Aberrant muscular hyperplasia of the hand and PIK3CA related overgrowth spectrum disorders. A case series study

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ABSTRACT

Introduction. Congenital muscular hyperplasia of the hand is a rarely described entity, characterized by the presence of aberrant or accessory muscles in the hypothenar eminence, which has been always reported as sporadic anomaly in the medical literature. The aim of this paper is to report a series of cases with a phenotype of aberrant muscle hyperplasia associated with PIK3CA mutations.

Material and Methods. We describe a retrospective series of cases followed at our institution between 2008 and 2020, with a unique phenotypein the context of PIK3CA mutations.

Results. A total of 6 patients were included (4 males and 2 females), who presented with an enlargement of the hypothenar eminence of the hand and peculiar wrinkling of the overlying skin, associated with ulnar deviation of the metacarpo-phalangeal joints. In all cases, variable degrees of congenital overgrowth of the ipsilateral limb were observed. Skin punch biopsy (5 mm diameter and 3-5 mm depth) was performed on 4 patients, where striated muscle hyperplasia and the presence of striated muscular fibers in the dermis and hypodermis were observed in all of them. Genetic studies revealed PIK3CA mutation in 3 of the 4 patients whose affected tissue was analyzed, in a mosaic state ranging from 3 to 8% (His1047Arg, Glu542Lys, and Cys420Arg, 1 case each).

Conclusion. Aberrant muscular hyperplasia of the hand is a well-recognized entity scarcely described in association with PIK-3CA spectrum disorder in the pediatric population. The role of PIK-3CA in muscle overgrowth is not yet well understood.

KEY WORDS: Aberrant tissue; Congenital hand deformity; Human; Hyperplasia; PIK3CA Protein.

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HIPERPLASIA MUSCULAR ABERRANTE DE LA MANO Y SÍNDROMES DE SOBRECRECIMIENTO RELACIONADOS CON EL PIK3CA. SERIE DE CASOS

RESUMEN

Introducción. La hiperplasia muscular congénita de la mano es una entidad rara, caracterizada por la presencia de músculos aberrantes o accesorios en la eminencia hipotenar, que siempre se ha descrito en la literatura médica como una anomalía esporádica. El objetivo de este artículo es informar de una serie de casos con fenotipo de hiperplasia muscular aberrante asociada a mutaciones del PIK3CA.

Material y métodos. Serie retrospectiva de casos atendidos en nuestro centro entre 2008 y 2020, con un fenotipo único en el contexto de las mutaciones del PIK3CA.

Resultados. Se incluyeron un total de 6 pacientes (4 masculinos y 2 femeninos) con ensanchamiento de la eminencia hipotenar de la mano y arrugamiento peculiar de la piel suprayacente, asociado a desviación ulnar de las articulaciones metacarpofalángicas. En todos los casos se observaron grados variables de sobrecrecimiento congénito del miembro ipsilateral. Se realizó biopsia cutánea por punch (5 mm de diámetro y 3-5 mm de profundidad) en 4 pacientes con hiperplasia muscular y presencia de fibras musculares estriadas en dermis e hipodermis. Los estudios genéticos revelaron mutación del PIK3CA en 3 de los 4 pacientes, cuyo tejido afectado fue enviado a analizar, con mosaicismo de entre el 3 y el 8% (His1047Arg, Glu542Lys y Cys420Arg respectivamente).

Conclusión. La hiperplasia muscular aberrante de la mano es una entidad reconocida pero escasamente descrita en asociación con síndromes relacionados con el PIK3CA en la población pediátrica. A día de hoy sigue desconociéndose el papel del PIK3CA en el sobrecrecimiento muscular.

PALABRAS CLAVE: Tejido aberrante; Deformidad congénita de la mano; Humano; Hiperplasia; Proteína PIK3CA.

INTRODUCTION

Congenital muscular hyperplasia of the hand is a rarely described entity, characterized by the presence of aberrant or accessory muscles in the hypothenar eminence, which has been always reported as a spo-

radic anomaly in the medical literature. Unfortunately nomenclature is not uniform and this disorder has been previously referred with different terminology including ectopic muscle development, monomelic muscular hypertrophy, muscular hyperplasia or isolated muscle overgrowth among others[1-3].

