

# Archives of Plastic Surgery

## Proteus Syndrome: A Case Report and Updated Review of the Literature

Maria K Klimeczek Chrapusta, Marek Kachnic, Anna Chrapusta.

Affiliations below.

DOI: 10.1055/a-2300-7002

Please cite this article as: Klimeczek Chrapusta M K, Kachnic M, Chrapusta A. Proteus Syndrome: A Case Report and Updated Review of the Literature. Archives of Plastic Surgery 2024. doi: 10.1055/a-2300-7002

**Conflict of Interest:** The authors declare that they have no conflict of interest.

### Abstract:

Proteus syndrome is an exceptionally uncommon genetic disorder that has been documented in only about 250 cases in the literature spanning the past four decades. It is characterized by a disproportionate, asymmetric overgrowth of all types of tissues, provoked by a somatic activating mutation in serine/threonine protein kinase 1 (AKT1). We report a case of a Proteus syndrome in a two-year-old female patient with the following clinical features: unilateral overgrowth of connective tissue in the right buttock and a right foot, where multiple surgeries were performed to achieve a desirable aesthetic outcome and ensure psychological comfort of the young patient. The insights provided by this case underscore the pivotal role of obtaining pleasing aesthetic outcomes in the surgical management of untreatable genetic disorders, with the aim of nurturing psychological contentment in affected children.

### Corresponding Author:

student Maria K Klimeczek Chrapusta, Jagiellonian University Medical College, Clinic of Pediatric Surgery, Krakow, Poland, maria.klimeczek.chrapusta@student.uj.edu.pl

### Affiliations:

Maria K Klimeczek Chrapusta, Jagiellonian University Medical College, Clinic of Pediatric Surgery, Krakow, Poland

Maria K Klimeczek Chrapusta, Wojewodzki Szpital Specjalistyczny im L Rydygiera, Małopolska Burn and Plastic Surgery Center, Krakow, Poland

Marek Kachnic, Jagiellonian University Medical College, Clinic of Pediatric Surgery, Krakow, Poland

Anna Chrapusta, Wojewodzki Szpital Specjalistyczny im L Rydygiera, Malopolska Burn and Plastic Surgery Center, Krakow, Poland

## Proteus syndrome: Case Report and Updated Literature Review

Maria Kamila Klimeczek Chrapusta (ORCID: 0000-0001-9014-0389) [1,2], Marek Kachnic (ORCID: 0009-0007-4536-2872) [2], Anna Chrapusta (ORCID: 0000-0002-7820-974X) [1]

[1] Malopolska Burn and Plastic Surgery Center, Ludwik Rydygier Memorial Hospital in Krakow, 31-826 Cracow, Poland

[2] Jagiellonian University Medical College, Children's University Hospital in Kraków, Department of Pediatric Surgery, 30-663 Cracow, Poland

Corresponding Author: Maria Klimeczek Chrapusta, ul Jana Zamoyskiego 73/12, 30-519, Cracow, Poland, maria.klimeczek.chrapusta@student.uj.edu.pl

Contributions:

### **Klimeczek Chrapusta, Maria Kamila**

Conceptualization (Equal)

Data curation (Lead)

Formal analysis (Lead)

Investigation (Lead)

Resources (Equal)

Writing – original draft (Lead)

### **Kachnic, Marek**

Conceptualization (Equal)

Data curation (Supporting)

Investigation (Supporting)

Visualization (Lead)

Writing – review & editing (Equal)

### **Chrapusta, Anna**

Data curation (Supporting)

Formal analysis (Supporting)

Funding acquisition (Lead)

Investigation (Supporting)

Project administration (Lead)

Resources (Lead)

Supervision (Lead)

Validation (Lead)

Writing – review & editing (Supporting)

## Introduction

Proteus syndrome [PS] is an extremely rare genetic hamartomatous disorder characterized by a disproportionate, asymmetric overgrowth with skeletal deformations, vascular malformations and dysregulated adipose tissue [1].

