 DOI: 10.18231/2395-1362.2017.0041

Profile of rare disabling musculoskeletal diseases in the North-Eastern Region of India: A hospital based study

Bhaskar Borgohain[1,*], Tashi G. Khonglah[2], Cherry M. Tariang[3]

[1]Associate Professor, [2]Assistant Professor, [3]Senior Resident, Dept. of Orthopaedics, North Eastern Indira Gandhi Regional Institute of Health & Medical Sciences, Shillong

***Corresponding Author:**
Email:bhaskarborg@gmail.com

Abstract

Traditionally, research and development of treatments for rare diseases has been neglected in favour of more common diseases. Rare diseases are rare but rare disease patients may not be that rare in a populous country. It's ironic that rare diseases affect over 70 million people in India, yet there is so little being done by way of research, drug creation and counseling of patients and families across the country. The Swedish definition of a rare disease is a disorder resulting in an extensive disability with a prevalence of no more than 1 in 10,000 inhabitants. We retrospectively analyzed a series of very rare disabling musculoskeletal diseases over a period of seven years, presenting to the orthopaedic department of a tertiary care referral hospital located in the North-Eastern Region of India and present a snapshot of their pattern and barriers in their management. Diagnosis of specific clinical phenotype, prognostication and their management may not follow any clear protocol due to lack of guidelines and treatment may be a long drawn process. Critical information may not be readily available in the textbooks to provide proper counseling to the family and delays in diagnosis are commonly experienced by patients and may be due the small number of patients' affected and poor awareness of rare diseases by health professionals. Rare diseases are all the more challenging due to lack of knowledge bases and clinical expertise, leading to uncertainty in their practical management particularly in resource constrained settings.

Keywords: Rare diseases, Medical informatics, Diagnostic error, Genetic testing.

Introduction

A rare disease occurs infrequently in a population, but there is no universal definition. The World Health Organization (W.H.O.) has suggested that a rare disease should be defined as one with frequency less than 6.5 – 10 per 10,000 people.(1) In its 2014 Report on the State of the Art of the Rare Disease Activities in Sweden rare disease is defined as a disorder resulting in an extensive disability with a prevalence of no more than 1 in 10 000 inhabitants.(2) In China, rare disorder is defined as one that affects less than 1/500,000 people or one that has a neonatal morbidity of less than 1/10,000. Three elements to the definition as used in various countries are as follows: 1) the total number of people having the disease, 2) its prevalence and 3) non-availability of treatment for the disorder.(1) A formal definition helps a nation to identify such diseases that require financial support for the discovery and development of drugs and biologics. This in turn helps in encouraging the product development improving the funding for basic and clinical research on rare diseases. Awareness and understanding of rare diseases is often low, and such patients struggle to find adequate information about their condition. As a result, upon diagnosis, patients with rare diseases may feel overwhelmed, isolated, and unsupported.(1,2,3,4,5)

Materials and Method

We planned to report some important rare musculo-skeletal disorders characterized by disability from the resident population of the North Eastern over a period of seven years presenting to the orthopaedics department of a large tertiary care teaching referral hospital located in the capital of Meghalaya, North-east region of India that shares international borders. This paper aims to retrospectively analyze and present a snapshot of rare disorders affecting the musculoskeletal system in this region and the unique challenges such rare diseases engender to health care system.

Results and Discussion

We encountered extremely rare disorders with the prevalence of only 1/2,000,000 called Fibrodysplasia ossificans progressive (FOP) in an eight year old boy from Mizoram bordering Myanmar (Table 1). FOP is an extremely rare genetic condition in which soft connective tissues including aponeuroses, fascia, ligaments, tendons, and striated muscles transform into mature bone over time due to abnormal progressive heterotopic ossification;aptly named as "*stone man* syndrome".(6,7) Short deformed great toes were pathognomonic of FOP.(6,7) Multiple biopsies in two hospitals to rule out a sarcoma caused disease flare ups due to myositis that could have been avoided. Earlier physicians missed the telltale pathognomonic sign of bilateral congenital short great toes linked to FOP during clinical examination (Fig. 1a and 1b). This is the first case of FOP reported from the sub-Himalayan region of Indian subcontinent, which was successfully diagnosed without any further invasive tests in the OPD. Bilateral inverted nipples and unilateral ankylosed first MTP Joint were distinct new observations. The unique CT scan findings of symmetrical distribution of large heterotopic

ossification (HO) in the rather predictable regional pattern easily ruled out other theoretical differentials.

