

## Images in Genetics

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Albert E. Chudley, e-mail: [Chudley@cc.umanitoba.ca](mailto:Chudley@cc.umanitoba.ca)

# Hermann Friedberg's case report: an early description of CLOVES syndrome

Alomari AI, Thiex R, Mulliken JB. Hermann Friedberg's case report: an early description of CLOVES syndrome.

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CLOVES syndrome is a recently described overgrowth disorder with complex vascular anomalies. Careful analysis of the case report by the German physician Hermann Friedberg “gigantism of the right lower limb” published in 1867 revealed that the report probably represents one of the first written accounts of CLOVES syndrome.

### AI Alomari<sup>a</sup>, R Thiex<sup>b</sup> and JB Mulliken<sup>c</sup>

<sup>a</sup>Division of Vascular and Interventional Radiology, Children's Hospital Boston, Boston, MA, USA, <sup>b</sup>Division of Endovascular Neurosurgery and Interventional Neuroradiology, Brigham and Women's Hospital, Boston, MA, USA, and <sup>c</sup>Department of Plastic Surgery, Children's Hospital Boston and Harvard Medical School, Boston, MA, USA

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Corresponding author: Ahmad I Alomari, MD, Division of Vascular and Interventional Radiology, Children's Hospital Boston and Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA.  
 Tel.: 617 355 6221;  
 fax: 617 730 0541;  
 e-mail: [ahmad.alomari@childrens.harvard.edu](mailto:ahmad.alomari@childrens.harvard.edu)

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If you think you have found something new, it is because you cannot read German

(Anonymous)

CLOVES syndrome (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Skeletal/Scoliosis and Spinal abnormalities) has been recently characterized and differentiated from other overgrowth disorders with complex vascular anomalies (1, 2).

The detailed case report of limb ‘gigantism’ and vascular malformations by Dr Hermann Friedberg (3) has been cited repeatedly in the literature.

Based on a careful retrospective study of the signs and symptoms documented by Friedberg and those elegantly illustrated in the hand-drawn plates, his patient probably had CLOVES syndrome.

### Original case report

Hermann Friedberg published his case report ‘Riesenwuchs des rechten Beines’ (gigantism of the right lower limb) in the *Archiv für pathologische, Anatomie und Physiologie und für klinische Medizin* in 1867 (3). He recounted the chronological details of his patient in 20 pages and 3 plates.

The patient was a 10-year-old young German girl followed in his private clinic in Berlin. Her main clinical features were progressive massive overgrowth, particularly of the right leg, macrodactyly, truncal lipoma, scoliosis, 'venous telangiectasia' and chronic cutaneous eruptions. She was born of uncomplicated pregnancy and her family history was unremarkable.

The child was malnourished with pale, dry and withered skin; she had a normal temperature. The child had slow growth, but normal mental development. The overgrowth was disproportionate; the third and fourth toes were particularly large. In addition to a leg-length discrepancy of 7 in, there was asymmetry of the upper extremities with massive enlargement of the left upper arm.

The plates in his paper illustrate a complex asymmetric truncal mass involving the posterolateral and central cervicothoracic region with paraspinal and flank components (Fig. 1a,b). The larger mass was partially covered by a diffuse 'venous' stain, and as can be inferred from the plate, this is a capillary malformation. The hands were asymmetric in size (left larger and wider) with disproportionate overgrowth of the fourth and fifth fingers. Similarly, more marked changes were noted in her feet with widened space between the first and second toes (sandal gap). Violet-colored

'venous telangiectasia' (subcutaneous phlebectasia) was present on the chest, left axilla and arm. Two small, soft, irregularly shaped, mobile subcutaneous masses were palpated on the left anterior chest wall. The lungs, heart and abdominal organs were unremarkable by physical examination.

