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Original article

Familial Isolated Hemihyperplasia Recurrence in a Non-Consecutive Brother and Sister Punctuated by Unaffected Children: A Case Series with 10-Year Follow-Up and Review of Clinical Diagnostic Thresholds

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Keywords.
Asymmetry; Isolated Hemihyperplasia; Familial Recurrence; Pedigree; Alpha-Fetoprotein; Wilms' Tumour; Shoe Lift.

Abstract

Isolated hemihyperplasia (IH) is a rare congenital overgrowth disorder defined as regional body asymmetry involving bone, soft tissue, or both, without syndromic features. While predominantly sporadic with a postzygotic somatic aetiology, non-consecutive familial clustering within a single sibship is exceptionally rare and challenges conventional genetic paradigms. We report a unique familial case series of isolated hemihyperplasia affecting two non-consecutive siblings born to healthy, non-consanguineous Libyan parents with a negative family history. The pedigree includes five children, where the third child (Case 2, a 10-year-old female) and the fifth child (Case 1, a 1-year-old male) are affected, separated by healthy children. Case 1 presented at 12 months with left-sided lower limb hypertrophy exhibiting a 2 cm length discrepancy and a 13% thigh circumference mismatch (Left: 26 cm, Right: 23 cm), satisfying the >5% clinical diagnostic threshold. Case 2 initially presented at 7 months with right-sided lower limb hypertrophy. Over a 10-year longitudinal follow-up, she maintained a benign clinical course; serial abdominal ultrasonographies every 3–4 months and normal serum alpha-fetoprotein (AFP) profiles successfully ruled out embryonal malignancies. Her persistent 2.5 cm limb-length discrepancy and acral overgrowth were stably managed via a conservative custom shoe lift. Key pathognomonic markers of Beckwith-Wiedemann syndrome were consistently absent in both siblings. The recurrence of isolated hemihyperplasia in non-consecutive siblings suggests an underlying heritable germline susceptibility or parental mosaicism with incomplete penetrance. This series provides crucial 10-year prognostic data demonstrating that oncological risks diminish substantially toward late childhood. It underscores the clinical necessity of strict long-term tumour surveillance and early interdisciplinary orthopaedic management for active limb discrepancies.

Introduction

Hemihyperplasia is a rare congenital overgrowth disorder characterised by an asymmetric, gross overgrowth of one or more regions of the body compared to the contralateral side. This condition can manifest as an isolated clinical finding (Isolated Hemihyperplasia [IH]) or as a component of well-defined genetic overgrowth syndromes, most notably Beckwith-Wiedemann syndrome (BWS), Russell-Silver syndrome, Proteus syndrome, and Klippel-Trenaunay syndrome [1]. The estimated incidence of isolated hemihyperplasia ranges from approximately 1 in 13,200 live births to 1 in 86,000 live births, though prospective multi-centre screenings suggest a higher incidence closer to 1 in 5,000 [2]. The vast majority of these cases occur sporadically, resulting from postzygotic somatic mutations or epigenetic alterations on chromosome 11p15 [3]. The primary clinical significance of diagnosing hemihyperplasia in pediatric patients lies in its well-documented association with an increased risk (about 5% to 10%) of developing embryonic tumours, particularly nephroblastoma (Wilms' tumour) and hepatoblastoma [4]. This predisposition necessitates rigorous, long-term abdominal screening protocols during early childhood [5]. While the pathogenesis of sporadic cases involving the 11p15 chromosomal locus is relatively well-understood, the familial recurrence of isolated hemihyperplasia remains an exceptionally rare phenomenon that challenges standard etiologic paradigms [6]. The occurrence of isolated hemihyperplasia in multiple siblings within a single nuclear family is a clinical novelty. Such familial clusters suggest that heritable genetic mechanisms or parental germline mosaicism could play a role in a subset of cases, expanding the discussion beyond the conventional view that IH is an exclusively sporadic event [7]. Documenting these rare familial patterns, along with long-term follow-up data that track the natural progression of the disease and tumour risks into late childhood, is vital for expanding the current literature.

In this paper, we present a rare case series of two non-consecutive siblings—a 10-year-old female and her 1-year-old brother—who presented with isolated familial hemihyperplasia, separated by a healthy child and preceded by two healthy children. Furthermore, we provide a 10-year longitudinal follow-up of the older sibling, highlighting the benign long-term clinical course and structural bone evolution of this familial trait.