Congenital unilateral upper limb muscular hypertrophy without other malformations was first reported by Mizuoka et al. in 1962 as duplication of the thenar and hypothenar muscles in an offspring from a consanguineous marriage[4]. In some instances it has been misdiagnosed as windblown hand, a well reconized congenital hand anomaly described for the first time by Lanz in 1994. It was then described as a congenital unilateral muscular hyperplasia of the hand combined with ulnar deviation of the fingers, with anomalous or hyperplastic musculature acting on the proximal phalanges of the fingers, that contributes to the associated ulnar drift of the hand[5].

There are plenty of investigation on the muscular system of the upper limb and it is virtually impossible to exhaust the list of the anomalous muscles observed in this region of the body and reported since 1865[6]. First descriptions considered this entity as sporadic with no connective tissue nevus, epidermal nevus, dysregulated adipose tissue, vascular malformations, or facial phenotype association but later association to Proteus syndrome was reported[7]. More recently, Castiglioni et al. delineated the disorder in the context of PIK3CA related overgrowth spectrum (PROS)[8]. This term was created in 2013 by the National Institute of Health in Bethesda (Maryland) to designate all the phenotypes caused by PIK3CA mutation which include: MCAP (Megalencephaly-Capillary Malformation-Polymicrogyria Syndrome), CLOVES (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, Scoliosis/Skeletal and Spinal), FAO (Fibroadipose hyperplasia or Overgrowth), DMEG (Dysplastic Megalencephaly)[9]. These syndromes are often caused by heterozygous, somatic mosaic, pathogenic variants in PIK3CA coding for the catalytic subunit (p110α) of phosphatidylinositol 3-kinase (PI3K), a lipid kinase of the PI3K-AKT-mTOR pathway. PI3K plays a role in cell growth and division, cell migration and survival. Thus, when the p110α subunit is altered, an abnormal activity of PI3K leads to uncontrolled cells divisions. Consequently, segmental overgrowth of several tissues and venous and lymphatic malformations are frequently reported in fetuses and patients harboring PIK3CA mosaic mutations[10].

There are only few reports variably defining this condition as an "aberrant muscle syndrome or congenital monomelic muscular hypertrophy"[7,11-13]. In the present paper, we report our own six cases of this entity, called here "aberrant muscular hand hyperplasia", and its asociation with PIK3CA related overgrowth spectrum (PROS) disorders.

MATERIAL AND METHODS

We describe a retrospective series of cases followed at our institution between 2008 and 2020, with a phenotype characterized by aberrant muscle hyperplasia of the hand in the context of PIK3CA mutations.

A review of the clinical register of patients diagnosed with "congenital hand abnormality" was performed, and only those who presented these three clinical features described in the physical exam were included: enlargement of the hypothenar eminence of the hand, wrinkling of the overlying skin and ulnar deviation of metacarpo-phalangeal joints. Patients finally included were summoned afterwards in consultation where the objective of this study was explained and photographs were taken in those patients with no previous photographs, after obtaining the prior written consent of patients parents or legal guardians.

Data analysis was carried out through the review of the clinical register as well as the visualization of the photographs taken in the consultation, in order to describe and characterize the observed lesions. We analyzed demographic variables (age and sex), personal history (diseases and previous surgeries, concomitant medical pathology, treatment), clinical data from the affected hand and its association with other associated malformations. We also collected histological and genetic data in those patients whose affected tissue was previously analyzed, without performing any prospective biopsy or genetic additional studies. All patients and parents gave their consent to take pictures of the affected areas for research. Photographs were taken protecting the identity of each patient. Informed consent was given to each patient finally included, to request the use in this study of the results of the genetic studies, which was signed by their parents or legal guardians. The study protocol was conformed to the guidelines of the 1975 Declaration of Helsinki and was approved by our institutional review board and by the hospital ethics committee.

RESULTS

Six patients (4 males; 2 females) with aberrant muscular hyperplasia in the hypothenar eminence associated, wrinkling of the overlying skin and ulnar deviation of the metacarpo-phalangeal joints were included. Left hand was affected in five patients while bilateral involvement was only observed in one case. All patients presented ipsilateral upper extremity overgrowth, and bilateral upper limbs hypertrophy was observed in the patient with bilateral hand involvement. Shoulder and arm function were adequate in four patients. One patient presented difficulty in raising the arm above the shoulder, and another patient had limited elbow extension. However, these alterations did not limit the daily activities of these two patients.