At the age of four, the girl developed severe swelling of the chest wall and left arm accompanied by pain and chills. This eventually subsided, but the affected parts remained swollen. Several flare-ups followed. With the first inflammatory episode, small vesicles appeared in the left axilla, inner arm and shoulder area. These vesicles were filled with turbid or clear yellowish fluid and occasionally disappeared completely, only to recur with subsequent inflammatory episodes. Some of the vesicles burst and oozed blood. Friedberg documented several bouts of diarrhea and GI bleeding. He commented on the remarkable ability of the child to recover from these severe flare-ups. He refrained from prescribing medications for one of the episodes in order to observe natural history of her condition, and to his surprise, she did recover.

At the end of his lengthy report, Friedberg discussed the possible connection between the presence of lipomas and other features. He referenced other published cases of 'gigantism' of individual parts of the body in which there were cutaneous

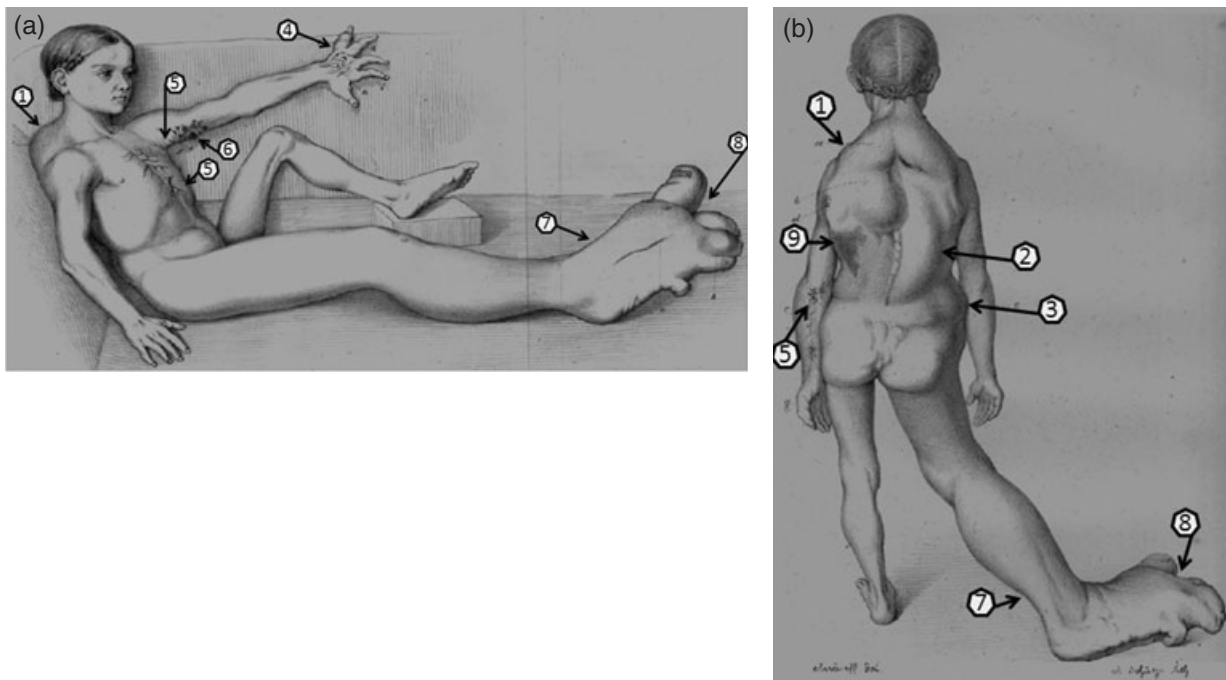


Fig. 1. Two plates (a, b) from Friedberg paper (3). The clinical signs were relabeled for easier identification. Truncal overgrowth with bilateral asymmetric masses (1) and involvement of the paraspinal musculature (2) and right flank (3). Wide hand with macrodactyly and superficial phlebectasia (4). Superficial phlebectasia (5). Axillary lymphatic vesicles and superficial phlebectasia (6). Massive right leg overgrowth with macrodactyly (7) and sandal gap (8). Capillary 'port-wine' stain (9). Note scoliosis and atrophic left leg.

venous anomalies, enlarged cutaneous veins and diffuse proliferation of fat and connective tissue, as noted in his patient.