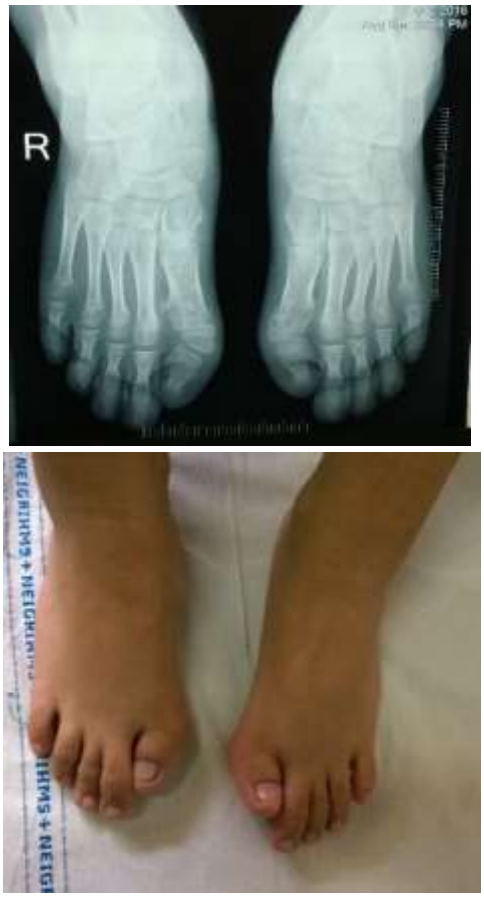

Fig. 1a & 1b. FOP: Radiograph picture of bilateral congenitally deformed short great toes and clinical

Another extremely rare disease CRMO (Chronic Recurrent Multifocal Osteomyelitis) with prevalence of only 1-2 /2,000,000 was diagnosed [8] in a six year old girl from Assam (Table 1). This was a curious auto-inflammatory disorder (Table 1). This child presented with delayed wound healing in her left elbow after incision & drainage performed elsewhere. Wound margin biopsy showed subacute nonspecific inflammation with prominent neutrophilic infiltration. Radiograph revealed osteitis and osteolysis in the lower end of humerus without sequestrum (Fig. 2 a & 2b). Magnetic resonance imaging ruled out neoplasms. Wound cultures were repeatedly negative for micro-organisms. There was past history of similar painful skin lesions and delayed wound healing. Diagnosis of chronic CRMO was entertained by a process of exclusion. She required a prolonged treatment with Salfasalazine, Methotrexate, NSAID and corticosteroids to control her disease [8, 9, 10] but this has led to dwarfism and Cushingoid features.

Other rare diseases with prevalence 1-2/100000 that affected a particular limb or region were one case each of congenital proximal focal femoral deficiency (PFFD), Congenital Pseudoarthrosis of Tibia (CPT) and Radial Club Hand (Table 2). Radial Club Hand case was lost to follow up after initial corrective plaster applications despite adequate counseling. The PFFD case had mild facial dysmorphism, a flexed, abducted, and externally rotated short right thigh, ipsilateral short tibia with laterally dislocated small patella and mild genu valgum.

Table1: List of extremely rare Musculoskeletal (MSK) diseases encountered in NER: Case Summary

Name of Disease and prevalence	Case presentation	Discussion: Learning points during assessment, diagnosis and Management
Fibrodysplasia ossificans progressive: FOP **1/2,000,000** [6,7]	Eight year old well built Mizo-speaking boy from the state of Mizoram presented with discrete Swellings at the back of neck for a year. B/L Short great toes noted during head to toe examination. No family history of FOP. Ambulatory without support and attending school at present.	Neck swelling, B/L Short great toes and 3Dimensional CT images confirmed the diagnosis. H/O Multiple biopsies in two hospitals to rule out a sarcoma causing flare ups. Earlier physicians missed the telltale sign of B/L Short great toes linked to FOP during clinical examination.
Chronic recurrent multifocal osteomyelitis: CRMO **1-2 /2,000,000** [8,9,10]	Six year old Assamese speaking girl child from Assam presented with a non-healing ulcer following debridement of lateral elbow "abscess". Multiple old cigarette paper like scars in the limbs. X-ray shows osteitis in distal humerus. Multiple biopsies and surgical debdridements attempted in multiple hospitals before for diagnosis. Microcytic hypochromic anaemia and high ESR noted.	Corticosteroids, NSAIDs, PPI used as mainstay therapy. Patient and family educated about Natural history of CRMO. Multiple inflammatory attacks on medications needing step up medications including steriods. Trial of salfasalazine and methotrexate failed to bring remission and therefore stopped. Steriod induced Dwarfism and cushingoid facie noted during treatment. Parents opted for Ayurveda.

