



Focal Fibroadipose Overgrowth of the Forehead: A Case Report

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Abstract

This article describes a rare case of isolated focal fibroadipose overgrowth of the forehead in a 15-year-old patient. Various overgrowth syndromes were considered in the differential diagnosis, including Proteus syndrome, facial infiltrating lipomatosis, and macrodystrophia lipomatosa. The diagnosis is primarily based on clinical presentation and imaging modalities. However, for academic and supporting diagnostic purposes a biopsy is advised, yet may not be in the best interest of the patient. Management was conservative with future perspective for surgical management after cessation of growth.

Key Clinical Message

Focal fibroadipose overgrowth can be caused by various overgrowth syndromes. Accurately diagnosing these syndromes is important, since there are differences in preferred therapeutic management and follow-up, including the need for cancer surveillance. In isolated, limited, benign focal fibroadipose overgrowth, the benefits of an invasive biopsy might be outweighed by the possible risks.

Keywords

Fibroadipose, Overgrowth, Adolescent Medicine

Introduction

Several overgrowth syndromes are well described in the literature and are usually divided into generalized or segmental overgrowth syndromes. Segmental overgrowth syndromes cause a localized overgrowth of the body involving different tissue types and can be either focal or have a mosaic distribution. Diagnosis is usually made on clinical grounds and confirmed by molecular analysis of the tissue. Most overgrowth syndromes are caused by mutations in the

PI3K/AKT/mTOR pathway of the affected tissue, a signaling cascade that plays an important role in cellular growth [1]. Treatment depends on the specific syndrome and the functional impact of the disease process. Cancer surveillance may be warranted, since several overgrowth syndromes are associated with higher rates of malignancies compared to the general population [2].

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Case report

A 15-year-old girl presented with a slow-growing mass of the right forehead, which had been present since birth, but became more pronounced during the preceding five months. The treatment-seeking symptoms included intermittent unilateral, right-sided headache, monocular vision disturbance, and aesthetic concerns. There was no significant medical and family history nor consanguinity. The clinical examination revealed an ill-defined mass of the right forehead, extending well beyond the hairline. It included a soft, rubbery enlargement, as well as a distinguishable solid component more distally. The mass was not painful and non-pulsatile. CT imaging showed significant hyperostosis of the calvarium (**Fig-1A** to **Fig-1C**). Furthermore, it revealed marked enlargement of both adipose tissue and skin proximal to the cranial hyperostosis (**Fig-1D**).

Bone scintigraphy and SPECT-scan using technetium-99m hydroxydiphosphonate ($^{99m}\text{Tc-HDP}$) were performed to assess the extent of active bone formation and to screen for similar lesions elsewhere. The SPECT scan revealed increased tracer uptake in the affected area, indicating active bone formation (**Fig-2**). No similar lesions were found elsewhere. Benefits of taking an invasive biopsy were deemed to be outweighed by the risks, since the affected area did not display radiographic features suspicious for malignancy. Hence, tissue analysis was postponed until after surgery. A consensus was reached to initially adopt a conservative approach, followed by secondary corrective osteotomy under neuronavigation guidance. This would be performed after cessation of active growth to reduce the chances of recurrence. This approach was supported by the two subsequent opinions sought by the family in other academic hospitals.

