PanAfrican Medical Journal

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Case report

Hereditary multiple exostoses and porencephaly in a Nigerian child: a case report

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Key words: Hereditary multiple exostoses, porencephaly, child, female, Nigerian

Received: 23/12/2017 - Accepted: 16/01/2018 - Published: 23/02/2018

Abstract

Hereditary multiple exostoses (HME) is a rare condition that is characterised by the development of bony swellings, usually at the growth ends of long bones. It is autosomal dominant, and may result in debilitating deformities. Porencephaly on the other hand is a cystic degeneration of the brain that is associated with the development of encephalomalacia. There is no established link between HME and porencephaly. This case report describes a seven year old female that has features of coexisting HME and porencephaly. She presented with afebrile seizures, learning impairment, stunted growth, macrocephaly and multiple bony swellings. Similar bony swellings were observed in the mother and the sibling of the index case. The coexistence of HME and porencephaly is rarely encountered in clinical practice. This presentation should stimulate the search for a possible link, which may perhaps herald the discovery of a new syndrome.

Pan African Medical Journal. 2018;29:131. doi:10.11604/pamj.2018.29.131.14680

This article is available online at: http://www.panafrican-med-journal.com/content/article/29/131/full/

Introduction

Hereditary Multiple Exostoses (HME) is a rare condition that is characterised by the development of outgrowths along the metaphyses of long bones [1]. Such lumps are often described as osteochondromas, hence the synonym Multiple Osteochrondromatosis. It is an autosomal dominant condition which is seen in 1 in every 50,000 persons [1]. The diagnosis is mainly clinical and radiological. This condition has been associated with mutation in three genes; EXT 1, EXT 2, EXT 3 [2]. These genes are believed to be vital in heparan sulfate synthesis, which in turn is crucial in chondrocyte synthesis and proliferation [3]. HME is reported to have up to 96% penetrance and individuals with EXT 1 mutations have been observed to present with the worst symptoms [4]. HME is not commonly associated with severe symptoms. However, depending on the location of the osteochondromas, affected persons could experience pain from nerve compression, vascular compromise, limb length discrepancy, shortened height, bowing of the limbs and limited range of movement [5]. Rarely, the osteochondromas may undergo malignant transformation [6]. Porencephaly is a rare congenital condition resulting in focal cavitatory lesions in the brain, which mostly communicate with the cerebral ventricles. The cavities result from brain destruction during the late fetal or early postnatal developmental stages [7]. Although, porencephaly is commonly attributable to factors such as ischaemic or haemorrhagic insults, the role of toxic agents, infections, trauma and drugs has also been reported [7, 8]. Mutations of the gene that encodes for type IV collagen alpha 1 (COL4A1) has been implicated in some cases of autosomal dominant porencephaly [8]. Type IV collagen is a main component of basement membrane, including the vascular endothelium. The clinical features of porencephaly vary widely and essentially depend on the location and extent of the lesion [7]. Individuals with the condition may manifest with motor deficits, intellectual impairment and seizure disorder [7]. Although, there have been very few reports of multiple exostoses among Nigerian children, cases of co-existing HME and porencephaly are rarely encountered in clinical practice [9-11].

Patient and observation

AA is a Nigerian female child who presented at the Paediatric Neurology clinic at the age of five years with history of recurrent afebrile generalised seizures that started when she was about two years old. Her delivery and immediate neonatal period was not adversely eventful. However, there was marked delay in the motor and speech milestones. In addition, the parents complained of multiple hard lumps around the child's limbs which were noticed when she was about 3 years old. Similar lumps are present around the upper limbs of the mother, as well as the elder sibling of the index case (Figure 1, Figure 2). Further evaluation revealed a young girl who had mild mental retardation and macrocephaly. She had multiple hard swellings around the ulna aspects of both forearms and the knees. There was bowing of the forearms bilaterally. Radiograph of the limbs showed bony outgrowths along the distal end of the ulna bones, as well as the distal ends of the femoral bones bilaterally (Figure 3, Figure 4). Computed Tomography image of the brain showed significant dilatation of the demonstrated ventricles with right sided poroncephalic cyst communicating with the ventricle (Figure 5). A diagnosis of HME, Poroencephalic cyst and Seizure disorder was made. She had been on Sodium valproate tablets and had been seizure free for more than a year.