Congenital Proximalfemoral focal deficiency: PFFD Aitken class A and Amstutz subtype 1 **1-2/200,000** [11,12]	Three year old Khasi speaking boy from Meghalaya came with mild facial dysmorphism, a flexed, abducted, and externally rotated short right thigh, ipsilateral short tibia with laterally dislocated small patella and mild genu valgum. No concomitant fibular hemimelia and no mental retardation and upper limbs were not involved. No family history of congenital deformities	He was initially using extension prosthesis to compensate the extreme shortening. Early femoral lengthening followed by tibial lengthening. Femoral lengthening stopped after 4 cm lengthening due to hip pain. Contractures during tibial bone lengthening and delayed union of proximal tibial corticotomy site needed bone marrow injections.
Congenital pseudarthrosis of the tibia: CPT Boyd type II with NFM type I **1-2:250,000** [13,14,15]	Six year old dialect speaking boy from Arunachal Pradesh presented with anterior bowing of leg. Past history of failed Plating. Fresh X-ray confirmed re-fracture of both bone leg. Multiple large *Café au lait* spots and axillary freckles noted. Congenital anterior bowing of tibia, spontaneously fracture on minor trauma < 2 years of birth and tapered, rounded & sclerotic bony ends at pseudoarthrosis and hourglass constriction of tibia and No family history of congenital deformities or NFM.	The commonest variety with worst prognosis especially with Neurofibromatosis. Resection of pseudoarthrosis and fibular bone graft, IM Rod plus Ilizarov Ring fixator. Middle tibial segment moved distally to provide metaphyseal lengthening & pseudarthrosis compression. Delayed union of proximal tibial corticotomy required bone marrow injection, Valgus angulation at knee $>7^0$ occurred. Lisch nodules were found in ophthalmological examination

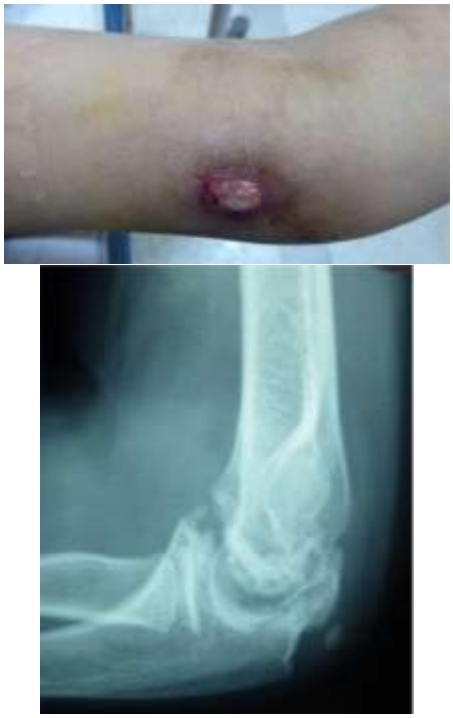

Fig. 2a & 2b: CRMO: Clinical and radiographic views of elbow lesions

Clinical and radiological evaluation the diagnosis was confirmed as Aitken class A and Amstutz subtype 1 congenital PFFD [11, 12]. Early femoral lengthening followed by tibial lengthening was performed using external fixation (Orthofix LRS Device: S.H.Pitkar, India) sequentially to correct the shortening. Femoral lengthening of 4 cm achieved (Fig. 3). Overall 8 cm of lengthening achieved and patient is ambulatory with minimum heel raise at present. The CPT Child had multiple *Café au lait* spots confirming with NFM I. CPT (Boyd type II) with NFM type I diagnosed. Boyd type II is the most common type& has the worst prognosis especially with Neurofibromatosis. [13, 14]