It is provoked by a somatic activating mutation in serine/threonine protein kinase 1 (AKT1), causing mutation in the chimeric cells [2]. This activation limits apoptosis and promotes growth among other effects.

It was first described by Cohen and Hayden in 1979 [3]. A few years later, in 1983, Hans-Rudolf Wiedemann, a German pediatrician named it after sea god Proteus, who could change his shape to evade capture [4,5]. The prevalence of this syndrome is believed to be less than 1:1000000 [6]. Symptoms can manifest in various parts of the body and commonly commence during infancy [7]. They primarily revolve around skeletal overgrowth, yet this disorder exhibits significant pleiotropy, encompassing central nervous system (CNS) overgrowth, neuronal migration abnormalities, vascular anomalies, overgrowth of various other organs and tissues, and the development of bullous or cystic lung diseases [8]. This syndrome itself is not inherited and does not pass to the offspring, however the life expectancy is short, due to many complications, most common being deep vein thrombosis, as a result of large venous capillary malformations [5].

With fewer than 250 cases documented in the literature, the rarity of its occurrence provides justification for this report [9]. This is the case report of a 22-month-old female patient who presented herself at the plastic surgery clinic with a rare case of Proteus syndrome, confirmed by genetic testing. The primary objective of our study is to present the results of the highly radical surgical resection of the overgrown tissue in this rare genetic disorder.

### **Case Report**

A two-year-old female patient was presented at a plastic surgery clinic with the following clinical features: unilateral overgrowth of connective tissue in the right buttock and the right foot, where overgrowth of bone tissue was also found. When the child was 22 months old, the patient's parents complained of a systematic growth of a right buttock and difficulty in finding fitting shoes for the patient's right foot.

The parents of the patient affirmed that there was no family history of genetic disorders. The patient underwent genetic testing at the age of 20 months with a positive result for a somatic embryonal mutation of AKT1 gene. Due to a high risk of deep vein thrombosis and embolism, additional genetic investigations were conducted. [Table 1] Upon detecting a heterozygous mutation in MTHFR (metylenothetrahydrofoliate reductase enzyme gene), the patient was recommended for an annual screening of blood homocysteine levels. Furthermore, the parents were informed about their child's heightened need for vitamin B12 and folic acid.

When the patient was 9 months old, they underwent a surgical procedure at another facility to amputate the distal phalanges of the IVth and Vth toes due to overgrowth. As time progressed, tissue overgrowth persisted, and the aesthetic results of the surgery remained unsatisfactory [Fig 1].

Physical examination and radiological screening prior to the correction surgery did not reveal any additional abnormalities. Patient's parents gave an informed consent for the surgery of their child.

The patient underwent their initial surgery at our plastic surgery clinic at the age of 5 to address soft tissue hypertrophy in the foot [Fig 2.]. The procedure, performed under general anesthesia, was notable for its careful approach. Tissue dissection was carried out without ischemia, despite the placement of a tourniquet on the thigh. A skin marker was used to mark the extent of skin excision on the lateral surface of the foot, including the Vth toe and the heel. Once the skin was exposed, masses of adipose tissue located between the dermis and muscle tissue were revealed. Removal of the overgrown adipose tissue along with excess skin from the lateral surface of the heel, the lateral surface of the foot and the Vth toe of the foot was performed [Fig 3.]. After proper hemostasis of the wound bed was achieved, the tissues were sutured, and a layered dressing was applied [Fig 4.].

