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Endocrine Phenotypes and Hormonal Treatment in Meier-Gorlin Syndrome: Report of Two Cases and a Systematic Review of Literature

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ABSTRACT

Background: Meier-Gorlin-syndrome (MGORS) is a rare cause of primordial dwarfism stemming from pathogenic variants in genes involved in DNA replication. The classic clinical triad is microtia, absent patella and short stature. MGORS can mimic endocrine causes of short stature or delayed/atypical pubertal development.

Methods: We report two new cases of MGORS. A systematic literature search of all cases published up to 31 March 2026 was done to identify the cases reporting any endocrinopathy or hormonal therapy, focussing on growth-hormone-deficiency (GHD) and response to growth hormone (GH).

Results: We describe a 14 year-old girl, the first MGORS case with *CDC6* variant and mammary hypoplasia. Another 11-year old boy with *GMNN* variant had severe short-stature with GHD and had significant height improvement with GH. Among 29 cases (out of ~150 published), the classic triad was absent in 18.5%. Short stature was almost universal (median height-*Z*-score −4.4), with 70% exhibiting delayed bone age, 42.9% low IGF-1 and 35.3% GHD. Among 10 GH-treated cases with response data, 6 had reported improvement in height-SDS/growth-velocity. Those with GHD and delayed bone age were more likely to benefit from GH. Among females, all post-pubertal cases had mammary hypoplasia, while 23.5% had clitoromegaly with hypoplastic labia. Among males, cryptorchidism, hypoplastic scrotum and micropenis were common. However, gonadal hormones and gonadotrophins were normal. Data on the effect of estrogen on hypoplastic mammary glands or labia was variable.

Conclusion: MGORS should be kept in mind as a differential of multiple endocrinopathies. Cases of MGORS should undergo screening for GHD. Available data, mostly from case-reports or small series, suggest that response to GH has been reported in some individuals, particularly where GHD or delayed bone age was present, but evidence remains very limited.

1 | Introduction

Meier-Gorlin syndrome (MGORS) is a rare syndrome classified under primordial dwarfism with generally autosomal recessive inheritance, characterised by primordial dwarfism, microtia, and patellar hypoplasia/absent patella [1]. It was first reported in the year 1959 by Meier and Rothschild [2], followed by a second case reported by Gorlin in 1975 [3]. DNA replication is a complex multiprotein process that is tightly regulated. Till date, fewer than 150 cases of MGORS have been reported worldwide, and variants in 13 genes involved in DNA replication are associated [4]. Reduction of the overall growth with patellar hypoplasia/aplasia and microtia form the classic triad of MGORS [5]. Other associated

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features include a variety of skeletal deformities, facial dysmorphism, microcephaly, including microstomia with full lower lip, micrognathia, retrognathia, and beaked nose. There is no existing consensus or guidelines on the management of MGORS. Knowledge about its clinical course is based on published cases and is mostly supportive or guided by manifestations. Common complications include feeding problems due to a small stomach, sometimes needing gastrostomy, pulmonary complications including congenital pulmonary emphysema, broncho/tracheal/laryngomalacia, tracheomalacia or laryngomalacia, cranial neuropathies, conductive hearing loss, and cardiac septal defects [5, 6]. The care of patients with MGORS needs a multidisciplinary team. To an endocrinologist, MGORS might mimic multiple hormonal diseases that might lead to short stature, skeletal deformities, poor breast development, and amenorrhoea. Lack of awareness may delay recognition of MGORS and lead to unnecessary endocrine investigations or inappropriate interpretation of syndromic developmental features as isolated endocrine diseases. Common differentials would thus include Turner syndrome, hypopituitarism in the form of combined or isolated growth hormone deficiency, and other etiologies of primordial dwarfisms (Table 1). There is a dearth of literature regarding the contribution of hormonal defects in MGORS, as well as the role of GH in improving height or of estrogen in improving breast size in MGORS.

A recent study has extensively reported all genetic variants that have been reported till date that have been associated with MGORS and also conducted a literature review of the data available on response to GH [7]. The authors report a possible role of the underlying molecular defect on the response to GH, but definitive conclusions could not be drawn due to the paucity of data. The authors themselves reported a good response in their case to pegylated GH, in spite of having normal IGF-1 for age, which was discordant from prior studies reporting inadequate response in those with normal IGF-1. The authors did not report on GH deficiency (GHD) and bone age. The largest series of MGORS reported by deMunnik et al had published data on stimulated GH values and bone age [5]. Some of the cases in literature have been reported in duplicate, based on their findings at different ages. Since MGORS mimics several endocrinologic disorders which present with both short stature and absence/poor development of secondary sexual characteristics, it became pertinent to do an updated literature review assimilating available data on all hormonal evaluation, with special emphasis on GH and gonadal hormonal evaluation as well as to evaluate the discrepancy regarding the response to GH. We report two new cases of MGORS in this series, a girl carrying a novel *CDC6* variant, and a boy with a novel *GMNN* variant having documented GHD/GH response. We performed a systematic review of the literature to assimilate available information on all published cases of MGORS who have data on hormonal evaluation and/or the effect of therapy with GH, gonadal hormones or any other hormonal treatment in MGORS.

2 | Methodology

We report a series of two cases of MGORS with distinct variants and clinical presentations and describe their clinical course and management. Informed assent was taken from both the cases and informed consent from their parents/legal guardians for publication of their data and their unblinded photographs.