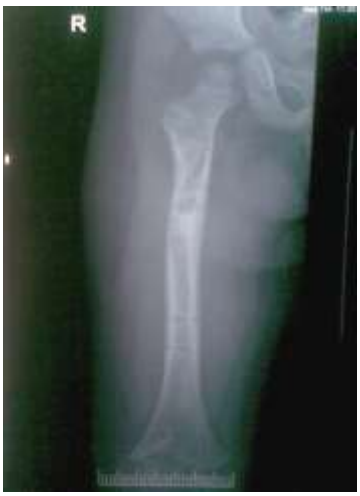

Fig. 3: PFFD (right sided) after femoral lengthening

He was twice operated elsewhere but refracture occurred due to improper postoperative brace compliance. The Ilizarov technique emerged as being the optimal method, having the highest rate of fusion (75.5%) of pseudarthrosis and rate of success in correction of the additional deformities.[14,15]In view of this resection of pseudoarthrosis and fibular bone graft (Fibular graft was used to prevent early graft resorption)

and retrogradely placed intramedullary (IM) rush rod plus Ilizarov ring fixation for internal bone transport was performed as a two stage procedure (Fig. 4). Middle tibial segment moved distally to provide metaphyseal lengthening & pseudarthrosis compression.

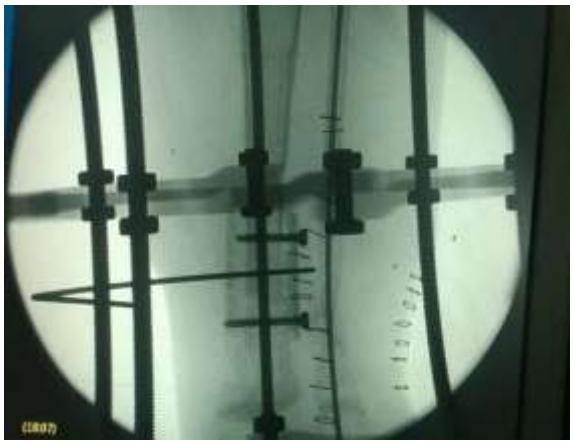

Fig. 4: CPT after resection of pseudoarthrodesis and sandwich fibular graft and retrogradely placed intramedullary (IM) rush rod plus Ilizarov ring fixation for internal bone transport

One case of congenital amyoplasia was diagnosed in a five year old boy having multiple contractures of the joints including severe bilateral club foot (Table 2). In fact amyoplasia is the most common type of AMC (Arthrogryposis Multiplex Congenita).[16] He required multiple contracture releases starting with stiff right elbow for gaining hand to mouth movement for feeding and bilateral talectomies for one stage correction of severe club foot and hamstrings releases for both knee contractures. The hip release with VDRO (Varus derotation osteotomy) for correction of unilateral subluxation of hip is pending yet.

There was a single case of Hypophosphatemic rickets most possibly X-linked on clinical ground with a prevalence of 1:20,000. It is the most common form of hereditary hypophosphatemia.[17] This was treated with combination of weekly high dose vitamin D and daily Calcitriol and phosphate rich diet. Periodic blood tests were performed to monitor serum levels of calcium, phosphate and ALP to reduce risk of hypervitaminosis D and nephrocalcinosis.[18]

Other rare disabling disorders encountered that affect multiple sites were two cases each of HME (Hereditary Multiple Exostosis) and Osteogenesis Imperfecta (OI) with slightly higher prevalence of 1:20,000. The OI cases presented with severe deformities of bilateral femora and required pulse pamidronate therapy for osteoporosis and subsequent surgical corrections with good and timely healing of the osteotomies. [19, 20] One case of HME needed surgery to remove a large popliteal exostosis that was causing mechanical restriction to knee movements and also raised concerns for malignant transformation (Fig. 5).