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Case Presentations

Family Pedigree and History

The patients are two non-consecutive siblings born to healthy, non-consanguineous parents with no prior familial history of overgrowth syndromes, congenital anomalies, or embryonal malignancies. The nuclear family consists of five children in total. The birth order breakdown reveals a unique inheritance pattern: the first two children are completely healthy, unaffected males; the third child is the first affected female (Case 2, currently aged 10 years); the fourth child is another healthy, unaffected male; and the fifth child is the second affected male (Case 1, currently aged 1 year).

Case 1. The 1-Year-Old Male

The index patient is a 1-year-old male who was evaluated at a tertiary outpatient department for progressive asymmetric growth of his lower extremities. He was born via Normal full-term spontaneous vaginal delivery following an uneventful pregnancy, with unremarkable developmental milestones. At his 12-month evaluation, his body weight was 9.5 kg, and his length was 71 cm. Physical and anthropometric examinations revealed a distinct, isolated left-sided lower limb hemihyperplasia predominantly localised to the lower limb. Anthropometric measurements demonstrated a significant limb-length discrepancy (LLD), with the right lower limb 2 cm shorter than the left. Marked soft-tissue asymmetry was also present, characterised by an upper left thigh circumference of 26 cm relative to a contralateral upper right thigh circumference of 23 cm. This reflects a precise 13% localised volumetric overgrowth on the affected left side, clearly exceeding the standard 5% clinical diagnostic threshold required to confirm regional hemihyperplasia [3,4]. A comprehensive systemic examination revealed completely normal cardiovascular, respiratory, and neurological findings. Importantly, pathognomonic features of syndromic overgrowth—such as macroglossia, omphalocele, or umbilical hernia—were absent. Baseline laboratory investigations, including blood sugar levels, were within the normal range, ruling out neonatal or persistent hypoglycemia. The clinical presentation was concluded as isolated familial hemihyperplasia, and the patient was enrolled in a strict multi-disciplinary follow-up protocol involving pediatric and orthopaedic surgery subspecialties to manage his ambulatory milestones and LLD evolution.

Case 2. The 10-Year-Old Female

The second patient is the 10-year-old elder sister of Case 1. She initially presented at 7 months of age (weight 6.2 kg) due to a detected cardiac murmur and visible body asymmetry. Her early medical history noted a referral at 4 months of age to exclude developmental dysplasia of the hip (DDH), which was completely ruled out via orthopaedic imaging. Her initial cardiovascular evaluation revealed a soft, grade 2/6 systolic ejection murmur localised at the left upper sternal border with normal ECG parameters. Transthoracic echocardiography confirmed an entirely normal cardiac anatomy with intact septa and a benign maximum aortic pressure gradient of 6.8 mmHg, concluding the murmur as functional and innocent. Physical assessment during infancy confirmed an isolated right-sided hemihyperplasia. Over a 10-year longitudinal follow-up period, the patient demonstrated a benign and stable clinical course. Key syndromic markers of Beckwith-Wiedemann syndrome (BWS) were thoroughly and repeatedly checked [6]; there was no clinical history of macroglossia, facial dysmorphism, or omphalocele. To screen for embryonal malignancies associated with hemihyperplasia, a rigorous surveillance protocol was maintained during her early childhood [5]. Serial abdominal ultrasonographies performed every 3 to 4 months consistently revealed normal intra-abdominal organs with no evidence of hepatoblastoma or Wilms' tumour (nephroblastoma). Furthermore, serum tumour markers were closely monitored, with alpha-fetoprotein (AFP) levels and blood sugar profiles remaining within normal physiological limits. Currently, at 10 years of age, her growth and limb asymmetry have stabilised. Her documented body weight is 25 kg, and her height is 137 cm. Anthropometric and orthopaedic re-evaluation demonstrates a long-standing, persistent lower limb-length discrepancy (LLD) of 2.5 cm, with the right leg being longer than the left. Additionally, a notable foot size asymmetry is present, with the right shoe size being three sizes larger than the left, indicating selective acral soft-tissue and bony overgrowth on the affected side [7]. This chronic discrepancy has been successfully and stably managed via conservative orthopaedic interventions, specifically utilising a custom-made shoe lift, allowing the patient to maintain normal physical mobility and excellent quality of life without developing pelvic tilt, compensatory scoliosis, or spinal complications [10].