2.1 | Data Sources and Search Strategy

We performed a comprehensive systematic review of literature using PubMed and Google Scholar databases, further supplemented by a manual screening of reference lists from the relevant articles, for all relevant articles published in English language till 31 of March 2026. The search string involved using the keywords and Boolean operators in the following format: 'Meier-Gorlin syndrome' OR 'MGORS' OR 'Meier-Gorlin Syndrome' OR 'Meier Gorlin Syndrome' OR 'Ear-patella-short stature syndrome' OR (ORC1) OR (ORC4) OR (ORC6) OR (CDT1) OR (CDC6) OR (GMNN) OR (CDC45) OR (MCM3) OR (MCM5) OR (MCM7) OR (GINS2) OR (GINS3) OR (DONSON) OR (MICROTIA AND 'SHORT STATURE') OR (MICROTIA AND 'ABSENT PATELLA') OR ('SHORT STATURE' AND 'ABSENT PATELLA') OR ('SHORT STATURE' AND 'HYPOPLASTIC PATELLA') OR ('PRIMORDIAL DWARFISM' AND 'MICROTIA') OR ('PRIMORDIAL DWARFISM' AND 'HYPOPLASTIC PATELLA') OR ('PRIMORDIAL DWARFISM' AND 'ABSENT PATELLA'). Filters were applied to select only case reports/series, clinical study, clinical trials, comparative studies, meta-analyses, multi-centre study, observational study, randomised controlled trials, datasets. Historical article, letters, scoping and systematic reviews. On the Google Scholar, articles were screened by relevance till the 15th page (10 articles/page). Further filters were applied to select only articles published in English and on human participants. The retrieved citations were imported into an Excel sheet and screening for duplicates was done manually by comparing the titles, authors, year of publication, and digital object identifiers (DOIs). Full texts of all the potentially eligible studies were retrieved and assessed independently for eligibility. The full texts were accessed through open-access sources or using institutional subscriptions, through the ONOS (One-Nation-One-Subscription) system and membership access for society journals. Studies for which full texts could not be obtained despite reasonable efforts were excluded. The full-text versions were reviewed for eligibility according to the predefined inclusion and exclusion criteria. Two reviewers (R.B. and S.M.) independently did the screening of the titles and abstracts of the retrieved articles for selection based on the set inclusion criteria. Any discordance between the reviewers was resolved by either reaching a consensus or consulting with a third reviewer. The PRISMA flow diagram for the literature search strategy is given in Supporting Information S1: Figure 1. The review protocol has been registered with PROSPERO (registration number: CRD420261407820). No form of artificial intelligence was used for literature search or writing of this article.

2.2 | Article Selection

We included only cases of MGORS who either had any known endocrinopathy or underwent some hormonal analysis or had been treated with any kind of hormone replacement, including GH, estrogen, or testosterone (n = 41). If there were multiple cases in the same article, those cases were excluded which had no data on hormonal evaluation or therapy. In some instances, the same cases were found to be described in multiple publications, in which case we excluded the duplicates from analysis. Two cases of siblings with MGS were found, but they were not included since they did not fit the inclusion criteria. Twins were reported as individual cases where hormonal evaluations were mentioned. Applying the inclusion and

TABLE 1 | Differential diagnoses of Meier-Gorlin Syndrome presenting to endocrinologists.

Differential diagnosis	Clinical features in common	Features specific to MGORS not typically seen in the differential	Features specific to the differential diagnosis not typically seen in MGORS	Preferred investigation for confirmation of the differential diagnosis
Turner syndrome	Short stature, Facial dysmorphism, Hypoplastic breasts, Ear abnormalities, conductive deafness, Congenital cardiac malformation	Microtia, Retrognathia, Absent patellae, Long slender bones, affects both males and females, Normal menstrual cycles in females	Webbed neck, Cubitus valgus, Brachy-metacarpia, Shield chest; Not a diagnosis in phenotypic males; In most cases, primary ovarian insufficiency with high FSH, low estradiol, low AMH; Higher prevalence (1: 2500 live births)	Peripheral blood cell karyotyping to diagnose Turner Syndrome—45, X (Classic Turner syndrome); mosaicism of 46, XX or 46, XY with 45, X cell lines; isochromosome Xq; deletions of Xp; ring chromosome X etc
Combined pituitary hormone deficiency	Short stature, poor breast development in females, cryptorchidism in males, dysmorphic facies	Microtia, retrognathia, absent patellae; Normal levels of anterior pituitary hormones and normal pituitary size	Midline defects, septo-optic dysplasia, features of acquired causes like tumour/radiation; Concomitant presence of other anterior pituitary hormone deficiencies like central hypocortisolism, central hypothyroidism or central Diabetes Insipidus; Disorders of the hypothalamo-pituitary region seen on imaging (Hypoplastic pituitary/ empty sella/redundant stalk/ectopic posterior pituitary bright spot/masses of the sellar-suprasellar region) on imaging	MRI of the hypothalamo-pituitary region; Evaluation of anterior pituitary hormones
Noonan syndrome and other RASopathies	Short stature; Dysmorphic facies; Skeletal deformities, Cryptorchidism in males; Congenital cardiac anomalies	Microtia; Hypoplastic/ Absent patellae; Microcephaly; micrognathia, retrognathia; Hypoplastic breasts	Partial ptosis of eyes, Webbing of neck, lymphedema; Cubitus valgus, pectus carinatum. excavatum; Bleeding diathesis; Predominantly right sided cardiac anomalies	Exome sequencing to detect mutations in *PTPN11, SOS, RAF1, RIT1, KRAS, NRAS, SOS* etc genes
Chronic undernutrition	Proportionate Short stature; Underweight for age; Low MUAC for age; Poor breast development in females; No mental retardation	Dysmorphic facies, microtia, absent patellae; Long slender bones	Delayed bone age; Tell-tale features of micronutrient deficiency like sparse thin hair/flag hair/flaky-paint dermatosis/angular cheilitis/ glossitis/Bitot spots/pitting edema etc; h/o chronic diarrhoea may be present	Appropriate nutritional history; evaluation for malabsorptive disorders like celiac disease; low albumin; screening for micronutrient levels
Chronic illnesses	Proportionate Short stature; Underweight for age; Poor breast development in females; Chronic cardiac/	Dysmorphic facies, microtia; hypoplastic/ absent patellae; Slender long bones; Normal menstrual cycles	Tell-tale features of the underlying chronic disease	Relevant investigations for suspected underlying disorder

(Continues)

TABLE 1 | (Continued)