We found one interesting rare case of ulcerating tophaceous gout involving knee and ankle in an educated twenty nine year old male from Assam complicated by falciparum malaria. Malaria is endemic to Assam Meghalaya and many NE states. Recent research shows that Falciparum malaria is known to increase serum uric acid level ;[21] study even indicates that allopurinol can be an additive to quinine to bring about both faster eradication of Plasmodium falciparum. [22]

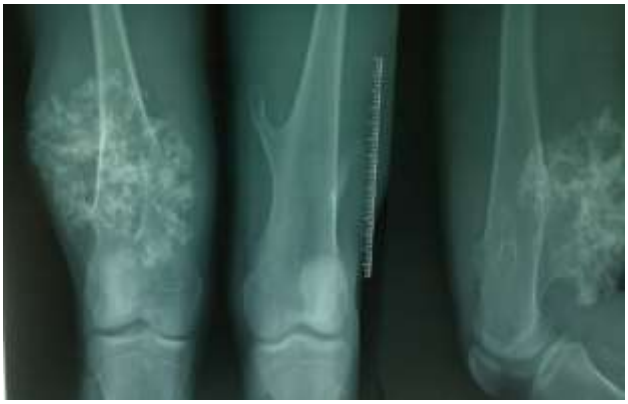

Fig. 5: HME: Knee radiograph showing a large popliteal Osteochondroma

The fever, joint pain and wound condition improved after starting anti-malarials. He may need drugs like Pegloticase or Lesinurad in the future.[24] Lastly, the single rare case of Poland's Syndrome (Fig. 6) was not so disabling but affected his choice of vocation and self confidence. [25]

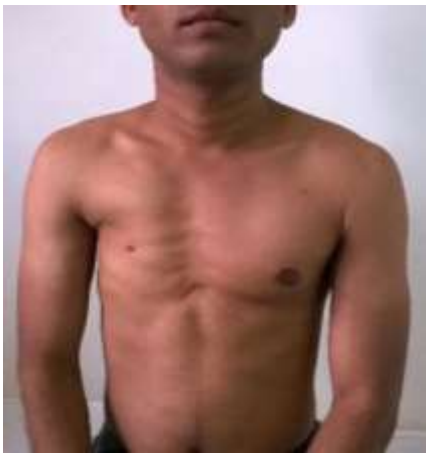

Fig. 6: Clinical picture of Poland Syndrome affecting right pectoralis major muscle and chest wall

It was realized that initial good directive counseling, explanation of known natural history of the rare disease and setting achievable intermediate term treatment goals and a clear treatment roadmap may ensure better family support, longer follow ups and patient cooperation. It is possible that there are significant numbers of unreported

extremely rare to rare disabling musculoskeletal diseases in the resident population of NE region.

Table 2: List of very rare MSK diseases encountered in NER: Case Summary

Name of Disease and prevalence	Case presentation	Discussion: Learning points during assessment, diagnosis and Management
Radial Club hand Modified Byne and Klug type 4 **1:100,000 /Live births [(26)]**	Nepali speaking parents from Meghalaya came with a first new born girl child. There was no bad peri-natal history. X-ray confirms Modified Byne and Klug type 4 (most common type) radial club hand	Initially managed conservatively with counseling and serial weekly plaster correction. The need for centralization and pollicization was explained to the parents. Patient was lost to follow up within 3 months of treatment.
Poland syndrome **3: 100,000** [(25)]	This 18 year old Bengali speaking boy from Meghalaya was found medically unfit during a paramilitary Recruitment drive. He had a small nipple and a small chest on the right side. He had excellent shoulder function and no clinical symptoms at all.	Counseling focused that treatment for this disorder is supportive. Plastic surgery may be recommended rarely to rebuild the chest wall for cosmesis. Treatment was directed toward physiotherapy to improve shoulder and chest muscles. Option for cosmetic correction with plastic surgery with its dangers and limitations. Told that he is fit to work in many low demand occupations.
Congenital Amyoplasia: Type II AMC **1-9 / 100 000 [(16)]**	Five year old Bengali speaking boy from Assam came due to inability to stand and walk. There was stiff right elbow, B/L knee and hips. Severe B/L clubfoot was present. All limbs were thin. Unilateral Syndactyly of index and middle finger noted. Facial dysmorphism.Delayed presentation withsevere deformities	Delayed presentation mandated extensive surgeries. Surgical correction started first with B/L Talectomy for correction of severe clubfeet. Posterior release of right Elbow improved flexion from 30 to 90 degree. Planti-grade feet achieved but stiff hips prevented walking. Right subluxated hip awaits surgical reduction. Patient and family educated about Natural history of AMC
Hereditary multiple exostosis:HME **1: 50,000**	Eight year old Bengali speaking Adolescent girl from Barak Valley, Assam. Presented with multiple bony swelling near the knee and shoulder girdle. Pelvis and scapula lesion documented after X-ray examination.	No surgical intervention. Patient education about natural history of HME with simple flow chart in Bengali for follow up plan. Small Risk of low grade malignant transformation in pelvis and scapular lesions (Flat bones) and cardinal signs explained (27).
Hereditary multiple exostosis: **HME**	Thirteen year old Nepali speaking boy from the state of Assam presented with multiple bony swellings around the knee and a huge popliteal bony swelling over 8 x7 cm. Physical restriction in knee flexion prevented his squatting ability. Malignancy ruled out by MRI and biopsy. No family history of HME.	Patient education about HME. Removal of the large popliteal exostosis due to mechanically restricting knee flexion. Improved after successful excision using a posterior approach. Excision biopsy shows no malignancy Biopsy showed no malignant change that corresponded well with the pre-operative MRI report. Small Risk of malignant transformation to explained.