Discussion

The diagnosis of HME is made when there are two or more bony outgrowths, commonly arising from the metaphyses of long bones [**1**]. The outgrowths are usually not noticeable at birth [1]. Our patient had such multiple outgrowths which were not noticed until the third year of life. Furthermore, the fact that similar outgrowths were present in the sibling as well as the mother of our patient buttresses the autosomal dominant nature of the condition. There are only a handful of reported cases among Nigerian children and fewer cases of the disease manifesting among first degree relatives [9-11]. Linkage analysis has established that mutations in EXT 1 on 8q24.1 and EXT 2 on 11p13 are responsible for about one half and one third of HME cases respectively [2]. These genes (EXT 1 and EXT 2) are believed to regulate chondrocyte maturation and differentiation, which are necessary for normal endochondral ossification within the growth plate [3]. The molecules encoded by EXT 1 and EXT 2 are involved in the regulation of cell surface heparin sulphate proteoglycans (HSPGs) [3]. A defect in the HSPG biosynthesis causes a local error in the normal negative feedback loop that regulates chondrocyte proliferation and maturation, which may result in premature differentiation and abnormal development at the growth plate [3, 12]. HME is usually a benign condition and symptoms are often mild [5]. However, the abnormal growth at the

rapidly developing ends of the long bones often leads to debilitating deformities such as bowing of the bones and stunted height, as noted in our patient [5]. Surgical procedures can either correct or limit the progression of some of these deformities. AA also has features of porencephalic cysts on Computed Tomography. Porencephaly is a very rare disorder that results in cystic degeneration and encephalomalacia [7]. The condition may result from various factors, common among which are vascular and ischemic insults that occur in utero [8].

Genetics have been shown to play a role in the aetoiopathogenesis of porencephaly, as mutations in COL4A1 gene has been implicated in some cases [8]. This gene is responsible for the expression of type IV collagen which is present in the basement membrane of cerebral blood vessels and other body tissues [13]. Mutation of this gene leads to weakness of cerebral blood vessels and this increases the possibilities of intracerebral bleeding and the subsequent formation of porencephalic cysts in utero [13]. The clinical manifestations of porencephaly vary widely, and depend essentially on the size and location of the cysts. Cerebral palsy, seizure disorder, learning impairment, macrocephaly are some of the common manifestations [7]. Our patient presented with seizures, learning impairment and also had macrocephaly which are in keeping with the constellation of symptoms associated with porencephaly. The management is non-specific and essentially directed at the prevailing clinical manifestations. Although, our search has not yielded a direct link between HME and porencephaly, a possible connection may be the effect of EXT 1 gene on fibroblast growth factor (FGF); It is well established that the mutation in EXT 1 gene is responsible for up to half of the cases of HME and it is also known that beyond HME, EXT 1 gene is involved in the activity of fibroblast growth factors (FGF) [2, 14]. Furthermore, FGFs have been shown to be potent mitogens for angiogenesis [15]. Thus, disrupted angiogenesis that occur from abnormal FGFs function may perhaps lead to cerebrovascular insufficiency, which is an established risk factor for the development of porencephaly [8]. There has been a reported case of multiple exostoses and schizophrenia in three first degree relatives, who similar to our patient, also had ventriculomegaly [16]. There was another reported case of HME, macrocephaly, mental retardation and congenital heart disease; however, this particular individual had normal FISH study of EXT1, EXT2 and EXT3 genes [17]. It may be quite possible that the coexistence of HME and porencephaly in our patient is merely coincidental. However, we think that this interesting and rarely encountered association requires further evaluation as it may herald the discovery of a new syndrome.

Conclusion

We have reported a rare and hitherto unreported combination of Porencephaly and Hereditary multiple exostoses. Although presently, there is no established or specific link that has been described between the two rare diseases, we think efforts should be made to unravel the possibility of the existence of a common pathway between the two conditions.

Competing interests

The authors declare no competing interests.

Authors' contributions

Idris Adedeji conceived, designed and wrote the manuscript. He is also responsible for any query arising thereof. Hamza Ahmed contributed to the intellectual content of the manuscript; he also critiqued and approved the final draft. Abdulazeez Tella, Muhammad Bashir and Yusuf Salisu read and made valuable contributions to the manuscript. All the authors read and approved the final draft for publication.