Differential diagnosis	Clinical features in common	Features specific to MGORS not typically seen in the differential	Features specific to the differential diagnosis not typically seen in MGORS	Preferred investigation for confirmation of the differential diagnosis
	pulmonary diseases; No mental retardation			
Skeletal dysplasias	Short stature; Dysmorphic facies; Normal gonadal hormones; Usually normal age-appropriate gonadal hormones and gonadotropins; Hip dysplasias; No mental retardation	Microtia, absent patellae; Hypoplastic breasts	Often disproportionate short stature—predominant involvement of the vertebrae or long bones; Characteristic finger anomalies like trident hand; Marked epiphyseal and metaphyseal irregularities; Progressive bony deformities ± neurologic deficits if spinal cord involvement; Often severe vertebral involvement	Radiographs of vertebrae; long bones; hands and skull; MRI of the spine
Other causes of Primordial dwarfism with facial dysmorphism				
Russell-silver syndrome (RSS)	Proportionate short stature; pre- and postnatal growth restriction; Facial dysmorphism; often underweight with h/o feeding difficulties Cryptorchidism in males may be seen; No significant intellectual disability; Usually normal age-appropriate gonadal hormones and gonadotropins;	Microtia; absent patellae; Micrognathia, retrognathia Slender long bones; Hypoplastic breasts in females, Congenital cardiac malformations	Relative macrocephaly at birth; Prominent forehead; Triangular face, small jaw, limb asymmetry; h/o severe IUGR; 5th finger clinodactyly; intelligence may be mildly affected	Netchine–Harbison Clinical Scoring System for RSS; MS-MLPA and exome sequencing to detect hypomethylation at 11p15 (IGF2/H19) to detect maternal uniparental disomy of chromosome 7 or mutations in *CDKN1C* gene
Dubowitz syndrome	Proportionate short stature; pre- and post natal growth restriction; Microcephaly; Facial dysmorphism; Ear anomalies; Cryptorchidism; Cardiac congenital malformations (occasionally seen)	Microtia; absent patellae; Micrognathia, retrognathia slender long bones; hypoplastic breasts in females, congenital cardiac malformations	Broad nasal bridge, microcephaly, triangular face, drooping eyelids; Developmental delay/ intellectual disability often seen; Immunologic defects and eczema common; Hyperactivity with short attention span	Causative gene and mutation yet unidentified – no confirmatory test, mostly a clinical diagnosis
Microcephalic osteodysplastic primordial dwarfism (MOPD)	Proportionate short stature; pre- and postnatal growth restriction; Microcephaly; Facial dysmorphism; often	Microtia; absent patellae; Micrognathia, retrognathia Slender long	Severe microcephaly with prominent eyes, Prominent nose, receding forehead; Extreme short stature (adult height < 100 – 120 cm), Generalized skeletal dysplasia, hip abnormalities, radial head	Exome sequencing to detect mutations in *PCNT* (MOPD II), *RNU4ATAC* (MOPD I) genes

(Continues)

TABLE 1 | (Continued)

Differential diagnosis	Clinical features in common	Features specific to MGORS not typically seen in the differential	Features specific to the differential diagnosis not typically seen in MGORS	Preferred investigation for confirmation of the differential diagnosis
	underweight with h/o feeding difficulties cryptorchidism in males may be seen	bones; Hypoplastic breasts in females	dislocation, scoliosis; teeth crowding with enamel anomalies; cerebrovascular diseases common with Moyamoya/intracranial aneurysms/arterial stenosis reported; Insulin resistance/dysglycemia and hypertension common during adolescence/ adulthood; mild intellectual disability	
Seckel syndrome	Proportionate short stature; pre- and post-natal growth restriction; Facial dysmorphism; Microcephaly; Cryptorchidism; Cardiac congenital malformations occasionally seen; Hip deformities seen occasionally		Bird like beaking of the nose, micrognathia; Severe short stature; Very low birth weight; Intellectual disability common; Severe microcephaly; Clinodactyly; Hematologic abnormalities (pancytopenia, aplastic anemia, MDS) may be seen	No single confirmatory test; Exome sequencing detect mutations in the *ATR, ATRIP, CEP152, RBBP8, CENPJ* genes
3 M syndrome (Miller-McKusick-Malvaux syndrome)	Proportionate short stature; pre- and post-natal growth restriction; Facial dysmorphism; Slender long bones; preserved intelligence; Cryptorchidism in males		Relative Macrocephaly at birth; dolicocephaly, thick bushy eyebrows, long philtrum, full lips, pointed chin; Winged/prominent scapulae; Pes planus with prominent heels; Tall vertebral bodies, hyperlordosis; Severe short stature (adult height often < 120–150 cm)	Exome sequencing to detect pathogenic mutations in *CUL7, OBSL1 or CCDC8* genes
SHOX haploinsufficiency states (except Turner Syndrome) (Léri–Weill Dyschondrosteosis: heterozygous mutation/ deletion of SHOX Langer mesomelic dysplasia: (homozygous or compound heterozygous mutation of SHOX)	Proportionate short stature; facial dysmorphism; ear anomalies and hearing deficits may be present; bone deformities	Microtia; absent patellae; Micrognathia, retrognathia slender long bones; hypoplastic breasts in females	Mesomelic short stature with characteristic involvement of radius, tibia (often bowed) with fibular sparing; Madelung deformity due to abnormal alignment of radius and ulna; Cubitus valgus and brachy-metacarpia common; Normal secondary sexual characteristics; Family history often positive due to autosomal dominant inheritance pattern	Exome sequencing/MLPA to detect mutations/deletions of the *SHOX* gene

Abbreviations: AMH, anti mullerian hormone; FSH, follicle stimulating hormone; MGORS, Meier Gorlin Syndrome; MLPA, multiple ligand dependent probe amplification; MRI, magnetic resonance imaging; MS-MLPA, methylation sensitive multiple ligand dependent probe amplification; MUAC, mid-upper arm circumference.

exclusion criteria, finally, a total of 27 cases were included from literature review.

2.3 | Variables of Interest

Data were collected regarding the author names, year and country of publication, gender, ethnicity or country of origin of the case, consanguinity between parents, history of prematurity, birth weight, length, head circumference, and latest data on height & weight as given in the published case report/series/study. The presence or absence of the classic triad—short stature, microtia and patellar hypo/aplasia—was recorded. Mammary hypoplasia and genital anomalies were recorded separately. For radiological and hormonal data, bone age, insulin-like-growth factor 1 (IGF1), and GH reserve (normal or deficient) assessed using any of the recommended GH stimulation tests were considered. For data on GH treatment, data were collected regarding the age of initiation, dose, and duration of GH and response to therapy in the form of height velocity or change in height - SDS. Endocrinopathies other than GH-IGF1 axis abnormalities were documented, along with the treatment provided. Genetic data were reported as mentioned by the author, including variants in only genes known to have a probable relationship with MGORS. Favorable changes in either height-SDS (Ht-SDS) or velocity were defined as improvement in Ht-SDS > 1 SD and/or annualized height velocity > 50th centile for age and gender on standard height velocity charts for Indian girls and boys between 5 and 17 years (including the pubertal growth spurt) [5, 8]. The presence/absence of mammary hypoplasia was considered only in girls ≥ 9.5 years, considering the median age of thelarche in the country [9]. Since data on endocrinologic evaluation were available only for a small group of published cases of MGORS, the proportion of endocrine manifestations such as GHD, low IGF-1, mammary hypoplasia and endocrine abnormalities are expressed as proportions among selected reported/evaluable cases and not as overall prevalence estimates for MGORS.