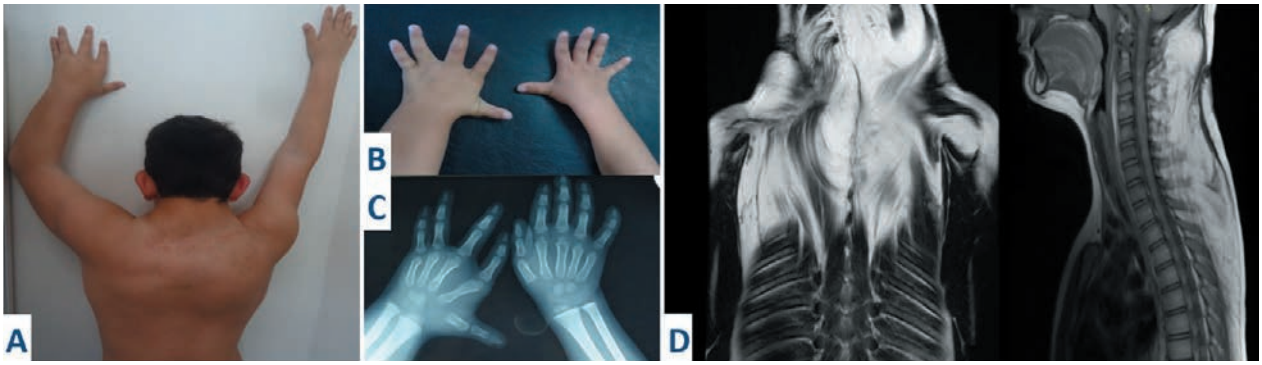

Figure 1. 10-year-old boy that presented aberrant muscle left hand hyperplasia with hemihypertrophy of the ipsilateral upper limb and cervico-thoracic lypomatosis associated. He also had a functional alteration of the left elbow associated, with limitation for the extension and flexion of the same, without involvement of the ipsilateral shoulder (A). The hand was hypertrophic and the MP joints of the fingers were ulnarly deviated. The thumb was extended and abducted (B). Under X-ray, the left hand was hypertrophic, and the enlargement of the intermetacarpal spaces of the left hand was remarkable (C). MRI showed the remarkable extension of cervico-thoracic lipomatosis, that required surgical treatment twice (D).

Figure 2. 6-year-old boy with aberrant muscle left hand hyperplasia and ipsilateral hemihypertrophy of the upper limb in the context of CLOVES syndrome (A). He presented a remarkable ulnar deviation of the MP joints on the left hand, wich was hypertrophic and the palmar side was bulky (B). The ulnar side was wider compared to the radial side. In this patient, the right hand had hyperplasia in the radial region, with symptomatic overgrowth on the second and third fingers, that required amputation of the third finger and shortening of the metacarpal of the second finger. However, we can not classify this as AMH because unlike the left hand, there was no involvement of the hypothenar region, which must be presented in all cases with AMH. He also presented capillary malformations associated in the pectoral and axilar region and in the pads of the fingers of both hands (C and D).

Peculiar wrinkling of the overlying skin and ulnar drift of the fingers in the metacarpophalangeal joints was presented in the 100% of patients, while flexion contractures of the metacarpophalangeal joints was only observed in two patients. One patient presented hand deformities and functional limitations that required surgical treatment. In this case, accessory muscles were found intraoperatively and were resected. Massive cervico-thoracic lypomatosis was presented in one patient and a large combined capillary-venous-lymphatic malformation was observed in two patients. CLOVES síndrome was presented in the other three cases. *Figures 1-6* show clinical and radiological features observed in these patients.

A biopsy of the affected area of the hand was performed in four patients, which showed in all of them peculiar striated muscle hyperplasia. Striated muscular fibers were also observed in the dermins and hypodermis, revealing the presence of aberrant ectopic muscle. In relation to genetic studies conducted to date, a somatic pathogenic variant in PIK3CA could be demonstrated in three out of four cases whose affected tissue was analyzed, in a mosaic state ranging from 3 to 8% (His1047Arg, Glu542Lys, and Cys420Arg, 1 case each). Hereditary dependence or association with other malformations has not been observed. Clinical and genetical features of all patients are shown *in table I*.