A year after the reduction of the soft tissues of the foot, the child was qualified for the second procedure, the reduction of hypertrophy of the right buttock [Fig 5]. Prior to the surgery, the child was prepared with oral laxatives to ensure the best comfort in the postoperative period. The operation was performed under general anesthesia with endotracheal intubation in the prone position. After the preparation of the surgical field, a longitudinal skin incision was planned in the medial quarter of the buttock and a transverse incision around the gluteal fold. After cutting the skin, masses of overgrown adipose tissue were exposed, which penetrated through the fascial septa towards the gluteal fissure. Reduction of the soft tissue hyperplasia consisted of an excision of a designated dermal-fat tissue and removal of an overgrown adipose tissue from between the septum connecting the skin and the muscle fascia [Fig 6]. The amount of removed soft tissues and the postoperative effect are shown in the pictures [Fig 7]. No drain was left after the procedure. Good hemostasis was achieved during the operation. The wound was sutured in layers and a stabilizing dressing was applied. The child remained in the clinic for two days and was discharged in a good general and local condition after the dressing control.

Following both surgeries, the patient received acetaminophen (orally, 4 times a day 15 mg/kg). The healing period was uneventful, devoid of complications, and the sutures were removed on the 14th day after the surgery. A significant hypertrophic tendency of scars was observed during the control visits, despite the use of compression therapy [Fig 8.]

There have been no indications of overgrowth recurrence observed in the two years period following the foot reduction surgery. The foot that underwent surgery continue to exhibit consistent proportions with the healthy

one, considering the child's growth, without experiencing any unhealthy overgrowth of tissues since the operation [Fig 8].

The second buttock surgery, initially established in the treatment plan, is delayed by 2 years as the current size satisfies both parent and child. In the light of absence of relapse in foot overgrowth, the treatment for it was limited to observation only.

The overall quality of life, functional and aesthetic outcomes were evaluated two years after the foot surgery, using the Pediatric Quality of Life Inventory TM (PedsQL TM) parent and patient report for young children aged 5- 7. [Table 2] Total score of 97.5 for the parent report and 95 for the child report is very satisfactory and means a high health related quality of life.

### **Discussion**

Proteus syndrome is a rare asymmetrical and progressive hamartomatous syndrome that may affect many tissues and is barely noticeable at birth. In most cases, this condition initially manifests between 6 and 18 months of age in an irregular, progressively worsening manner, as exemplified by the patient in this report, who exhibited an increasing discrepancy between their body parts as the months passed [10]. This genetic disorder has highly variable clinical features, due to mosaic lesion distribution and sporadic occurrence, which can lead to misdiagnosis and confusion with other overgrowth syndromes [1].

We conducted a review of literature on this topic [Table 4.] Proteus Syndrome original studies and case reports were selected using PubMed, Embase and Web of Science, these databases were searched for English language publications published from January 2014 to December 2023. The following search terms were used: (proteus [Title]) AND (syndrome [Title]). The inclusion criteria aimed to select PS studies that described skeletal and soft tissue malformations, limb deformities in cases with confirmed AKT1 mutation, that were treated (surgically or/and pharmacologically) and included a follow up after treatment. Out of the 115 records initially identified, 80 full-text articles underwent eligibility and quality assessment after exclusion during the abstract review. 9 studies, that met the inclusion criteria were included in the analysis. Some of the recent studies [20-23, 26] show results of experimental gene targeting pharmaceutical therapy with sirolimus, ARQ 092 or miransertib- AKT1 inhibitors, originally designed to treat cancer. While these papers consistently highlight a reduction in area of cerebriform connective tissue nevus (CCTN), the improvement in the size of limb deformities hasn't been entirely satisfactory and patients might still require surgery to restore regular function.

There were several studies published concerning diagnostic criteria for Proteus syndrome. In 1999 Biesecker et al [11] developed phenotype based diagnostic standards, which they subsequently updated and refined in 2006

[12]. In 2011 Lindhrust et al [2] identified somatic activating mutation in AKT1, as a cause of PS, supporting the hypothesis of somatic mosaicism and implicating the activation of the PI3K-AKT pathway in the distinctive clinical manifestations of overgrowth and susceptibility to tumors in this condition. This finding discredited theory proposed earlier in the XXI century that the PTEN hamartoma syndrome (also known as Cowden syndrome or Bannayan- Riley- Ruvalcaba syndrome) and Proteus syndrome had the same cause [13, 14]. Current understanding reveals that loss-of-function mutations in PTEN (Phosphatase and TENsin, located on 10q23.3) activate AKT1, leading to certain shared features with Proteus syndrome. However, this activation results in a separate clinical phenotype [2].