2.4 | Statistical Analysis

Statistical analysis was done using GraphPad Prism v.8 for Mac. Results were expressed as mean (SD) or median [Q1, Q3] for quantitative variables and *n* (%) for categorical variables. For height, weight, length, and head circumference (at birth), age and gender specific *Z* scores calculated from regional data, wherever available, were considered in the analysis. Comparison of clinical and biochemical characteristics was done using a Mann–Whitney for quantitative and Fisher's *t*-test for categorical variables. A p value of <0.05 was considered significant.

3 | Results

3.1 | Description of Current Cases

3.1.1 | Case 1

A 14-year-old girl presented with complaints of failure to gain height and weight, and lack of any breast development. However, she had a spontaneous menarche with regular menstrual cycles since the age of 12 years. She was born out of a nonconsanguineous marriage, at term, by normal vaginal delivery, and with a birth weight of 2000 g (0.1th percentile; *Z* score: −3). The perinatal and neonatal periods were uneventful. However, since infancy, she had poor height gain, with the mother emphasizing a characteristically poor appetite and early satiety. Developmental milestones were slightly delayed compared to the peers, but the speech and intellect were apparently normal. There was no family history of short stature, and her younger sister was healthy and taller than her. She was quite playful and enjoyed a friendly relationship in society. She had no other significant medical illness and never underwent any surgery. Her height was 129 cm (< 3rd percentile according to the Indian Academy of Paediatrics, i.e., IAP 2015 growth chart, −3.85 SDS), weight was 18 kg (below 3rd percentile according to IAP), head circumference was 45 cm (< 3rd centile, IAP 2015, −4.98 SDS), BMI 10.82 kg/m^2, −3.78 SDS. The mid-parental height was 148 cm. She had a small triangular face, a high nasal bridge, and beaked nose, bilateral low-set ears with microtia, and narrow external ear canal (Figure 1). She had small oral orifice with full lips, micrognathia, retrognathia and high arched palate, teeth were normal (Figure 1). She had long, slender fingers and wide sandal gaps in her feet (Figure 1). A careful examination of the knee joint revealed the absence of the patella bilaterally, which was confirmed on radiographs. Regarding her secondary sexual characteristics, her breast development was stage B1, pubic hair P4, axillary hair was present, and her labia majora were hypoplastic. The rest of her general and systemic examination was unremarkable. Biochemical tests, including complete hemogram, liver function test, and kidney function test, were normal, as were the levels of gonadal and pituitary hormones, including Luteinising hormone (LH), Follicle Stimulating Hormone (FSH), Prolactin, Insulin-like Growth Factor-1 (IGF-1), and Thyroid Stimulating Hormone (TSH) (Supporting Information S1: Table 1). Gonadal hormones and gonadotrophins were measured during the early follicular phase (Day 3 of menstrual cycle) Serum Estradiol, LH and FSH were normal for age and pubertal stage (Table 1). Uterine volume was 2.8 cc with bilateral ovaries, volume 2 cc without any cystic changes. Thus, internal Mullerian structures were pubertal in size, but slightly on the lower side of the normal reference dimensions for her age [10, 11]. She used to consume approximately 1200 kcal and 22 grams of protein per day. She used to feel full after every meal and was habituated to taking small but frequent meals. There were no tell-tale clinical features of any micronutrient deficiency. There were no clinical suggestions of other chronic respiratory, cardiac, gastrointestinal, or urinary disease. Routine biochemical tests including complete blood counts, renal and liver function tests, urine routine examination, stool examination for ova-parasites and occult blood were all normal. Screening for celiac disease was done using anti-tissue-transglutaminase IgA antibodies, which came out to be negative. Echocardiography was normal. In the background of short stature, microtia, absent patella, and mammary hypoplasia, a provisional diagnosis of MGORS was made.

Genetic analysis using whole exome sequencing identified a homozygous missense variant in the *CDC6* gene, NM_001254.4:c.1376 T > C, predicted to result in the amino acid substitution p.(Leu459Pro). The variant was classified as a variant of uncertain significance (VUS) according to the criteria of the American College of Medical Genetics and Genomics (ACMG). To the best of our knowledge, this variant in *CDC6* gene has not been previously reported as a pathogenic variant nor as a benign variant. This variant is absent in population databases including the gnomAD Exomes and has not been submitted previously to the ClinVar database. The reference