DISCUSSION

The congenital hand alteration described in the present paper is characterized by unilateral muscular hyperplasia, aberrant or accessory muscles and ulnar drift of the metacarpo-phalangeal joints. Aberrant muscular hand hyperplasia has been so far reported as an isolated pathology without associated malformation and outside of recognized

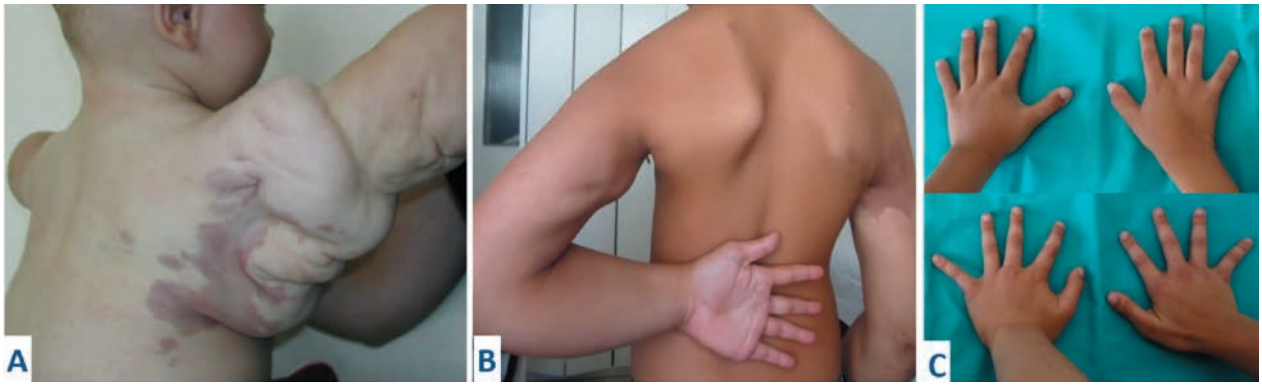

Figure 3. 12-year-old boy with aberrant muscle left hand hyperplasia associated with a large bilateral combined capillary-venous-lymphatic malformation of the trunk and upper limbs, which is showed at the age of two (A) and at the age of twelve (B). The left hand presented ulnar deviation of the MP joints of other digits, without abduction and extensión deformity of the thumb. Unaffected brother´s hand above (C).

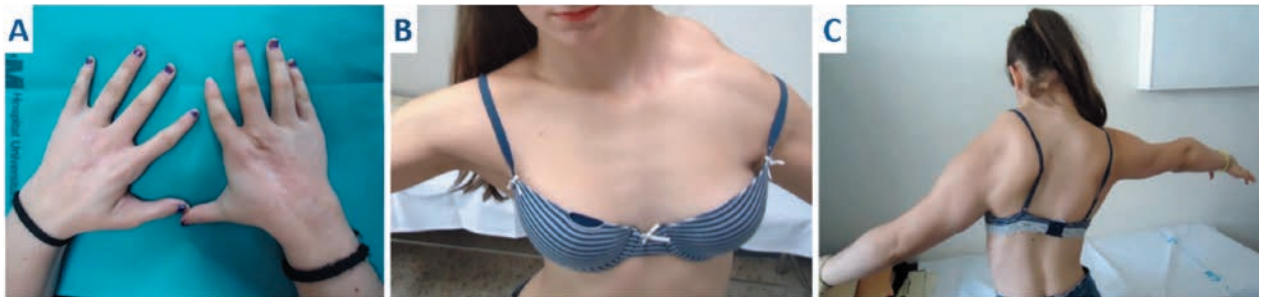

Figure 4. 14-year-old adolescent with aberrant muscle hand hyperplasia with bilateral involvement and ulnar deviation of the MP joints (A). She presented a left cervical-brachial combined capillary-venous-lymphatic malformation associated that produced symptoms, for which surgical intervention was required (B). It associates functional limitation in the abduction of the left upper limb, without affecting the extension or flexion of the elbow (C).