In 2019, Sapp et al. [15] introduced a novel diagnostic framework for identifying Proteus syndrome based on cases of 75 individuals. This system utilized a weighted, point-based approach to assess phenotypic attributes and subsequently incorporates potential molecular test results, classifying cases into one of two designations: AKT1-related Proteus syndrome or AKT1-related overgrowth spectrum. We consider this system to be an effective diagnostic tool for Proteus syndrome. It accounts for a wide array of PS manifestations, recognizing the mosaic pleiotropic nature of the disorder, while also considering the presence of pathogenic AKT1 gene variants [15].

In the case reported herein the mutation of ATK1 gene was confirmed by genetic testing. Patient was presented with asymmetric, disproportionate overgrowth of a lower limb, of a fast progressive fashion, as they required two reduction surgeries within a short time interval. There were manifestations of skeletal involvement in the overgrown feet. Dysregulated adipose tissue was found in the affected buttock, as well as vascular malformations. This exact clinical presentation has not been described yet in the literature [1-17], which implies how this disease can manifest in many ways.

All pleiotropic disorders have phenotypic overlap, and it can be challenging to distinguish them [15]. Proteus syndrome must be differentiated from other overgrowth syndromes such as PTEN hamartoma tumor syndrome, Klippel-Trenaunay syndrome and CLOVES syndrome [1] to avoid unnecessary testing and procedures. Table 3. summarizes characteristics and distinguishing features of mentioned disorders. In 2007, Sapp et al. [17] initially identified CLOVES syndrome in seven individuals previously diagnosed with Proteus syndrome. Distorted skeletal structures in CLOVES patients were primarily associated with major surgical interventions, contrasting with unoperated areas that remained unaffected. Hence surgeons should differentiate these two syndromes, as surgical procedures on the hands or feet in patients with CLOVES syndrome may induce skeletal overgrowth resembling that seen in Proteus syndrome. [17,1].

Early surgical procedures of distorted tissues are expected to not only improve aesthetic outcomes but also preserve proper psychological functioning. It is worth noting that there is a lack of evidence on this subject in the literature concerning Proteus syndrome. A study focused on the quality of life of children aged 2-12 years with capillary malformations of the lower limbs, particularly those affected by Klippel-Trenaunay syndrome, suggested that venous and orthopedic complications in children were significantly associated with a decrease in their quality of life [18]. This observation remains significant as Klippel-Trenaunay syndrome may exhibit overlapping features with Proteus syndrome, including tissue overgrowth, which demands careful differentiation.

Another study, which enrolled adult patients, presented similar findings concerning overgrowth syndromes. Within this cohort, 95 patients were diagnosed with psychiatric conditions, 23.2% of the total, with depression (15.1%) and anxiety (5.1%) being the most identified conditions [19].

In our study, the strength of our foot reduction surgery lies in the application of a highly radical resection technique, potentially contributing to a lasting outcome. The buttock surgery involved tumor excision in three planes, reducing height, width, and projection. Notably, the procedure extended to subcutaneous removal of extensive adipose tissue clusters, compartmentalized by numerous fibrous septa, reaching towards the gluteal cleft. It enhanced aesthetic results and hygiene maintenance. Limitation is the challenging scarring process. The mid-foot and heel scars improved only after a year, while gluteal scars exhibited excessive growth despite compression therapy, remaining firm and broad. We expect a future relapse of the overgrowth in various body areas, due to progressive nature of the disorder, which is why our patient stays under observation.