Figures

Figure 1: Frontal radiograph of both forearms of the mother of the index case, showing bilateral bony outgrowth from the proximal lateral margin of the right ulna bone and left radius with associated bony expansion, shortening of the left ulna bone and pseudoarthrosis

Figure 2: Frontal radiograph of both forearms of the sibling of the index case, showing bony outgrowth from both proximal ulna bones with associated bony expansion of both radial and ulna heads

Figure 3: Lateral radiograph of the index case, showing proximal bony outgrowth with associated bony expansion and bowing of the ulna bones bilaterally

Figure 4: Frontal knee joint radiograph of the index case, showing bilateral bony outgrowth from lateral and medial distal femoral ends bilaterally

Figure 5: Axial non contrast enhanced computed tomographic image of the brain at the level of the frontal horn of the lateral ventricle of the index case, showing significant dilatation of the demonstrated ventricles with right sided proncephalic cyst communicating with the ventricle

References

1. Weinstein S, Buckwalter J. Turek's orthopaedics principles and their applications-6th ed, Philadelphia. Lipincott. 2005. **Google Scholar**

2. Legeai-Mallet L, Margaritte-Jeannin P, Lemdani M, Merrer ML, Plauchu H, Maroteaux P et al. An extension of the admixture test for the study of genetic heterogeneity in hereditary multiple exostoses. Hum Genet. 1997; 99(3): 298-302. **PubMed** | **Google Scholar**

3. Duncan G, McCormick C, Tufaro F. The link between heparan sulfate and hereditary bone disease: finding a function for the EXT family of putative tumor suppressor proteins. J Clin Invest. 2001; 108(4): 511-516.**PubMed** | **Google Scholar**

4. Porter DE, Lonie L, Fraser M, Dobson-Stone C, Porter JR, Monaco AP et al. Severity of disease and risk of malignant change in hereditary multiple exostoses: a genotype-phenotype study. J Bone Joint Surg Br. 2004; 86(7): 1041-1046. **PubMed** | **Google Scholar**

5. Shapiro F, Simon S, Glimcher MJ. Hereditary multiple exostoses: anthropometric, roentgenographic and clinical aspects. J Bone Joint Surg Am. 1979; 61(6A): 815-824. **PubMed** | **Google Scholar**

6. Ochsner PE. Multiple cartilaginous exostoses and neoplastic degeneration: review of the literature. Z Orthop Ihre Grenzgeb. 1978; 116(3): 369-378. **PubMed** | **Google Scholar**

7. Tonni DG, Ferrari B, Defelice C, Centini G. Neonatal porencephaly in very low birth weight infants: Ultrasound timing of asphyxial injury and neurodevelopmental outcome at two years of age. The Journal of Maternal-Fetal & Neonatal Medicine. 2005; 18(6): 361-365. **Google Scholar**

8. Yoneda Y, Haginoya K, Arai H, Yamaoka S, Tsurusaki Y, Doi H et al. De novo and inherited mutations in COL4A2, encoding the type IV collagen α2 chain cause porencephaly. Am J Hum Genet. 2012; 90(1): 86-90. **PubMed** | **Google Scholar**

9. Yinusa W, Owoola AM, Esin IA. Hereditary multiple exostosis: case report. Niger J Clin-Pract. 2010; 13(2): 218-222.

10. Adelowo O, Adebayo S. Hereditary multiple exostosis in two Nigerian siblings. BMJ Case Rep. 2009; 2009: bcr09.2008.0901. Epub 2009 Apr 7. **PubMed** | **Google Scholar**

11. Eke GK, Omunakwe HE, Echem RC. Hereditary multiple exostoses in a 15 year old boy: a case report and review of literature. Niger J Paediatr. 2016; 43(4): 295-298. **Google Scholar**

12. Vortkamp A, Lee K, Lanske B, Segre GV, Kronenberg HM, Tabin CJ. Regulation of rate of cartilage differentiation by Indian hedgehog and PTH-related protein. Science. 1996; 273(5275): 613-622.**PubMed** | **Google Scholar**

13. Thomas L. Genetic mutation predisposes to porencephaly. Lancet Neurol. 2005; 4(7): 400. **PubMed** |**Google Scholar**

14. Mundhenke C, Meyer K, Drew S, Friedl A. Heparan sulfate proteoglycans as regulators of fibroblast growth factor-2 receptor binding in breast carcinomas. Am J Pathol. 2002; 160(1): 185-194. **PubMed** |**Google Scholar**

15. Montesano R, Vassalli JD, Baird A, Guillemin R, Orci L. Basic fibroblast growth factor induces angiogenesis in vitro. Proc Natl Acad Sci U S A. 1986; 83(19): 7297-7301. **PubMed** | **Google Scholar**

16. Aizenberg D, Blumensohn R, Shalev A, Munitz H. Multiple exostosis, brain ventricular enlargement and schizophrenia. Psychiatr J Univ Ott. 1989; 14(1): 298-300. **PubMed** | **Google Scholar**

17. Hanan Hamouda I, Sawasan Abdulhasan, Sadika Al-awadi. Hereditary multiple exostoses, macrocephaly, congenital heart disease, developmental delay and mental retardation in a female patient: A possible syndrome? Or new association. Egyptian Journal of Medical Human Genetics. 2011; 12(1): 95-98.**PubMed** | **Google Scholar**