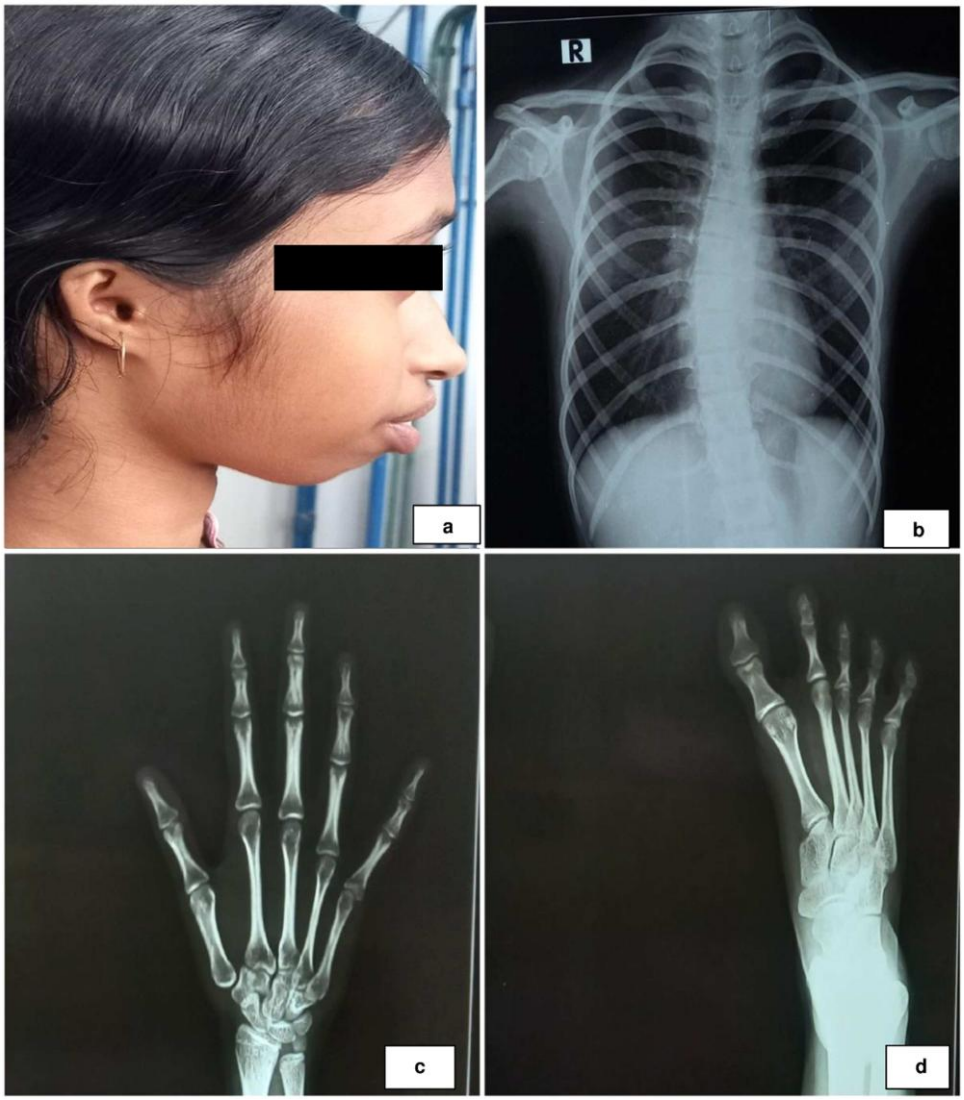

FIGURE 1 | (a) Clinical photographs of a 14-year old girl with Meier-Gorlin Syndrome showing the lateral aspect of the face showing micrognathia/retrognathia with fuller lower lip, beaked nose, and microtia (b) Chest PA view showing long, slender ribs, (c) AP view of Right Hand showing long slender bones of fingers and, (d) AP view of foot showing long slender metatarsals and increased sandal gap. [Color figure can be viewed at wileyonlinelibrary.com]

amino acid at this position in *CDC6* gene is predicted as conserved by GERP++ and PhyloP across 100 vertebrates. The amino acid leucine at position 459 is changed to proline, changing the protein sequence and it might alter its composition and physicochemical properties. In silico analysis using multiple lines of computational evidence (Polyphen-Probably damaging, SIFT-Damaging and MutationTaster-Disease causing) predicts a damaging effect on protein structure and function for this particular variant. However, segregation analysis or Sanger sequencing in the parents could not be done due to logistic constraints. To date, only two cases of MGORS due to *CDC6* variants have been reported prior to this. The girl refused GH therapy and a trial of estrogen for her mammary hypoplasia.

3.1.2 | *Case 2*

An 11-year-old boy presented with complaints of short stature, micropenis, and small pinna since birth. He was born out of a consanguineous marriage with a birth weight of 2200 g with an uneventful perinatal and neonatal period. The child had poor gain in height and weight since early infancy. He had no other medical illness in the past. On examination, his height was 122 cm (< 3rd percentile, Ht-SDS = −2.88), weight was 21 kg (< 3rd percentile, Weight SDS = −2.37), BMI was 14.11 kg/m^2, and head circumference was 52 cm. The mid-parental height was 151 cm. He had bilateral low-set ears with microtia with narrow external ear canals (Figure 2). In addition, the eyes were small, the lips were full, the boy had micrognathia, and he had a wide sandal gap in the feet. Patellae were absent bilaterally (Figure 2). He had pre-pubertal testicular volume of 2 mL bilaterally, pubic hair stage P1, and absent axillary hair. His stretched penile length was 4 cm. A provisional clinical impression of MGORS was made due to the short stature, microtia, and absent patellae. Whole exome sequencing confirmed a likely heterozygous VUS as per ACMG guidelines, though based on multiple lines of computational evidence suggesting it might be deleterious, the geneticist opined it could be a VUS