The identified rare diseases of the region are characterized by a wide diversity of symptoms and signs that vary not only from disease to disease but also from patient to patient suffering from the same disease. Therefore, for making diagnosis and managing these rare diseases require not only quality discussions among the physicians but also some rare tests to adequately sub-classify its phenotypes to correctly prognosticate or prescribe rare yet highly desirable medications for a prolonged period for effective treatment. There is no dedicated rare disease clinic, regional genetic counseling centre or rare diseases study group in this region yet. Genetic counseling by trained genetic counselor is very important but often inadequate or neglected during treatment due to both lack of knowledge base and dedicated clinics in resource constrained settings. [(28)]

Fortunately, the information boom and open access via the internet is now a powerful source for updated information on natural history and evidence based treatment of rare diseases. Orphanet Sweden also provides open access quality online information about national and international rare diseases.[(29)]While

searching the internet the authors came across many American and European open access rare disease portals, databases and gateways like NORD (National Organization for Rare Disorders, USA), EUCORDIS (European Organization for Rare Diseases), GARD (Genetic and Rare Diseases Information Center) etc. providing further useful link websites are available online to get information in English.

Table 3: List of rare MSK diseases encountered in NER: Case Summary

Name of Disease and prevalence	Case presentation	Discussion: Learning points during assessment, diagnosis and Management
Osteogenesis imperfect: OI (Silence type III) **1:20,000** [19,20]	Three year old Khasi speaking girl child from Meghalaya presented with wheelchair bound status. X-ray pelvis with hips and thighs confirmed severe B/L coxa vara and B/L bowing of femora. Blue sclera, significant Kyphoscoliosis and dwarfism noted. There was no hearing loss. There was no dentigenesis imperfecta. Diagnosis made on clinic-radiological ground.	Multilevel "Kabab" osteotomy both femora, including B/L subtrochanteric osteotomy and IM Rush rods as internal splint in centre-centre positioning in AP and lateral views followed by PVC Bracing. Pulse pamidronate therapy for osteoporosis given. One S/C femoral fracture occurred distal to the rush rod after 2 years of surgery. Improved, can stand with support but refuses further pending corrective surgery and rod exchange.
Osteogenesis imperfect: OI (Silence type IV)	Nine year old Khasi speaking boy from the state of Meghalaya presented with recent pathological fracture femur with minor. Multiple B/L bone deformities seen in the limbs. Past H/O multiple fractures on trivial injury. Moderately affectedand few fractures with less bowing. Normal looking sclera and teeth.	Pulse pamidronate therapy. Corrective osteotomy B/L Femora and locking plate. Improved: ambulatory without support and attending school but refuses further pending corrective surgeries of legs. Plates removed. No new fracture occurred in the 2 year follow up before or after plate removal.
Hypophosphatemic rickets (X-Linked?) **1:20,000** [17,18]	Five year old Assamese speaking boy from Assam presented with florid rickets not responding to Vit D and calcium supplement for year. Normal at birth and no developmental delays until 2 years of age. Inability and stand and walk after 2 years of age and gradual widening of B/L wrists and ankles. Dwarfism noted for his age. No family history of developmental / congenital deformities. Treated as Rickets, but unresponsive to standard treatment for rickets with Vit D_3.	This Hereditary renal phosphate-wasting disorder characterized by hypo-phosphatemia, rickets and diminished growth. Treated with combination of weekly High dose vitamin D and daily Calcitriol, phosphate rich diet. Periodic blood tests to monitor serum levels of calcium, phosphate and ALP done. Extra phosphate salts could not be used. Improvement noted and child could stand up and walk with minimum support besides Radiological healing ~~noted.~~ Patient and family educated about Natural history of VDRR. Drugs like Amiloride and / or hydrochlorothiazide may be needed to enhance calcium re-absorption and to reduce risk of nephrocalcinosis.