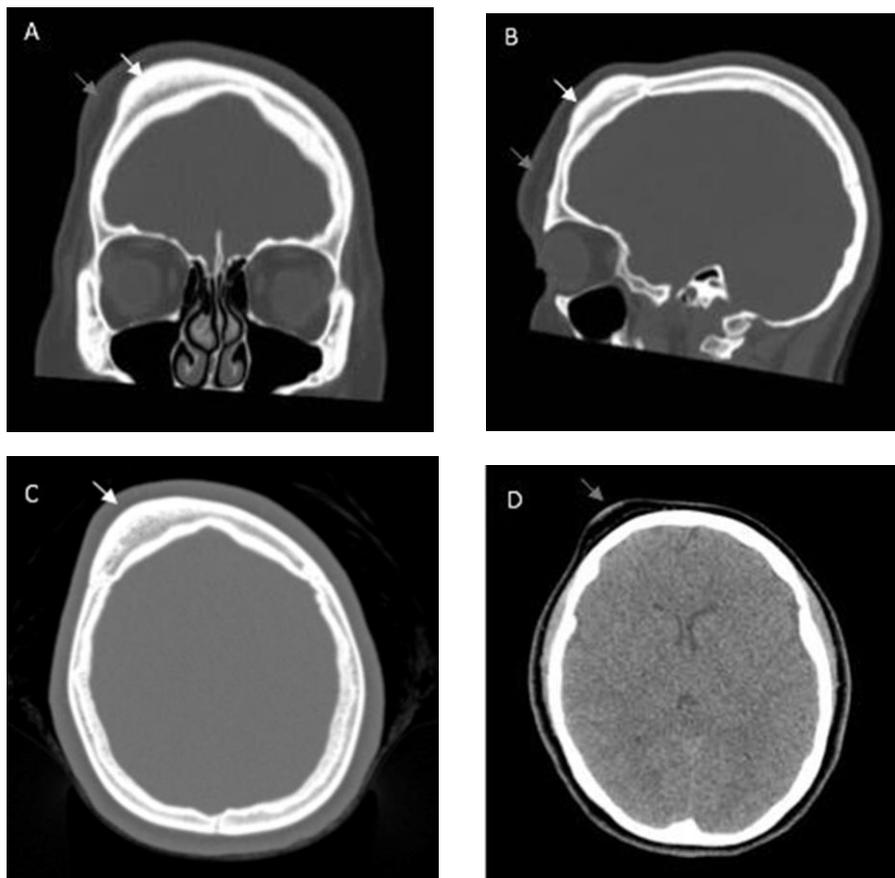
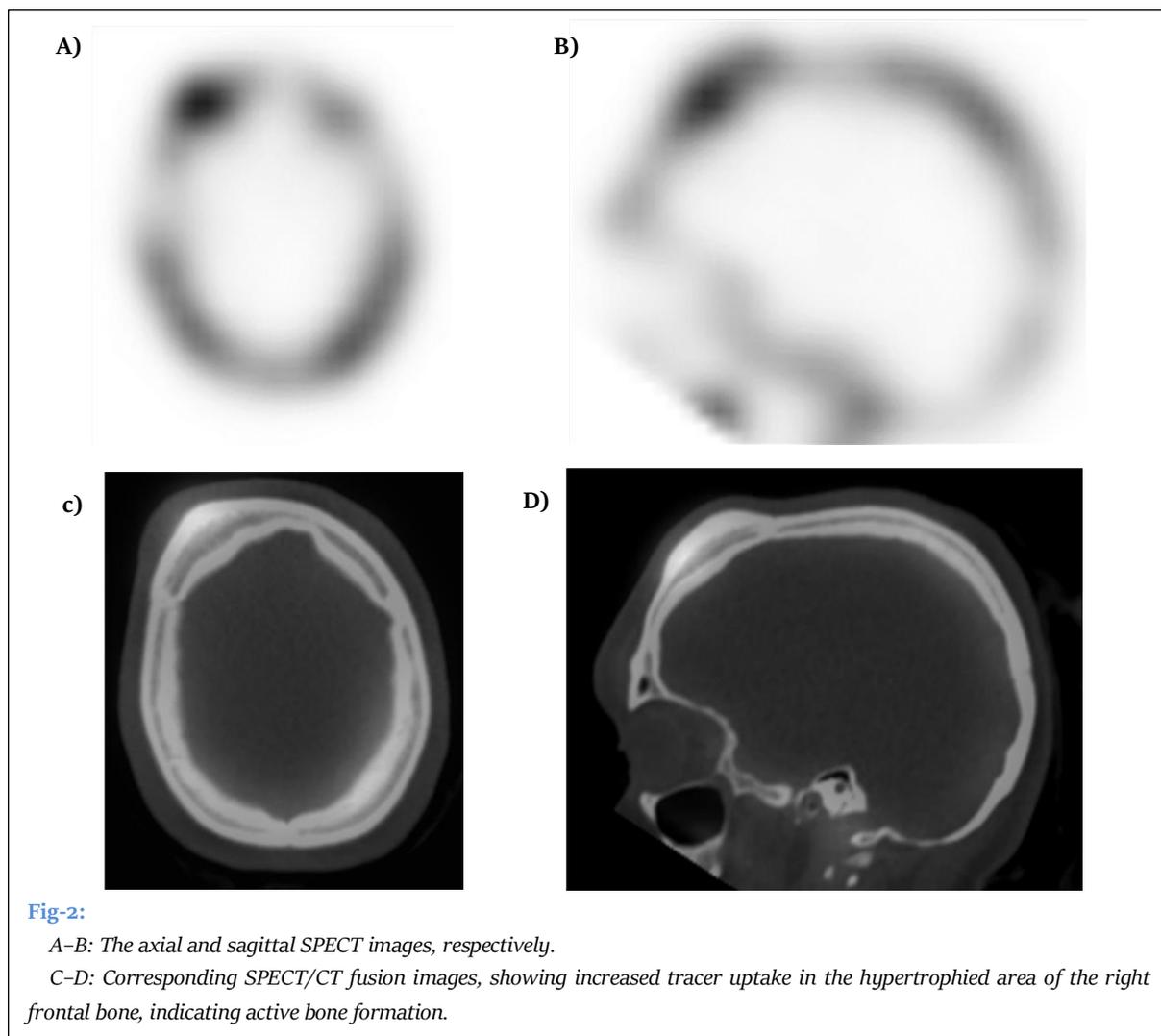


Fig-1: CT imaging of the head.