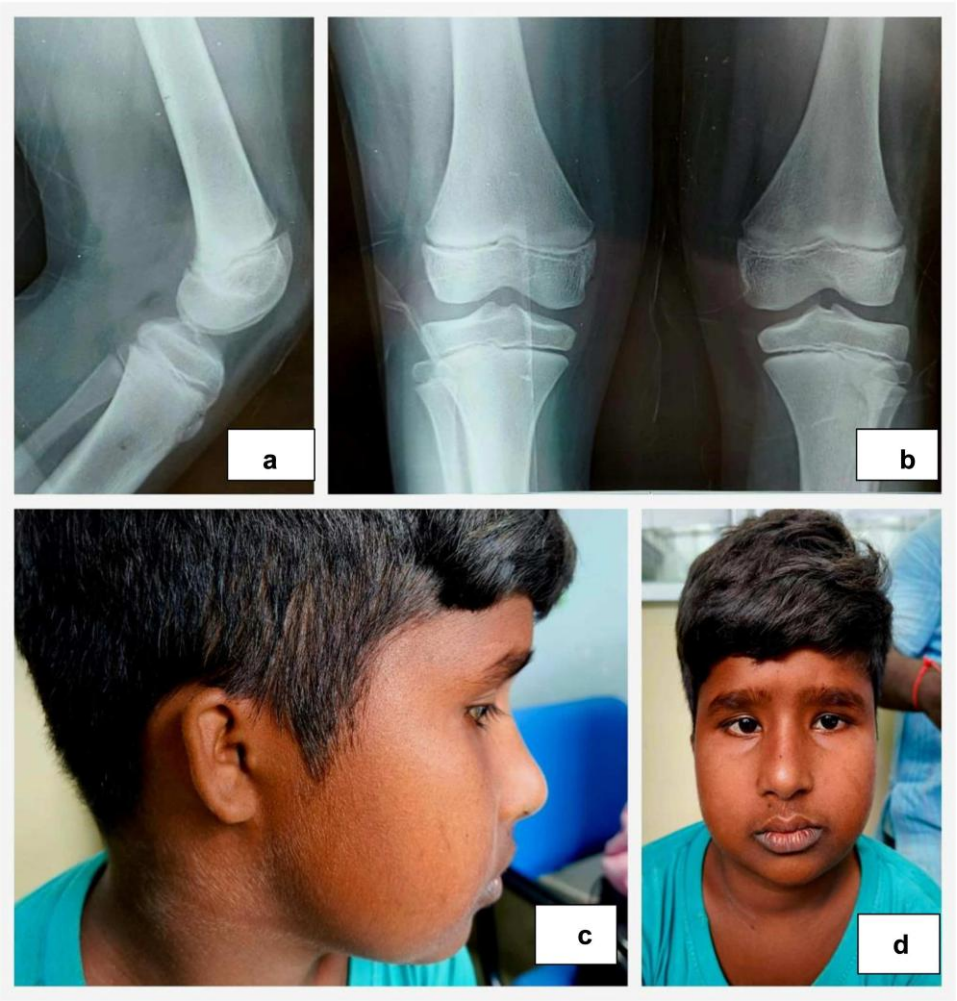

FIGURE 2 | Radiographs (skiagrams) and clinical images of Case 2—an eleven-year old boy with with Meier-Gorlin Syndrome. (a) Lateral view skiagram of Right knee (b) Anterior view skiagram showing bilateral absent patellae (c). Microtia with narrow ear canal (d) Narrow palbebral fissure, telecanthus, full lips. [Color figure can be viewed at wileyonlinelibrary.com]

with probable damaging effect—c.37 A > T (p.Lys13Ter) at exon 2 of the *GMNN* gene on chr6:24777511 A > T. The observed nonsense substitution (p.Lys13Ter) is predicted to cause premature termination of the geminin protein, the truncated protein being predicted to have a length of 12 amino acids (aa) as opposed to the original length of 209 aa and likely to lack the C-terminal region of the protein. However, in the absence of direct evidence for the pathogenicity of truncating variants is not well established in this gene, therefore, it was labelled as 'VUS'. We were unable to perform segregation analysis or Sanger sequencing in the parents due to financial constraints. This variant has not been previously reported in the literature, though other truncating variants in the *GMNN* gene have previously been reported as likely pathogenic in the literature with respect to MGORS6 [12]. In this, the authors reported three variants in exon 2 of GMNN, which is the first coding exon of *GMNN* gene. They found a heterozygous c.16 A > T (p.Lys6*) nonsense (stopgain) mutation in *GMNN* in one subject leading to replacement of lysine (Lys) by a stop codon at amino acid position 6. In another subject, they reported a heterozygous c.35_38delTCAA (p.Ile12Lysfs*4) frameshift deletion, which is predicted to produce a premature stop four positions downstream. In a third subject, they identified a missense mutation in the second-to-last nucleotide of exon 2 of GMNN gene, c.50 A > G (p.Lys17Arg), which was predicted by ESE finder to eliminate an exonic splice enhancer (ESE) target site of serine/arginine-rich splicing factor 5 (SRSF5). The *GMNN* gene encodes geminin, whose degradation is mediated by a nine-amino-acid destruction box at the N terminus of the protein from Arg23 to Pro31 (RRTLKMIQP). The destruction box is encoded by DNA sequences in exon 3 of the *GMNN* gene and lies downstream of the three exon 2 mutations that were identified in this study. All the variants were predicted to be deleterious by the in-silico prediction tool MutationTaster and were found to alter sites 5' to residue Met28 of the protein located within the destruction box. In the absence of this destruction box, the half-life of geminin is increased leading to inhibition of cell proliferation [12]. Thus, the authors' findings supported a gain-of-function mechanism of the GMNN mutations resulting in proteins lacking the destruction box with resultant increase in protein stability and prolonged inhibition of DNA replication as a cause for MGORS.

His IGF-1 SDS was −0.79 and we planned to assess his GH reserve. Due to a lack of resources, we could not perform serum IGFBP-3 assessment. After excluding hypothyroidism,

undernutrition and common chronic illnesses that might attribute to low IGF-1, the patient was primed with testosterone followed by which he underwent GH stimulation testing with provocative stimuli. GH stimulation was done using oral clonidine (0.15 mg/m^2) and intramuscular glucagon (0.015 mg/kg). The peak GH values were 2.45 and 3.01 ng/mL for clonidine and glucagon stimulation tests, respectively. We considered a cut-off of 7.0 ng/mL to define GHD and thus, he was found to have low stimulated levels of GH on both tests. His height was more severely affected than his weight; also, according to dietary recall from the primary care-giver—his mother, his daily calorie and protein intake were adequate for his age. At the start of GH therapy, his bone age was 7 years, and he had prepubertal status. The rest of the pituitary hormones were normal. (Supporting Information S2w: Supplemantary Table S1). Magnetic resonance imaging of the brain revealed normal sized pituitary. He was started on recombinant human growth hormone (rhGH) therapy and had a gain in height of 15 cm in 2 years while receiving rhGH, and currently, has a height of 137 cm, Ht SDS = −2.17. There was a + 0.71 change in Ht- SDS after 2 years of GH therapy. After 2 years of therapy, he had a pubertal testicular volume of 4 cc, pubic hair was P2 but the SPL did not increase till then. Given that peak height velocity due to pubertal growth spurt is expected to occur at an average age of 13.5 years (starting after 13 years of age) and usually coincides or succeeds other pubertal changes like increase in penile length, the improvement in his Ht-SDS might be attributed at least partly to the effect of rhGH therapy [8, 9]. No adverse effects of rhGH were observed.

3.2 | Results of Systematic Review of Literature

3.2.1 | *Demographics and Biological Data*

Among all published cases of MGORS in the literature, a total of 29 cases were included for analysis, including the two index cases in our series, of which n = 17 (58.6%) were females. (Table 2) The classic triad of MGORS was not seen in n = 5 among 27 cases (18.5%) with available data, and all of them had the presence of patellae. There was no preponderance of any ethnicity or geographical distribution among the reported cases. Though no family history of a similar syndrome was reported, consanguinity among parents was seen in 10 cases (out of 21 with available data, 47.6%).