A systematic, generic primary-care approach to rare disease may reduce problems such as lack of coordinated care, lack of information, delayed diagnosis, and other difficulties encountered by people with rare diseases and their caregivers.[30] Many patients with rare diseases will present their symptoms first to a general practitioner (GP). They will also attend a GP in between visits to the specialist, they will require diagnosis and treatment of common ailments, and will benefit from the preventive health services offered by general practices. They will require the accessible, relationship-based advocacy and support role that is at the heart of good general practice. The GP can play five potential roles as a non-specialist in rare diseases: awareness of rare diseases, holistic approach, knowledge base, advocacy and empowerment of the patient and their families. [30]

Conclusion

Rare diseases are important and challenging but often neglected in the North-East region of India due to lack of knowledge base, expertise and concerted efforts. Diagnosis as well as treatment may be difficult and a long drawn process. Rare Disease database creation in major local languages appears to be important step for India too. A national plan for rare diseases and related actions may be welcome. Such plan may include

establishing a few regional centers of expertise for rare disorders, maintain rare disease Registries, neonatal screening policy and very importantly genetic testing and professional counseling for the families affected. National alliances of patient organizations and patient representation will provide new windows of opportunity for the true stakeholders. A regional level online diseases registry on rare diseases may be welcome step to pool clinical materials and resources in the near future.