### **Conclusion**

Currently there is no effective treatment for this syndrome, however given its monogenic nature, it is an excellent candidate for targeted therapy. We note that the extreme rarity of this disorder limits the researchers' opportunities for finding a favorable pharmacological cure. Considering our experience, we can presume that highly radical resection of pathological tissues may contribute to a longer lasting outcome. This is the first case report of this disease, explaining in such details the surgical approach, followed by a successful long-lasting result in this area of the body. We conclude that early diagnosis of patients with Proteus syndrome and subsequent surgical treatment may improve their quality of life and avoid social stigma.

### **References**

1. Cohen MM Jr. Proteus syndrome review: molecular, clinical, and pathologic features. *Clin Genet.* 2014;85(2):111-119. doi:10.1111/cge.12266
2. Lindhurst MJ, Sapp JC, Teer JK, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. *N Engl J Med.* 2011;365(7):611-619. doi:10.1056/NEJMoa1104017
3. Cohen MM Jr, Hayden PW. A newly recognized hamartomatous syndrome. *Birth Defects Orig Artic Ser.* 1979;15(5B):291-296.
4. Amer N, Al Helal J, Al Hajji M, et al. Proteus Syndrome, a rare case with an unusual presentation: Case report. *Int J Surg Case Rep.* 2020; 72:339-342. doi: 10.1016/j.ijscr.2020.06.052
5. Munhoz L, Arita ES, Nishimura DA, et al Maxillofacial manifestations of Proteus syndrome: a systematic review with a case report. *Oral Radiol.* 2021;37(1):2-12. doi:10.1007/s11282-019-00416-y
6. Furquim I, Honjo R, Bae R, et al. Proteus syndrome: report of a case with recurrent abdominal lipomatosis. *J Pediatr Surg.* 2009;44(4): E1-E3. doi: 10.1016/j.jpedsurg.2008.12.016
7. Ou M, Sun Z, Zhu P, Sun G, Dai Y. Proteus syndrome: A case report and review of the literature. *Mol Clin Oncol.* 2017;6(3):381-383. doi:10.3892/mco.2017.1140
8. Buser et al. 2020 Cold Spring Harb Mol Case Stud 6: a005181
9. Duarte Santos C, Lizardo Grácio R, Costa Pires T, et al. Proteus Syndrome: A Rare Case in An Adult Ward. *Eur J Case Rep Intern Med.* 2021;8(4):002554. Published 2021 Apr 28. doi:10.12890/2021\_002554
10. Rocha RCC, Estrella MPS, Amaral DMD, Barbosa AM, Abreu MAMM. Proteus syndrome. *An Bras Dermatol.* 2017;92(5):717-720. doi:10.1590/abd1806-4841.20174496
11. Biesecker LG, Happle R, Mulliken JB, et al. Proteus syndrome: diagnostic criteria, differential diagnosis, and patient evaluation. *Am J Med Genet.* 1999;84(5):389-395. doi:10.1002/(sici)1096-8628(19990611)84:5<389:aid-ajmg1>3.0.co;2-o
12. Biesecker L. The challenges of Proteus syndrome: diagnosis and management. *Eur J Hum Genet.* 2006;14(11):1151-1157. doi:10.1038/sj.ejhg.5201638
13. Zhou X, Hampel H, Thiele H, et al. Association of germline mutation in the PTEN tumour suppressor gene and Proteus and Proteus-like syndromes. *Lancet.* 2001;358(9277):210-211. doi:10.1016/s0140-6736(01)05412-5.
14. Cohen MM Jr, Turner JT, Biesecker LG. Proteus syndrome: misdiagnosis with PTEN mutations. *Am J Med Genet A.* 2003;122A(4):323-324. doi:10.1002/ajmg.a.20474