Friedberg briefly pointed to the short published excerpt by Benjamin Simpson describing an Indian male patient with overgrowth of the left foot (16). On review of this article, the patient had only isolated acral overgrowth; there is no mention of any vascular, skeletal or cutaneous abnormalities.

Who was Hermann Friedberg?

Hermann Friedberg was a German physician, born in Rosenberg, a small town in Silesia (Kingdom of Prussia, now part of Poland), to a Jewish family on 5 July 1817. He lived there for the next 13 years (4). He received his secondary school diploma in Brieg (1836) before moving to Bratislava. He attended the Medical School of Breslau University. His thesis on the blood circulation in amphibians was given an award of excellence by the *Ordo Medicorum* in 1840. He also studied at the universities of Berlin, Vienna, Prague and Paris. After passing the practical examinations, he moved to Berlin.

Friedberg started his surgical training in 1841 and became board-certified in Forensic Medicine in 1849. He was appointed as an assistant at the surgical hospital of the University of Berlin between 1849 and 1852 under Prof Bernhard Rudolf Konrad von Langenbeck (1810–1887). In January 1852, he was admitted to the *Honoured Ordo Medicorum* of Berlin University and ordained with the *Venia Docendi*, the license to become an academic lecturer, and was promoted to a *privatdozent* (assistant professor) in surgery and pharmacology. Throughout this period, he ran a private clinic for the treatment of surgical and ophthalmological diseases. While in Berlin, Friedberg's research focused on the histology of blood. In 1866, he was appointed as professor of pharmacology at the University of Breslau, Breslau, Silesia (the old German name for Wrocław, Poland). His passion for medical jurisprudence flourished there and it became his primary professional and academic interest.

Very little is known about Friedberg's private life. His personal interests seem to have extended beyond medicine; perhaps to philosophy and politics. Karl Marx (1818–1883), the famous communist philosopher, and his youngest daughter Tussy (1855–1898) were befriended by Friedberg during their stay in Karlsbad (5) in 1874.

Dr Friedberg was an illustrious toxicologist, surgeon and forensic medical expert. He authored

and co-authored many papers and books in surgery, pharmacology, cardiology and medical jurisprudence. He wrote several books including 'Chirurgische Klinik. Beobachtungen und Erläuterungen in dem Gebiete der Chirurgie' (in which he presented surgical cases with elaborate records and practical observations) (6), 'Pathologie und Therapie der Muskellähmung', 'Die Vergiftung Durch Kohlendunst', 'Gerichtsärztliche Gutachten, Erste Reihe' and 'Gerichtsärztliche Praxis. Vierzig Gutachten'.

Friedberg died in Breslau on 2 March 1884. In a brief obituary, the Weekly Medical Review described him as a 'gentleman of great learning and quite a prolific writer' (7).

Analysis of the clinical features in Dr Friedberg's patient

There is a remarkable similarity between the features of Friedberg's patient and those presented in the two published cohorts of CLOVES syndrome (1, 2) (Fig. 2). He described the truncal overgrowth and vascular and skeletal abnormalities (Table 1). The thoracolumbar truncal fatty masses, particularly involving the paraspinal muscles and the flank, are classic findings in CLOVES syndrome. The vascular anomalies (including capillary malformation, phlebectasia and lymphatic vesicles and malformations with periodic flares), skeletal anomalies (progressive asymmetric overgrowth, macrodactyly preferentially affecting the middle digits, sandal gap, scoliosis, wide feet and hands) are also characteristic of CLOVES. In addition, poor growth and normal mental function, as documented by Friedberg, are often noted in CLOVES.