3.2.2 | *Genetic Variants*

Genetic data were available for 22 cases; among them, n = 5 had pathogenic/likely pathogenic variants in the *ORC1*, n = 4 in *CDT1*, n = 3 in *ORC4*, n = 2 in *CDC6*, n = 2 in *GMNN*, n = 2 in *GINS3*, n = 1 in *MCM5*, n = 1 in *DONSON*, n = 1 in *CDC45* and n = 1 in *MCM7* genes (Table 3). While one patient refused genetic testing, no known pathogenic/likely pathogenic/VUS variant was found in the other 6 cases in relation to MGORS.

3.2.3 | *Birth Data*

A history of premature birth was documented in 7 out of 20 cases (35%). Of the cases born at term, the median (Q1, Q3) birth weight was 2000 g (1470, 2267.5) and the median *Z*-score of birth weight was −3.2 (−3.9, −2.4). All the cases for which data were available had low weight as well as length for age at birth, though head circumference was not universally low. The median *Z*-score of birth length and head circumference was −4.5 (−5.3, −2.27) and −2.2 (−3.2, −0.47) (Table 2).

3.2.4 | *Anthropometry*

Short stature for age was almost universally seen, the median *Z* score for the height of the cases among non-adult cases being −4.4 (−5.7, −4) at the time of diagnosis. Only one child, who was 9 years old, had normal stature for age despite having a history of symmetric intrauterine growth retardation (IUGR). (Supporting Information S1: Table 3) The median *Z* score of the weight of the cases was −4.15 (−5, − 2.6) at baseline. All the cases were found to have underweight for age, except one who

TABLE 2 | Summary of baseline demographics, birth details, and anthropometric data of reported cases, including the two index cases.

Parameters	Values
No of cases of MGORS that have any diagnosed endocrinopathy/data regarding hormonal evaluation/results of hormonal treatment (excluding duplicates)	29 Duplicates (Same case mentioned as part of: 14)
Median age of diagnosis in years (Q1, Q3)	7.65 (4, 14.75)
Male: Female	12: 17
Consanguinity	10/21
Premature birth	7/20
Genetic mutation	*ORC*, n = 5; *CDT1*, n = 4; *ORC4*, n = 3; *CDC6*, n = 2; *GMNN*, n = 2; *GINS3*, n = 2; *MCM5*, n = 1; *DONSON*, n = 1; *CDC45*, n = 1; *MCM7*, n = 1
Median birth weight SDS	−3.2 (−3.9, −2.4)
Median birth length SDS (Q1, Q3)	−4.5 (−5.3, −2.27)
Median head circumference SDS (Q1, Q3)	−2.2 (−3.2, −0.47)
Median height SDS (Q1, Q3)	− 4.4 (−5.7, −4)
Median weight SDS (Q1, Q3)	− 4.15 (−5, − 2.6)
Number of cases not having classic triad of MGORS	5/27

TABLE 3 | Status of the GH-IGF1 axis, response to growth hormone therapy, urogenital anomaly, mammary hypoplasia, other hormonal dysfunction/therapy, bone age and genetic variants in all published cases, including two index cases.

Author, year	Gender	IGF1 status for age	GH reserve	Bone age	Genetic mutation	Age of initiating GH	Dose of GH (mg/Kg/week)	Age of discontinuing GH	Response to GH	Other endocrine/metabolic disorder	Other hormone therapy	Uro-Genital anomaly	Mammary hypoplasia
Loeys (1999) [14]	M	Normal	Deficit	Delayed	Not found	NR	NR	NR	NA	Nil	Nil	Cryptorchidism, Hypoplastic scrotum, Glandular hypospadias	NA
Bongers (2001) [15], Bicknell (2011) [13], de Munnik (2012) [16]	F	Low	Normal	NA	*ORC1*	4.4 years	NR	6 years	No significant change	Nil	Nil	NA	Y
Bongers (2001) [15], de Munnik (2012) [16], Burrage (2015) [12]	M	NR	Deficit	Corresponding	Not found	3 years	NR	14 years	3.8 SD height gain	Nil	Nil	Shawl scrotum, Hypoplasia of corpora cavernosa, Cryptorchidism, Urethral stenosis	NA
Bongers (2001) [15]. Bicknell (2011) [13], de Munnik (2012) [16]	M	Normal	NR	Delayed	*CDC6*	2.5 years	NR	6.8 years	No significant change	Nil	Nil	Micropenis, Cryptorchidism	NA
Bongers (2001) [15], Bicknell (2011) [13] de Munnik (2012) [16], Guernsey (2011) [17]	F	NR	NR	Delayed	*ORC4*	1.5 years	NR	15 years	NR	Nil	Nil	Prominent clitoris, Hypoplastic labia	Y
Bongers (2001) [15], Bicknell (2011) [13], de Munnik (2012) [16], Guernsey (2011) [17]	F	NR	NR	Delayed	*ORC4*	2 years	NR	15 years	NR	Nil	Nil	Prominent clitoris, Hypoplastic labia	Y
Cohen (2002) [18]	M	NR	Normal	Delayed	Not found	8 years	NR	9 years	No significant change	Nil	Nil	h/o testicular torsion due to congenital defect of the tunica vaginalis	NA
Bicknell (2011) [19], de Munnik (2012) [16]	M	Normal	Deficit	NR	*ORC1*	NR	NR	4.5 years	NR	Nil	Nil		NA
Bicknell LS, 2011 [13], de Munnik (2012) [16]	M	NR	NR	NR	*CDT1*	3.5 years	NR	7.5 years	NR	Nil	Nil	Cryptorchidism	NA
de Munnik (2012) [16]	F	NR	Not done	Delayed	*ORC4*	3 years	NR	10 years	1.8 SD height gain	Nil	Nil		NR
de Munnik (2012) [16]	M	Low	Normal	Delayed	Not found	5.5 years	NR	7.5 years	2 SD height gain	Nil	Nil		NR
Shawky RM 2014 [20]	F	NR	Normal	NR	Not found	NG	NG	NG	NA	Nil	Nil		NA

(Continues)

TABLE 3 | (Continued)