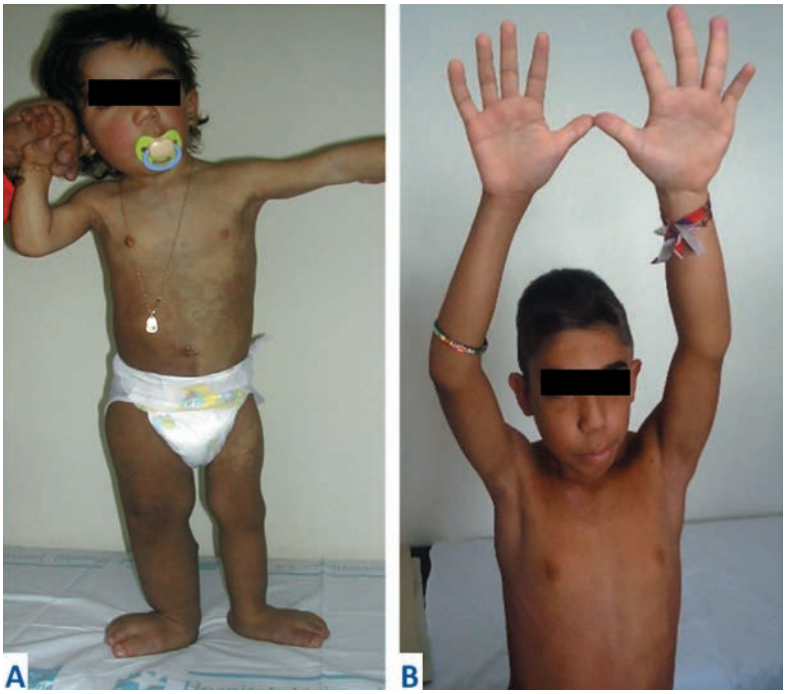

Figure 5. 8-year-old boy with involvement of the left hand with aberrant muscle hyperplasia and right lower limb hemihypertrophy associated, at age of three (A). The thumb was hyperabducted and the MP joints of the fingers were flexed and ulnarly deviated (B).

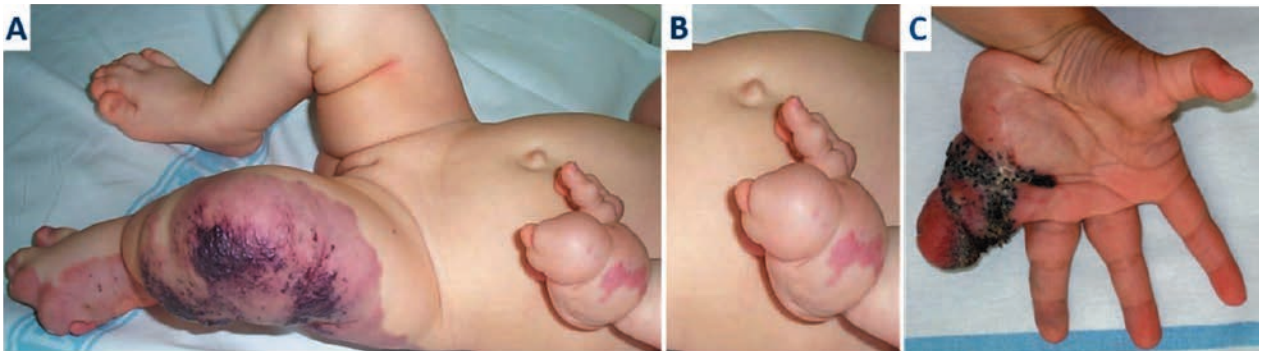

Figure 6. This 7-year-old girl presented at birth an aberrant muscle hyperplasia of the left hand in the context of CLOVES síndrome, with extensive combined capillary-venous-lymphatic malformation that affects the entire lower left limb (A). The fifth finger of the left hand associates a capillary malformation that extends from the base to the distal phalanx (B). Appearance of the hand at 7 years old above (C).

Table I. Patient's clinical and genetic findings.

	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*
Gender	Male	Male	Male	Female	Male	Female
Age (years)	10	6	12	14	8	7
Affected side	Left	Left	Left	Left	Left	Left
Ulnar deviation	Yes	Yes	Yes	Yes	Yes	Yes
Flexion of MP joint	No	No	No	No	Yes	Yes
Thumb hyperabducted hyperextended	Yes	Yes	No	Yes	Yes	Yes
Functional alteration	No	Yes	No	Yes	No	No
Other limb alteration	No	Ulnar hyperplasia of right hand	No	No	Right lower limb hemihypertrophy	Capillary malformation on the fifth finger of the left hand
Ipsilateral hemihypertrophy of the upper limb	Yes	Yes	Yes	Yes	Yes	Yes
Associated findings	Cervico-thoracic lypomatosis	CLOVES syndrome	Combined capillary-venous-lymphatic malformation of the trunk and upper limbs	Cervical-brachial combined capillary-venous-lymphatic malformation	CLOVES syndrome	CLOVES syndrome
Surgical treatment required	Yes	Yes	No	Yes	No	No
PIK3CA mutation	p.His1047Arg (8% in tissue)	Not done	Not found	Not done	p.Cys378Arg (10% in tissue)	p.Glu542Lys (3% in tissue)

syndromes. This is, to our knowledge, the first case series reporting this condition in the context of PIK3CA related overgrowth spectrum disorders (PROS).