15. Sapp JC, Buser A, Burton-Akright J, Keppler-Noreuil KM, Biesecker LG. A dyadic genotype-phenotype approach to diagnostic criteria for Proteus syndrome. *Am J Med Genet C Semin Med Genet.* 2019;181(4):565-570. doi:10.1002/ajmg.c.31744.
16. Biesecker LG, Sapp JC. Proteus Syndrome. 2012 Aug 9 [Updated 2023 May 25]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023.
17. Sapp JC, Turner JT, van de Kamp JM, van Dijk FS, Lowry RB, Biesecker LG. Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome) in seven patients. *Am J Med Genet A.* 2007;143A(24):2944-2958. doi:10.1002/ajmg.a.32023
18. Robert J, Marchand A, Mazereeuw-Hautier J, et al. Quality of life of children with capillary malformations of the lower limbs: Evolution and associated factors. Data from the French national paediatric cohort, CONAPE. *Ann Dermatol Venereol.* 2022;149(4):271-275. doi:10.1016/j.annder.2022.03.010
19. Harvey JA, Nguyen H, Anderson KR, et al. Pain, psychiatric comorbidities, and psychosocial stressors associated with Klippel-Trenaunay syndrome. *J Am Acad Dermatol.* 2018;79(5):899-903. doi:10.1016/j.jaad.2018.05.1245
20. Weibel L, Theiler M, Gnannt R, et al. Reduction of Disease Burden With Early Sirolimus Treatment in a Child With Proteus Syndrome. *JAMA Dermatol.* 2021;157(12):1514-1516. doi:10.1001/jamadermatol.2021.4305
21. Ours CA, Sapp JC, Hodges MB, de Moya AJ, Biesecker LG. Case report: five-year experience of AKT inhibition with miransertib (MK-7075) in an individual with Proteus syndrome. *Cold Spring Harb Mol Case Stud.* 2021;7(6):a006134. Published 2021 Dec 9. doi:10.1101/mcs.a006134
22. Leoni C, Gullo G, Resta N, et al. First evidence of a therapeutic effect of miransertib in a teenager with Proteus syndrome and ovarian carcinoma. *Am J Med Genet A.* 2019;179(7):1319-1324. doi:10.1002/ajmg.a.61160
23. Lindhurst MJ, Yourick MR, Yu Y, Savage RE, Ferrari D, Biesecker LG. Repression of AKT signaling by ARQ 092 in cells and tissues from patients with Proteus syndrome. *Sci Rep.* 2015;5:17162. Published 2015 Dec 11. doi:10.1038/srep17162
24. Crenshaw MM, Goerlich CG, Ivey LE, et al. Orthopaedic Management of Leg-length Discrepancy in Proteus Syndrome: A Case Series. *J Pediatr Orthop.* 2018;38(3):e138-e144. doi:10.1097/BPO.0000000000001121

25. Modlin EW, Slavotinek AM, Darling TN, et al. Late-onset Proteus syndrome with cerebriiform connective tissue nevus and subsequent development of intraductal papilloma. *Am J Med Genet A*. 2022;188(9):2766-2771. doi:10.1002/ajmg.a.62761

26. Keppler-Noreuil KM, Sapp JC, Lindhurst MJ, et al. Pharmacodynamic Study of Miransertib in Individuals with Proteus Syndrome. *Am J Hum Genet*. 2019;104(3):484-491. doi:10.1016/j.ajhg.2019.01.015

27. Popescu MD, Burnei G, Draghici L, Draghici I. Proteus Syndrome: a difficult diagnosis and management plan. *J Med Life*. 2014;7(4):563-566.

28. He M, Zhao W. Proteus syndrome of the foot: A case report and literature review. *Exp Ther Med*. 2020;20(3):2716-2720. doi:10.3892/etm.2020.8986

**Fig. 1** Chart presenting undergone surgical procedures.

**Fig. 2** Photos of the patient's feet taken before the first tissue reduction surgery at our clinic, after the initial amputation surgery of distal phalange of IVth and Vth toe, performed at a different facility.