## Discussion

Friedberg's report has been referenced many times in the medical literature under different disease categories including 'vascular bone syndrome' (8), 'maldevelopments of the vascular system' (9), vascular anomalies (10), hemihypertrophy (11) and Klippel–Trenaunay syndrome (KTS) (12). Of interest, Klippel and Trenaunay, in their original description (13) briefly referred to Friedberg's observation regarding the congenital, progressive nature of the 'hypertrophy'. Overgrowth in KTS is predominantly fatty and affects the lower extremity and pelvis with slow-flow (capillary, lymphatic and venous) malformations. Major differentiating features of CLOVES syndrome from KTS include the presence of truncal



*Fig. 2.* Clinical photographs of patient with CLOVES syndrome. (a) Bilateral upper posterior truncal fatty masses partially covered with capillary malformation. (b) Overgrown hands (left > right) with macrodactyly, capillary stains and superficial phlebectasia. (c) Lymphatic vesicles of right axilla and upper arm.

mass-like fatty overgrowth with aggressive and progressive behavior, spinal/paraspinal high-flow lesions, central phlebectasia, renal, spinal and other musculoskeletal anomalies.

Friedberg also highlighted the coexistence of fatty masses 'lipomas' and vascular malformations.

Current research has shown that angiogenesis, vasculogenesis and adipogenesis are spatially and temporally coupled during development and the relationship between the coordinated growth of endothelial cells and adipocytes is possibly mediated by paracrine interactions (14, 15).

Table 1. Clinical summary of major features of CLOVES syndromes (as reported by Sapp et al. (1) and Alomari (2) compared to Friedberg patient; table modified from Ref. (2))

Clinical feature	Saap et al.	Alomari	Friedberg
Number of patients	7	18	+
Asymmetric disease	7	18	+
Family history	0	0	0
Linear epidermal nevus	4	2	NA
Lipomatous mass	6	18	+
Vascular malformations – low-flow (one or more)	7	18	+
Paraspinal/spinal high-flow malformations	NA	5	NA
Wide feet/hands	7	9	+
Scoliosis	6	6	+

+, present; –, absent, NA, data not available.

Friedberg's report illustrated the natural history of CLOVES syndrome with a long-term follow-up. The inflammatory flare-ups around the skin vesicles are well-known complications of lymphatic malformations. The causes of these episodes are typically infections and intralesional bleeding. As the report documented, these episodes resolve without any treatment in the vast majority of patients, except with major bacterial infections and sepsis. Lymphatic malformations typically contain lymph, a light amber fluid. Friedberg's description of the fluid contents as 'turbid or clear yellowish' refers to the changes of lymph characters from the usual, clear one to the turbid fluid secondary to infections. Cutaneous lymphatic vesicles are known to change in location, size, and symptoms, as noted by Friedberg.

In addition to CLOVES syndrome, several other overgrowth disorders with complex vascular anomalies have been described, including Klippel–Trenaunay syndrome, Parkes Weber syndrome, PTEN hamartoma syndrome (Banayan–Riley–Ruvalcaba syndrome and Cowden syndrome) and Proteus syndrome. CLOVES syndrome can be confused with other overgrowth disorders, particularly Proteus syndrome. The latter is characterized by disproportionate, asymmetric postnatal overgrowth, particularly involving the skeleton, along with cerebriform connective tissue nevi; epidermal nevi; dysregulated adipose tissue and vascular malformations (17). CLOVES syndrome differs because of the characteristic truncal fatty-vascular mass, spinal–paraspinal fast-flow lesions, acral abnormalities and lack of cerebriform connective tissue nevi. The clinical features of

CLOVES, such as truncal overgrowth, are evident at birth. In contrast, overgrowth in Proteus syndrome is usually minor or absent at birth (18). Furthermore, vascular anomalies (both slow-flow and fast-flow) are very common in CLOVES, and are rare in Proteus syndrome.

In conclusion, Friedberg's case report is a valuable historical reference. We believe that it probably represents one of the first written accounts of CLOVES syndrome.

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## Hermann Friedberg's case report

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