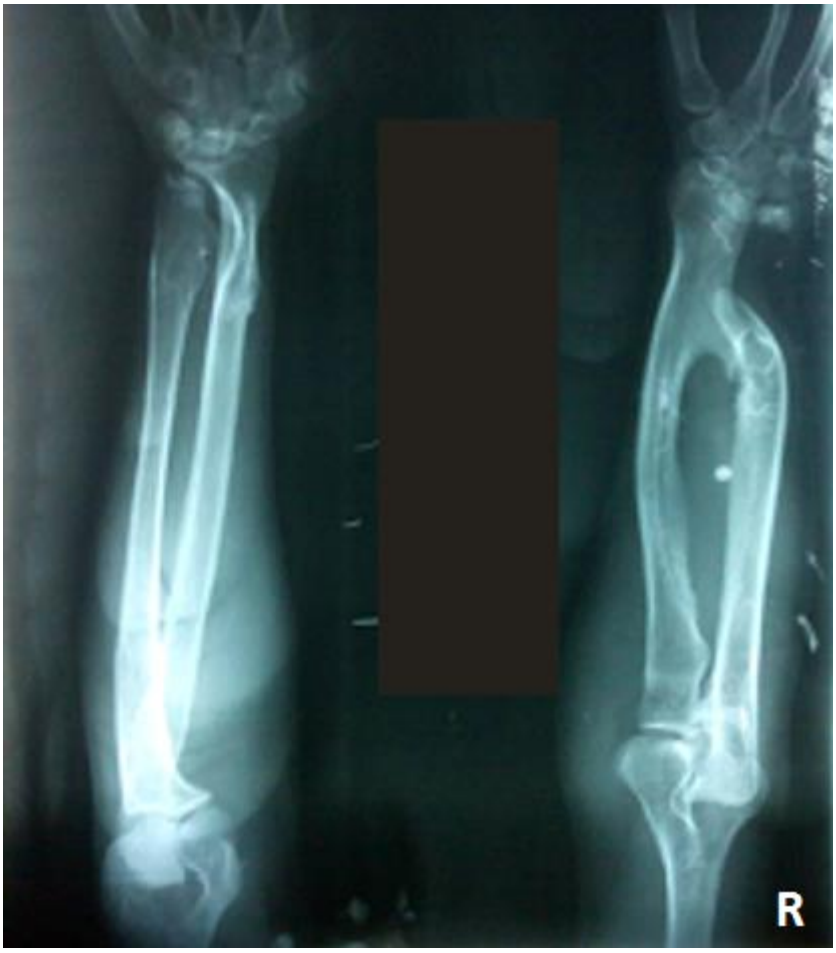

Figure 1: Frontal radiograph of both forearms of the mother of the index case, showing bilateral bony outgrowth from the proximal lateral margin of the right ulna bone and left radius with associated bony expansion, shortening of the left ulna bone and pseudoarthrosis

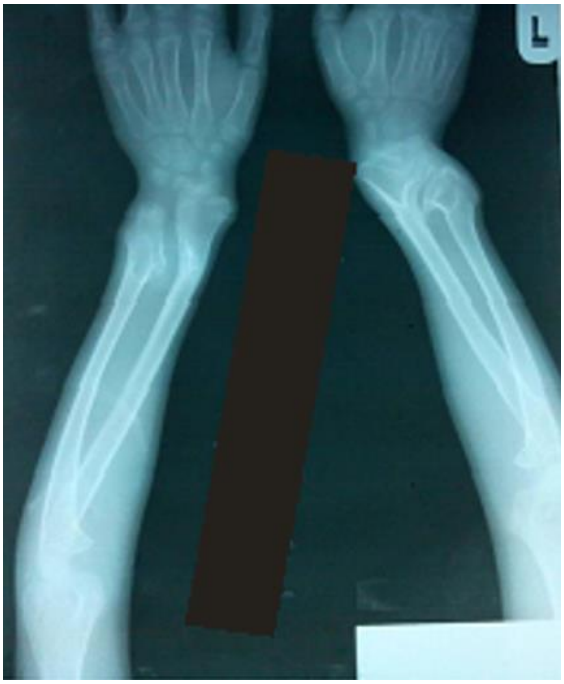

Figure 2: Frontal radiograph of both forearms of the sibling of the index case, showing bony outgrowth from both proximal ulna bones with associated bony expansion of both radial and ulna heads