- A. The picture of the overgrown tissues on the lateral side of the right foot, mostly prevalent in the IVth and Vth toe.
- B. The picture of the overgrown tissues of the right heel

**Fig. 3**

A photo showing the amount of tissue removed during foot surgery.

**Fig. 4**

Photos A, B showing the result of the excess foot tissue removal surgery.

**Fig. 5**

Photos A, B showing preoperative tissue overgrowth of the right buttock.

**Fig. 6**

Photos A, B showing postoperative result of tissue reduction.

**Fig. 7**

Photo showing the amount of tissue removed from the buttock during surgery.

**Fig. 8**

Follow up photos taken 2 years after the foot surgery and 1 year after the buttock surgery.

Photo A. A photo showing the result of the buttock reduction surgery one year after procedure. No significant overgrowth has taken place during this one-year period. The hypertrophic scar on the buttock is visible.

Photos B, C, D showing the state of the patient's feet two years after the reduction surgery. No sign of overgrowth has been observed the follow up period.



**Table 1. The clinical significance of assessed gene mutations.**

<b>Gene</b>	<b>Analysed mutation</b>	<b>Clinical significane</b>	<b>Results</b>
<b>Factor 2</b>	Prothrombin gene mutation 20210G>A	A mutation in this gene increases the risk for deep vein thrombosis, arterial thrombosis, ischemic stroke and myocardial infraction, due to increased prothrombin production.	Negative
<b>Factor 5</b>	Arg534Gln (R506Q, factor V Leiden)	A mutation in this gene alters the composition of coagulation cascade factor V, rendering it resistant to the anticoagulant protein C. This mutation elevates the risk of deep vein thrombosis, arterial thrombosis, ischemic stroke, and myocardial infarction.	Negative
<b>MTHFR</b>	Ala222Val (C677T)	A mutation in this gene results in elevated levels of homocysteine in blood, tpotentially raising the susceptibility to cardiovascular diseases and hypercoagulability. In contrast to homozygous mutations, heterozygous mutations often present as asymptomatic.	Positive (heterozygous)

**Table 2. Results of the Pediatric Quality of Life Inventory™ (PedsQL™) Generic Core for young children aged 5- 7 questionnaire. Questionnaire evaluated four dimensions of patient’s life in the past month. Scores are presented on the scale from 0 to 100. The higher the score, the better health related quality of life (HRQOL).**

<b>Dimension</b>	<b>Number of items</b>	<b>Score for parents report</b>	<b>Score for child report</b>
<b>Physical functioning</b>	8	100	100
<b>Emotional functioning</b>	5	90	80
<b>Social functioning</b>	5	100	100
<b>School functioning</b>	5	100	100
<b>Total score</b>	23	97.5	95

Table 3. Characteristics and distinguishing features of overgrowth syndromes with overlapping phenotypes

Syndrome	OMIM	Mutation	Onset	Clinical characteristics
<b>CLOVES syndrome</b>	612918	PIK3CA	Prenatal	<ul style="list-style-type: none"> <li>- Asymmetric body overgrowth with skeletal, vascular, visceral and neural abnormalities</li> <li>- Linear epidermal nevus along Blaschko's lines, vascular or neural structures with a hyperkeratotic and papillomatous surface</li> <li>- Thoracic lipomatous hyperplasia</li> <li>- Soft overgrowth of hands and feet that tends to form wrinkles.</li> <li>- No connective tissue nevus</li> <li>- Mainly spinal, high flow arterio-venous malformations</li> </ul>
<b>Klippel-Trenaunay syndrome</b>	149000	PIK3CA	Prenatal or postnatal	<ul style="list-style-type: none"> <li>- Asymmetric limb hypertrophy and elongation (usually single lower extremity)</li> <li>- Slow- flow vascular malformations involving lower and upper limbs and/or trunk often with persistent lateral embryologic veins.</li> <li>- Laterally located cutaneous hemangiomas (port-wine stains)</li> <li>- Persistent embryonic lateral marginal vein of Servelle</li> <li>- More often males than females</li> </ul>
<b>PTEN hamartoma tumor syndrome</b>	601728	PTEN	Postnatal	<ul style="list-style-type: none"> <li>- Asymmetric overgrowth of adipose tissue (lipomas)</li> <li>- Development of non-cancerous growths (hamartomas) in different areas of the body</li> <li>- Term used to describe any patient with germline PTEN mutation (subtypes: Cowden Syndrome, Bannyan-Riley-Ruvalcaba Syndrome and Proteus-like Syndrome)</li> <li>- Inherited in autosomal manner.</li> <li>- Increased risk of thyroid, skin and colon cancer</li> <li>- Intellectual disability, autism spectrum disorder, delay in motor development</li> <li>- Macrocephaly</li> </ul>