Since the first description from Mizuoka in 1962 of congenital unilateral upper limb muscular hypertrophy without other malformation, multiple reports of patients with a spectrum of manifestations of this condition have been published, but never associated to lipomatous or fibroadipose abnormal tissues, vascular malformations or other established syndromes[4,7,8]. Although Proteus syndrome and macrodactyly are known as causes of upper limb hyperplasia, none of the reported patients matched these abnormalities. Proteus syndrome causes abnormal growth of the skin, bones, muscles, adipose tissue and blood and lymphatic vessels. In addition, some parts of the body develop more than others, causing exaggerated growth in one limb or lack of development in others. In our case series, abnormal growth is limited to the hypothenar eminence of the hand, with muscular hyperplasia at that level, associated with ulnar deviation of the meta-

carpo-phalangeal joints. Macrodactyly is a complex disorder of congenital origin, characterized by hypertrophy of phalanges, tendons, nerves, vessels, soft tissues, nails and skin, which can affect both feet or hands. The tissue samples analyzed in our patients demonstrate muscular hyperplasia without other alterations in the rest of the tissues, unlike what happens in macrodactyly[14]. In our study, lipomatosis was observed in one patient, combined capillary-veno-lymphatic malformation were associated in two patients, and three of them presented different forms of CLOVES syndrome. However, because only half of the patients (3 of 6) in our series had CLOVES syndrome, we cannot suggest altering the acronym CLOVES to CLOVEMS by including "Muscle abnormalities of the hand" in the spectrum.

In terms of histological involvement, there are few publications digging on muscle histology with this condition. In our case series, a biopsy of the affected area was performed in four patients where striated muscle hyperplasia was observed in all of them, associated with the presence of striated ectopic muscle fibers in the epidermis and hypodermis. This histological finding of ectopic muscle tissue has not been previously reported in the literature. However, we have not found in our patients the findings described by other authors, where besides increased variability of fibers associated with hypertrophic fibers, they observed increased perimysial and endomysial fibrosis, type 1 fiber predominance, disorganization of the intermyofibrillar network with multiple and polymorphic corelike areas[8,13,15].

Regarding the therapeutic options, there is no clear consensus in the surgical technique of choice in this pathology, although for most authors, the presence of symptoms or functional limitations are the main indicators of surgical treatment[5]. Debulking of the hyperplastic thenar eminence for cosmetic reasons has also been described. Crossed intrinsic transfers can also been performed for the index and middle fingers, in order to balance the muscle forces. Three of our patients required surgical intervention, two of them due to associated anomalies (cervico-thoracic lipomatosis and cervical-brachial combined capillary-venous-lymphatic malformation). The third patient had an ulnar hyperplasia, with symptomatic overgrowth on the second and third fingers, that required amputation of the third finger and shortening of the metacarpal of the second one. The rest of the patients presented asymptomatic hand involvement, which did not require surgical treatment.

The association with a PIK3CA activating mutation was first published in 2014 by Castiglioni et al. in a girl with non-progressive congenital muscle enlargement of the entire upper limb without additional malformations[8]. Confirmation of PIK3CA mutation has been validated in 75% of the patients whose affected tissue was analyzed. Afterwards, Frisk et al. reported clinical data and molecular findings of two patients with congenital muscle overgrowth of the upper extremities and aberrant anatomy in whom numerous ectopic muscles were found during debulking surgery. DNA sequencing followed by digital PCR was performed on these muscles and identified two PIK3CA mutations (His1047Arg and Glu542Lys)[16]. However, it has not been possible to demonstrate the existence of a correlation between the severity of the phenotype with the proportion of mutation found in each patient. Recently, specific inhibition of PIK3CA pathways has been proposed as a therapeutic option for these patients. Alpelisib is a specific alpha fraction inhibitor that has shown a safe profile in breast cancer clinical trials and has become a successful therapeutic option in order to improve the quality of life of PROS patients[17]. However, the underlying pathogenesis of the variable expressivity and clinical course of the same somatic PIK3CA mutations involved in these diverse conditions remains to be elucidated.

This study has several limitations, mainly those derived from being a unicentric study as well as those of its retrospective design features. Multi-centre studies with a higher number of patients may be needed.

In conclusion, aberrant muscular hyperplasia of the hand is a well-recognized entity scarcely described in association with PIK3CA spectrum disorder in the pediatric population. More studies are needed with a greater number of patients that allow characterizing this entity. Genetics research will help to distinguish it from other congenital hand malformations.

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