Patient Timeline

The following timeline synthesises the clinical milestones, interventions, and parallel diagnostic courses for both affected non-consecutive siblings over the longitudinal screening window.

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Table 1. Patient Timeline

Date/ Patient age	Case 2 (Older Sister) Clinical Courses	Case 1 (Younger Brother) Clinical Courses
Infancy (4 Months)	Referred for suspected DDH; hip imaging confirmed stable joints and completely excluded dysplasia.	Not yet born
Infancy (7 Months)	Initial presentation; diagnosed with isolated right-sided lower limb hemihyperplasia and an innocent grade 2/6 systolic murmur.	Not yet born
Early childhood (Ages 1 to 7 Years)	Maintained strict oncological surveillance: serial abdominal ultrasound every 3 – 4 months and periodic serum AFP markers; all consistently normal.	Not yet born
Sibling Birth	Normal pediatric course; asymmetry stabilised and managed conservatively via a custom shoe lift.	Normal Full-term spontaneous vaginal delivery following uneventful pregnancy.
Current Evaluation	Age 10 years: persistent 2.5cm LLD and + 3 right shoe size discrepancy. Tumour-free and cleared past the high-risk window.	Age 12 months: index presentation with isolated left lower limb hemihyperplasia (13% thigh mismatch, 2 cm LLD). Enrolled in screening protocols.

Table 2. Final Anthropometric and Clinical Surveillance Profiles of Affected Siblings

Clinical Parameter	Case 1 (Younger Brother)	Case 2 (Older Sister)
Current Age	12 months	10 years
Current Weight	9.5 kg	25 kg
Current Height / Length	71cm	137 cm
Side of Hemihyperplasia	Left side	Right side
Anatomical Type	Simple (Lower limb only)	Complex (Lower limb & foot)
(Limb-Length Discrepancy (LLD)	2.0 cm (Right leg shorter)	2.5 cm (Left leg shorter)
(Soft-Tissue Discrepancy)	Left thigh: 26 cm / Right thigh: 23 cm (13% Mismatch)	+3 right shoe sizes (EU sizing)
Cardiac Evaluation	Normal Systemic Exam	Innocent Functional Murmur (Grade 2/6 SEM)
Abdominal Ultrasound	Normal baseline (No organomegaly)	Normal (Serial scans every 3 to 4 months for 10 years)
Serum Tumour Markers (AFP)	Normal Blood Glucose	Normal AFP (2.3 ng/mL) & Blood Glucose
Clinical Management	Multi-disciplinary Orthopaedic Follow-up	Custom Shoe Lift (Conservative Alignment)
Oncological Outcomes	Tumour-free (Surveillance ongoing)	Tumour-free (Cleared past the high-risk window)

Table 3. Diagnostic Investigations and Long-Term Oncological Surveillance

Clinical Parameter	Case 1 (Younger Brother)	Case 2 (Older Sister)
Echocardiography Findings	Normal cardiac anatomy and function	Grade 2/6 Functional Systolic Murmur (Benign)
Electrocardiogram Parameters	Normal sinus rhythm	Normal sinus rhythm (PR: 0.12s / QT: 0.28s)
Hip Imaging (DDH Screening)	Stable joints, no dysplasia noted	Evaluated at 4 months; DDH completely excluded
Baseline Blood Glucose Profile	Normal (No neonatal hypoglycaemia)	Normal physiological glycemic control

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Discussion

The manifestation of isolated hemihyperplasia (IH) is historically regarded as an idiopathic, sporadic overgrowth phenomenon resulting from postzygotic somatic alterations or epigenetic mutations regulating cell proliferation on chromosome 11p15 [1, 2]. Consequently, the recurrence of IH within a single sibship separated by unaffected children presents a unique genetic interest that warrants exploration beyond conventional sporadic etiologic frameworks. This specific non-consecutive pedigree pattern proposes a hypothetical heritable germline susceptibility or parental gonadal mosaicism, where an unaffected parent might silently carry a mutation with incomplete penetrance and variable expressivity [8, 9] . However, because advanced molecular and epigenetic analyses of the 11p15 locus or whole-exome sequencing were not performed in this institutional series, these hereditary mechanisms remain strictly speculative. This lack of confirmatory genetic testing constitutes a primary limitation of our report, preventing the definitive exclusion of rare, coincidental postzygotic somatic mosaicism occurring independently in both siblings.