				- Multiple mucocutaneous lesions



Author, year	Study design	N	Sex	Age at the time of the treatment (years)	Age at the time of diagnosis (years)	Progression over time	Clinical features treated	Treatment	Follow up
<b>Weibel, 2019</b>	Case report	1	F	9	2	Present	<ul style="list-style-type: none"> <li>- Multiple lipomas on trunk</li> <li>- Hemihypertrophy of right leg</li> <li>- Plantar cerebriform connective tissue nevus (CCTN)</li> <li>- Soft tissue abdominal swelling</li> </ul>	Sirolimus	6 years follow up: <ul style="list-style-type: none"> <li>- reduction of 19,1% of plantar CCTN area,</li> <li>- reduction in size of abdominal lipomas</li> <li>- skeletal deformations remained stable</li> </ul>
<b>Ours, 2021</b>	Case report	1	M	18	6	Present	<ul style="list-style-type: none"> <li>- Leg length discrepancy (LLD)</li> <li>- Bilateral plantar CCTN</li> <li>- Musculoskeletal pain of the lower back and lower limbs</li> </ul>	Miranse tib	48 weeks follow up: <ul style="list-style-type: none"> <li>- Slowing of CCTN growth</li> <li>- Less pain declared by the patient</li> <li>- No improvement in leg length discrepancy</li> </ul>
<b>Leoni, 2019</b>	Case report	1	F	17	1	Present	<ul style="list-style-type: none"> <li>- Ipsilateral hand overgrowth</li> <li>- Hyperostotic fusion of all cervical</li> </ul>	Miraser tib	2 years follow up: <ul style="list-style-type: none"> <li>- Reduction in CCTN size</li> <li>- Increase in range</li> </ul>

							vertebrae, causing rotoscoliosis - Plantar CCTN		of motion in forelimbs and joints (hand, spine, knees) - Small reduction in size of the lesions on the hand and feet
<b>Lindhurst, 2015</b>	Case report	1	N/A	N/A	N/A	N/A	- Overgrowth of toes	ARQ 092	Phosphorylation of AKT was reduced in measured skin biopsies from overgrown toes.
<b>Crenshaw, 2018</b>	Original study	8	4 M, 4 F	9,4	N/A	Present	- LLD	Surgery	4.6 years follow up: - Improvement in LLD in all patients
<b>Modlin, 2022</b>	Case report	1	F	59	19	Present	- CCTN - Papule on the left great toe	Surgery	5 years follow up: - regrowth of CCTN, second surgery was needed - regrowth of left toe papule
<b>Kepler-Noreuil, 2022</b>	Original study	6	4 M 2 F	26,8	N/A	Present	- CCTN - Bony overgrowth	Miranse rtib	12 month follow up: - Decrease in size of CCTN, softer and pliable - No

										change in bony overgrowth
<b>Popescu, 2014</b>	Case report	1	M	5	1	Present	- Overgrowth of soft tissues of lower limb - LLD	Surgery	Complete recurrence of LLD	
<b>He, 2020</b>	Case report	1	F	35	35	Present	- Overgrowth of the left foot	Surgery	Recurrence	

