A–C: In respective order, they show coronal, transversal and axial views of the cranial hyperostosis (white arrows) and lipomatous overgrowth (grey arrows).

D: Axial brain window depicting the lipomatous and dermal overgrowth (grey arrow).



Discussion

Many different etiologies can cause cranial hyperostosis, such as osteoma, fibrous dysplasia, Paget's disease, infantile cortical hyperostosis, osteopetrosis, and hyperostosis frontalis interna [3]. However, in all previous etiologies, concurrent enlargement of accompanying soft tissues is absent. Hence, the concurrent overgrowth of soft tissues next to the cranial hyperostosis in the presented case relegated these causes of isolated cranial hyperostosis.

Various overgrowth syndromes were considered in the differential diagnosis, including Proteus syndrome (PS), facial infiltrating lipomatosis (FIL), and macrodystrophia lipomatosa (MDL). In the recent past, syndromes giving rise to a segmental overgrowth pattern (i.e. focal or mosaic) were classified and diagnosed according to clinical and/or radiological

criteria. However, recent advancements in the understanding of the molecular basis for the overgrowth have pushed the classification of these syndromes from a clinical to a molecular focus [4].

The most important pathway where mutations have been found to result in overgrowth abnormalities, is the PI3K/AKT/mTOR pathway [5]. Mutations that upregulate this pathway are amongst the most common mutations found in different types of cancer [2]. The segmental overgrowth syndromes are now classified as distinct disorders based on the molecular lesions that upregulate this pathway [1]. They include PS, the PIK3CA-related overgrowth spectrum (PROS), and the PTEN hamartoma tumor syndrome (PHTS) [6]. Since these overgrowth syndromes share overlapping clinical features, molecular analysis may support the definite diagnosis [4].

PIK3CA-Related Overgrowth Spectrum (PROS):

PROS includes a wide spectrum of rare disorders causing overgrowth of parts of the body due to somatic mutations in the PIK3CA gene [7]. This gene provides instructions for making PIK3CA, a subunit of the PI3K enzyme. Specific disorders in this spectrum include fibroadipose hyperplasia, congenital lipomatous overgrowth, vascular malformations, epidermal nevi and scoliosis/skeletal/spinal anomalies syndrome (CLOVES syndrome), megalencephaly-capillary malformation syndrome (MCAP syndrome), hemihyperplasia-multiple lipomatosis syndrome (HHML syndrome), hemimegalencephaly and facial infiltrating lipomatosis (FIL) [7]. PROS is often associated with an increased risk for vascular malformations, thrombosis, and pulmonary embolisms [7]. All disorders are congenital or have an early childhood onset. While some of the disorders include multiple features, others present with isolated features. One of the disorders falling in this spectrum is fibroadipose hyperplasia, characterized by mosaic, progressive overgrowth of subcutaneous, muscular, and visceral adipose tissue, sometimes associated with skeletal overgrowth. Another disorder in this spectrum is FIL or congenital infiltrating lipomatosis of the face, which displays similar clinical features compared with the presented case. FIL is a congenital disorder that causes an isolated overgrowth of one side of the face [8]. Patients usually present with facial asymmetry at birth or during early childhood, which evolves as the patients grow [8]. It is caused by the invasion of mature lipocytes into adjacent tissues (including bony structures, muscles, salivary glands, etc.), causing disproportionate unilateral facial soft tissue and skeletal hypertrophy [8]. The maxilla, mandible, and zygomatic bones are variably hypertrophied in FIL [9]. Other frequent findings include macrodontism, parotid gland invasion, and muscle involvement [9]. Overgrowth of the forehead or hypertrophy of the frontal bone, as seen in the presented case, has not been described in a patient with FIL [9].

PTEN Hamartoma Tumor Syndrome (PHTS):

The PTEN gene plays a crucial role in inhibiting PI3K/Akt signaling [6]. Hence, loss of function mutations can cause uncontrolled growth and are frequently found in a wide range of human

malignancies [10]. PHTS includes a spectrum of disorders caused by germline mutations in the PTEN gene, namely Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, adult Lhermitte-Duclos disease, and autism spectrum disorders associated with macrocephaly [11]. Most of the current knowledge is about Cowden syndrome, a rare multisystem disorder that entails an increased risk of different malignancies of the breast, endometrium, and thyroid as well as benign overgrowth of different tissues [12]. Since hyperostosis, as observed in the presented patient, is not seen in any of the disorders of PHTS and the patient did not display any other clinical features suggestive of PHTS, this was not considered a possible underlying etiology.