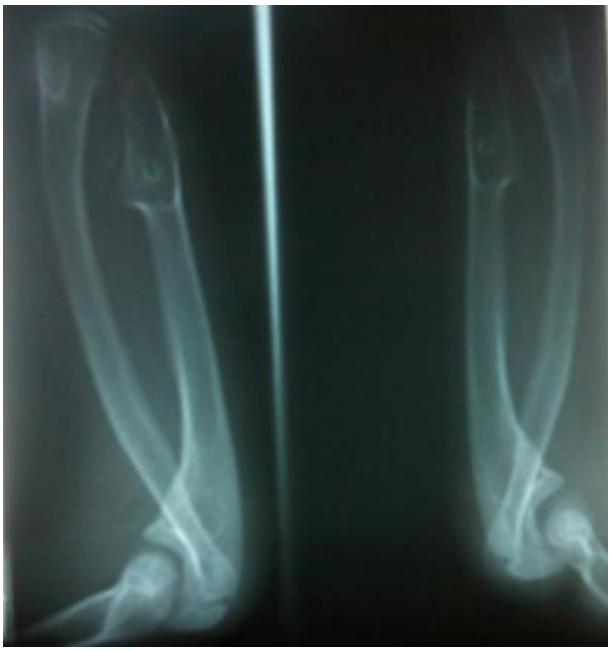

Figure 3: Lateral radiograph of the index case, showing proximal bony outgrowth with associated bony expansion and bowing of the ulna bones bilaterally

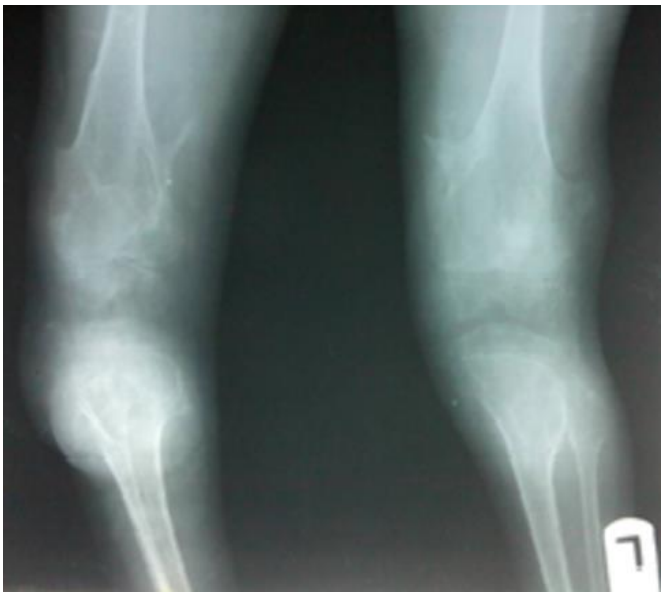

Figure 4: Frontal knee joint radiograph of the index case, showing bilateral bony outgrowth from lateral and medial distal femoral ends bilaterally

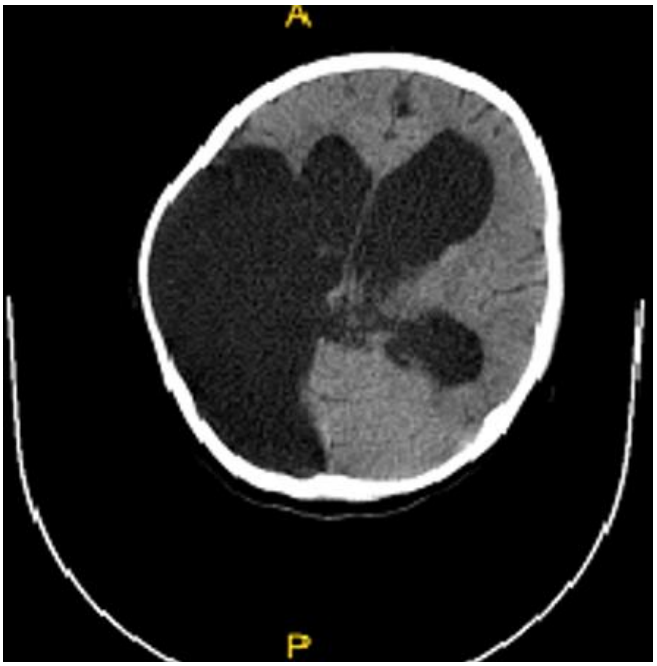

Figure 5: Axial non contrast enhanced computed tomographic image of the brain at the level of the frontal horn of the lateral ventricle of the index case, showing significant dilatation of the demonstrated ventricles with right sided proncephalic cyst communicating with the ventricle