formation in FOP mouse models[85]. Palovarotene, a retinoic acid receptor antagonist, is in a phase 3 clinical trial of FOP to assess efficacy and safety (https://clinicaltrials.gov/ct2/show/NCT03312634).

Future directions/summary

As genomics progresses and testing using both targeted panels and whole exome/genome sequencing becomes routine, diagnosis will become easier. Although we are still some way away from the application of artificial intelligence to the analysis and recognition of skeletal dysplasia from plain radiographs, the opportunity there is clear. New treatments are emerging for multiple bone diseases that will in time be applied from around the time of birth, and that have the potential to be both life saving and life transforming.

Conflict of interest statement

SAB has no conflicts of interest. NJB has held grants from Alexion and Amgen, and consulted and spoken at meetings for Mereo Biopharma and Alexion.

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