Proteus Syndrome (PS):

PS is characterized by progressive overgrowth of skin, bone, muscle, and fatty tissue with multisystem involvement. It is caused by an activating mutation in the AKT gene (c.49G>A, p.Glu17Lys) [13]. PS usually presents in childhood and presenting symptoms range from partial gigantism to macrocephaly, lipomas, or vascular malformations, which makes the diagnosis challenging [14]. Both cranial hyperostosis and overgrowth of adipose tissue are frequently observed in PS, with craniofacial hyperostosis present in approximately 30% of patients [15]. In the presented case, the localized cranial hyperostosis seemed to resemble the skull involvement often observed in PS. However, our patient had no signs of multisystem involvement and did therefore not fulfill the clinical criteria necessary to diagnose PS.

Macrodystrophia Lipomatosa (MDL):

A different entity, which is sometimes considered to be a focal variant of PS, is MDL [16]. MDL is a rare congenital disorder, characterized by progressive localized overgrowth of fibroadipose and bony tissues of extremities, usually ceasing after puberty. The exact pathophysiology of MDL, as well as its genetic bases, remains unknown. Endosteal and periosteal deposition of bone can cause osseous enlargement. The most-reported histopathologic finding is an increase in adipose tissue, typically shattered in a fine mesh of fibrous tissue [3]. Overgrowth usually occurs unilaterally and follows specific sclerotomes related to

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peripheral nerves. The diagnosis of MDL is primarily made through clinical presentation and imaging modalities, but can be supported by histopathological examination [17]. Surgical treatment is preferably delayed until after puberty to reduce the chances of recurring hyperplasia [18]. In the presented case, it could be argued that the overgrowth occurred along the distribution pattern of the right frontal nerve, a branch of the ophthalmic division of the trigeminal nerve. Hence, a comparison can be made with the clinico-radiologic presentation and evolution of MDL, namely congenital, progressive, unilateral focal overgrowth of both osseous, lipomatous and skin tissues following the distribution pattern of one peripheral nerve. However, the site of overgrowth is different than the usual affected site in MDL, which is along a nerve territory in the extremities.

Clinico Academic Dilemma

The diagnosis of focal overgrowth syndromes is based on clinical presentation and radiologic imaging. However, tissue analysis using targeted next generation sequencing is often performed to make a final diagnosis, since this can guide future management [19]. For example, overgrowth syndromes associated with macrocephaly can be caused by different overgrowth syndromes, all associated with different degrees of developmental delay [19]. Furthermore, some genetic mutations entail a higher risk of malignancy compared to others.

In the current case, the fibroadipose overgrowth was isolated, of limited extent, and not suspicious for malignancy. The patient and her parents preferred conservative management over invasive biopsy and/or surgery. While a clinical diagnosis of focal fibroadipose overgrowth could be made, the genetic base for this overgrowth remains uncertain. The informed decision against a biopsy was supported by the two subsequent opinions sought by the family in other academic hospitals.

Ethical Dilemma

In the current case, a biopsy would further augment the diagnosis and could guide further management. The patient and her parents decided against a biopsy after consultation regarding possible risks and

benefits. In recent decades, paternalistic medical opinion has been replaced by shared decision making between well-informed patients and their caregivers. Nevertheless, it is the medical fraternity's responsibility to evaluate the capacity and reasons for treatment decisions [20]. Our patient was an underaged 15-year old adolescent from a traditional Roma family. Adolescents under the age of 16 may be able to consent, depending on their maturity and ability to understand the medical implications of their decision. During the consultation, our patient deferred decisions to her parents. Collectively they did not deem the esthetic impact a priority for treatment. This well-informed decision in favour of regular follow-up sessions with surgical intervention in the future was deemed responsible and supported by several experts in the field.

Conclusion

Various overgrowth syndromes were considered in the differential diagnosis, including Proteus Syndrome (PS), Facial Infiltrating Lipomatosis (FIL), and MacroDystrophia Lipomatosa (MDL). A clinical diagnosis of focal fibroadipose overgrowth could be made, yet its genetic base remains uncertain. While a tissue biopsy is helpful to diagnose these overgrowth syndromes and to exclude malignant pathologies, its benefits might be outweighed by possible risks in limited fibroadipose overgrowth.

Contributors' Statement

1. Bram Boon conceptualized and wrote the article.
2. Jaques Van Heerden and Mania De Praeter were the main physicians of the patient and supervised the article.
3. Sander Jentjens was the nuclear medicine physician assigned to the case.
4. All authors reviewed and contributed equally toward the revision of the manuscript according to their specialties.

Conflict of Interest

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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