A fundamental challenge in clinical practice is establishing an accurate diagnosis of IH due to the historic lack of universal criteria. As highlighted in recent literature, an arbitrary but crucial diagnostic threshold requires that the gross regional growth asymmetry, whether in limb circumference or bone length, must be greater than 5% compared to the unaffected contralateral side to distinguish true hemihyperplasia from physiological variation [3]. In our series, Case 1 demonstrates a marked 13% upper thigh circumference discrepancy, confirming a profound soft-tissue overgrowth that satisfies this diagnostic criterion. According to Rowe's anatomical classification, Case 1 represents a simple IH localised to a single lower limb, while Case 2 exhibits a complex presentation affecting multiple segments [7]. Differentiating IH from comprehensive overgrowth syndromes, particularly Beckwith-Wiedemann Syndrome (BWS), is a mandatory step in clinical management [6]. BWS presents with a definitive triad of macroglossia, omphalocele, and organomegaly, along with structural facial dysmorphisms. In this series, syndromic entities were conclusively ruled out for both siblings based on the complete and persistent absence of these criteria, normal tongue texture, and normal baseline blood glucose profiles. The clinical significance of identifying pediatric IH lies in its well-documented 5% to 10% association with embryonal malignancies, most notably Wilms' tumour (nephroblastoma) and hepatoblastoma [4, 5].

Recent literature cautions that mild or asymptomatic cases often go undiagnosed during childhood, causing clinicians to underestimate neoplastic predispositions and miss critical screening windows [2]. Standard surveillance protocols advocate for abdomino-pelvic ultrasonography every 3 months until age 7 to 8 to screen for Wilms' tumour, paired with serum AFP measurements every 6 weeks to 3 months until age 4 for early hepatoblastoma detection [5, 6]. The 10-year longitudinal follow-up of Case 2 contributes invaluable prognostic validation to the literature. Her consistently negative abdominal scans and normal physiological AFP profiles support clinical evidence showing that isolated variants follow a stable, benign course where growth velocities normalise, and oncology risks diminish substantially toward late childhood and adolescence [5, 10]. Biomechanically, limb-length discrepancies (LLD) can result in compensatory scoliosis, pelvic tilt, or persistent musculoskeletal pain, which are frequently the only reasons these patients seek orthopaedic care later in life. Utilising a custom-made shoe lift for Case 2 allowed for normal physical development, serving as a highly effective clinical management roadmap for Case 1 as he reaches vital ambulatory milestones with his 2 cm discrepancy [10].

Conclusion

In conclusion, we report an exceptionally rare familial cluster of isolated hemihyperplasia (IH) affecting two non-consecutive siblings separated by completely healthy children. This pedigree pattern suggests that heritable genetic mechanisms or parental germline mosaicism could play a role in a subset of cases, expanding the discussion beyond the conventional view that IH is an exclusively sporadic event. We acknowledge that without comprehensive epigenetic and genomic profiling, a definitive mode of inheritance cannot be established. Therefore, we strongly recommend that future familial reports integrate advanced molecular investigations to delineate the precise aetiology of this phenotypic recurrence. The 10-year longitudinal follow-up of the older sibling demonstrates a benign long-term prognosis and confirms that the elevated risk of embryonal malignancies diminishes significantly after early childhood, validating current screening timelines. While the older sibling's clinical course provides a valuable prognostic roadmap, the younger sibling requires meticulous, multidisciplinary monitoring by paediatricians and orthopaedic surgeons to manage his active limb-length discrepancy.

Ethics Approval

Institutional Review Board (IRB) approval was waived by our institutional ethics committee because this is a retrospective clinical report of a de-identified case series and did not involve any experimental interventions or deviation from standard institutional care guidelines.

Consent for Publication

Written informed consent was obtained from the patients' legal guardians (parents) for the publication of this case series, clinical details, and any accompanying institutional data or materials.

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Availability of Data and Materials
All relevant clinical data supporting the findings of this case series are contained within the manuscript and its accompanying tables.

Competing Interests
The authors declare that they have no competing interests.

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