References

1. Aronson JK. Rare diseases and orphan drugs. British Journal of Clinical Pharmacology. 2006; 61(3):243-5.
2. Website of ORDI (Organization of Rare Diseases India. Available at http://ordindia.org/news/ordi-news/rare-disease-day-you-are-not-alone/ Last accessed May 4, 2017.
3. Report on the State of the Art of the Rare Disease Activities in Sweden 2014 Available as PDF copy online at http://ec.europa.eu/health//sites/health/files/rare_diseases/docs/2014report_rare_disease_activitieseu_1_en.pdf.Last accessed May 10, 2017.
4. Profile of Rare Diseases. (2010) in Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development; Field MJ, Boat TF, editors. Washington (DC): National Academies Press (US); 2010. ISBN-13: 978-0-309-15806-0ISBN-10: 0-309-15806-0.
5. IFPMA (international federation of pharmaceutical manufacturers & associations): rare diseases shaping a future with no one left behind: Feb 28, 2017. Available online at https://www.ifpma.org/resources/publications/ Last accessed May 10, 2017.
6. Fibrodysplasia-ossificans-progressiva. Website of Genetics Home Reference, The National Library of Medicine (NLM),National Institutes of Health, U.S. Department of Health and Human Services (HHS).Available at https://ghr.nlm.nih.gov/https://ghr.nlm.nih.gov/condition/fibrodysplasia-ossificans-progressiva. Last accessed May 10, 2017.
7. Fibrodysplasia-ossificans-progressiva. Website of NORD (National Organization for Rare Disorders, USA. Available at https://rarediseases.org/rare-diseases/fibrodysplasia-ossificans-progressiva/ Last accessed May 10, 2017.
8. Ferguson, Polly J., and Monica Sandu. "Current understanding of the pathogenesis and management of chronic recurrent multifocal osteomyelitis." *Current rheumatology reports* 2012; 14 (2): 130-41.
9. Eisenstein, E.M., Syverson, G.D., Vora, S.S. and Williams, C.B. Combination therapy with methotrexate and etanercept for refractory chronic recurrent multifocal osteomyelitis. *The Journal of rheumatology* 2011; *38*(4), 782-83.
10. Girschick, Hermann J., Christiane Zimmer, Guenter Klaus, Kassa Darge, Anke Dick, and Henner Morbach. "Chronic recurrent multifocal osteomyelitis: what is it and how should it be treated?." *Nature Clinical Practice Rheumatology* 2007; 3(12): 733-38.
11. Focal Femoral Deficienecy. Wheeless online texbook of orthopaedics. Available online at http://www.wheelessonline.com/ortho/proximal_focal_femoral_deficiencyLast accessed May 10, 2017.
12. Epps CH. Proximal femoral focal deficiency: evaluation and management. Orthopedics. 199; 14(7):775-84.
13. Shah H, Rousset M, Canavese F. Congenital pseudarthrosis of the tibia: Management and complications. Indian journal of orthopaedics. 2012; 46(6):616.
14. Grill, F., Bollini, G., Dungl, P., Fixsen, J., Hefti, F., Ippolito, E., Romanus, B., Tudisco, C. and Wientroub, S., 2000. Treatment approaches for congenital pseudarthrosis of tibia: results of the EPOS multicenter study. European Paediatric Orthopaedic Society (EPOS). *Journal of pediatric orthopedics. Part B*, *9*(2):75-89.
15. Neurofibromatosis, anterolateral bowing & congenital pseudarthrosis of tibia. Orthobullets orthopaedic reviews. Available online at http://www.orthobullets.com/pediatrics/4054/neurofibromatosis Last accessed May 10, 2017.
16. Kimber E. AMC: amyoplasia and distal arthrogryposis. Journal of children's orthopaedics. 2015;9(6):427-32.
17. X-linked Hypophosphatemic rickets. Disease search. Website of Orphanet. http://www.orpha.net/consor/cgi-bin/Disease_Search.php? Last accessed May 10, 2017
18. Seikaly, M.G. and Baum, M., 2001. Thiazide diuretics arrest the progression of nephrocalcinosis in children with X-linked hypophosphatemia. *Pediatrics*, *108*(1), e6-e6.
19. About Osteogenesis Imperfecta (OI). Osteogenesis Imperfecta Foundation. Available at http://www.oif.org/site/PageServer?pagename=AOI_FactsLast accessed May 10, 2017.
20. Van Dijk FS, Cobben JM, Kariminejad A, Maugeri A, Nikkels PG, van Rijn RR, Pals G. Osteogenesis imperfecta: a review with clinical examples. Molecular syndromology. 2011; 2(1):1-20.
21. Orengo, Jamie Marie, Aleksandra Leliwa-Sytek, James E. Evans, Barbara Evans, Diana van de Hoef, Marian Nyako, Karen Day, and Ana Rodriguez. "Uric acid is a mediator of the Plasmodium falciparum-induced inflammatory response." *PLoS One* 2009; 4(4): e5194.
22. Sarma PS, Mandal AK, Khamis HJ. Allopurinol as an additive to quinine in the treatment of acute complicated falciparum malaria. The American journal of tropical medicine and hygiene. 1998; 58(4):454-7.
23. Li, S., Yang, H., Guo, Y., Wei, F., Yang, X., Li, D., Li, M., Xu, W., Li, W., Sun, L. and Gao, Y. Comparative efficacy and safety of urate-lowering therapy for the treatment of hyperuricemia: a systematic review and network meta-analysis. *Scientific Reports* 2016; *6*.
24. Poland syndrome. Website of Genetics Home Reference, The National Library of Medicine (NLM),National Institutes of Health, U.S. Department of Health and Human Services (HHS).Available at https://ghr.nlm.nih.gov/condition/poland-syndrome Last accessed May 5, 2017.
25. De Jong, Johanna P., Steven L. Moran, and Simo K. Vilkki. "Changing paradigms in the treatment of radial club hand: microvascular joint transfer for correction of radial deviation and preservation of long-term growth." *Clinics in orthopedic surgery 2012;* 4.1:36-44.
26. Hereditary Multiple Osteochondromas. GARD: Genetic rare diseases information centre (NIH) Available at https://rarediseases.info.nih.gov/diseases/7035/hereditary-multiple-osteochondromas/cases/54436 Last accessed May 3, 2017.
27. Middleton, Anna, Georgina Hall, and Christine Patch. "Genetic counselors and Genomic Counseling in the United Kingdom." *Molecular genetics & genomic medicine* 2015: 3.2:79-83.

28. Rath A, Olry A, Dhombres F, Brandt MM, Urbero B, Ayme S. Representation of rare diseases in health information systems: the Orphanet approach to serve a wide range of end users. Human mutation. 2012; 33(5):803-8.
29. Knight AW, Senior TP. The common problem of rare disease in general practice. Medical Journal of Australia. 2006; 185(2):82.