Author, year	Gender	IGF1 status for age	GH reserve	Bone age	Genetic mutation	Age of initiating GH	Dose of GH (mg/Kg/week)	Age of discontinuing GH	Response to GH	Other endocrine/metabolic disorder	Other hormone therapy	Uro-Genital anomaly	Mammary hypoplasia
Burrage (2015) [12]	F	Low	Not Done[a]	Delayed	*GMNN*	NG	NG	NG	NA	Nil	Nil	Abnormal genitalia, Hypoplastic labia majora	NR
Shawky (2016) [21]	F	NR	Normal	Delayed	Not found	NG	NG	NG	NA	Nil	Nil	Clitoromegaly, Hypoplastic labia	NA
Kim (2017) [22]	F	Normal	Normal	Delayed	*CDT1*	NG	NG	NG	NA	Nil	Nil		NR
Kim (2017) [22]	M	Low	Normal	Delayed	*CDT1*	NG	NG	NG	NA	Nil	Nil		NA
Vetro (2017) [25]	M	NR	Normal	NR	*MCM5*	NG	NG	NG	NA	Nil	Nil	Bilateral cryptorchidism	NA
Belaid (2019) [26]	F	NR	NR	NA	Not done	NG	NG	NG	NA	Diabetes	Nil		Y
Vojtkova (2019) [27]	F	Normal	Not done[a]	NR	*ORC1*	NG	NG	NG	NA	Subclinical hypo-thyroidism	LT4		NR
Knapp (2020) [28]	F	NR	NR	NR	*DONSON*	'At teenage'	NR	NR	NR	Diabetes[b]	Nil		NR
Ting (2020) [29]	F	NR	Normal	Corres-ponding	*CDC45*	NG	NG	NG	NA	Nil	Lucrin depot	Clitoromegaly	Y
Knapp (2021) [23]	M	NR	NR	Corres-ponding	*MCM7*	NR	NR	NR	NA	Primary hypo-thyroidism, Addisonian Crisis, Hypertrigly-ceri-demia, Lipody-strophy	Hydro-cortisone, Levothyr-oxine		NA
Koomanaee S, 2022 [30]	F	Low	Deficit	Corres-ponding	*ORC1*	2.5 years	NR	4.5 years	NR	Primary hypo-thyroidism	Levothyr-oxine		Y
McQuaid (2022) [31]	F	NR	Normal	NR	*GINS3*	NG	NG	NG	NA	Nil	Nil		NA
Vakili (2022) [32]	M	Normal	Deficit	Delayed	*ORC1*	2 years	0.35	5 years	8-10 cm/year height velocity	Nil	Nil		NA
Li (2024) [7]	F	Normal	Normal	Delayed	*CDT1*	4 years	0.18-0.2	9 years	1.4 SD height gain	Nil	Nil		NA

(Continues)

TABLE 3 | (Continued)

Author, year	Gender	IGF1 status for age	GH reserve	Bone age	Genetic mutation	Age of initiating GH	Dose of GH (mg/Kg/week)	Age of discontinuing GH	Response to GH	Other endocrine/ metabolic disorder	Other hormone therapy	Uro-Genital anomaly	Mammary hypoplasia
Mehrjoo (2024) [24]	F	NR	NR	NR	*GINS3*	NR	NR	NR	No significant change	Nil	Nil		NR
Our case 1	F	Normal	Not done	Corres-ponding	*CDC6*	NG	NG	NG	NA	Subclinical hypo-thyroidism	Nil		Y
Our case 2	M	Low	Deficit	Delayed	*GMNN*	11 years	0.18	13 years	7.5 cm/year height velocity	Nil	Nil	Micropenis	NA

Abbreviations: Corresponding, corresponding to chronological age, F, female; GH, growth hormone; M, male, [m], Monozygotic twins; NA, Not applicable(like cryptorchidism in females or hypoplastic breasts in males or pre-pubertal females), ND, not done, NG, not given; NR, data not reported in published article; SD, standard deviation, yrs, years.

[a]IGFBP3 normal.

[b]Glucocorticoid induced.

had obesity, probably secondary to the usage of exogenous glucocorticoids, as noted by the authors in the corresponding article. Data regarding bone age were available for 20 cases, of whom $n = 14$ (70%) had delayed bone age, whereas 5 (25%) had bone age corresponding to their chronological age.

3.2.5 | *Secondary Sexual Characteristics and Gonadal Hormones*

Data regarding breast development in post-pubertal age were available for $n = 7$ out of the 17 females, all of whom showed mammary hypoplasia. Clitoromegaly with hypoplastic labia was seen in 4/17 (23.5%) females had, and one female had the isolated presence of labial hypoplasia. Of the males ($n = 11$), data regarding gonadal and genital status were available from 7 cases; of whom $n = 5$ had cryptorchidism, $n = 2$ each had hypoplastic scrotum and micropenis, including our male case, and $n = 1$ male had hypospadias (Table 3). One patient had a history of torsion of the testicular spermatic cord likely due to congenital defect of the tunica vaginalis. However, no data were available regarding gonadal hormones in these patients at evaluation with genital abnormalities except one patient who had normal genitalia and normal levels of gonadal hormones and gonadotropins. The male patient in our series too had normal gonadotropin and testosterone levels corresponding to his age.

3.2.6 | *Evaluation of the GH-IGF1 Axis*

Data on serum levels of IGF-1 were available for $n = 14$ cases, $n = 6$ (out of 14, 42.9%) of whom had low IGF1 levels for age (Table 3). GH estimation data were available for $n = 21$ patients; for four cases, GH stimulation was not done as either IGF1 or insulin-like growth factor binding protein 3 (IGFBP3) was normal for age. Out of the remaining $n = 17$ cases, 6 (out of 17, 35.3%) had documented GHD.

3.2.7 | *GH Therapy and Response*

A total of $n = 16$ cases had received GH replacement therapy. Among them, $n = 5$ (out of 16, 31.3%) cases had documented GHD, including our second case. The median age of GH initiation was 4 years (2.75, 6.75). Data on the GH dose used were available only for $n = 3$ cases and were grossly heterogeneous. Vakili R et al reported a GH dose of 0.35 mg/Kg/week. One patient from China was started on pegylated weekly GH at a dose of 0.18 mg/Kg/week, which was later increased to 0.2 mg/Kg/week. The male patient in our series was started on GH at a dose of 0.18 mg/Kg/week in daily divided doses (Table 3). No serious adverse effects or worsening of skeletal deformities were reported in the published cases with available follow-up, but safety data are sparse and subject to reporting bias.

Data regarding response to GH was available for 10 cases out of the 16 receiving GH. Among them, $n = 4$ had not reported improvement in Ht-SDS or height velocity during the duration of GH therapy at the time of publication. Data regarding adult height was not available for any of the cases. Favorable changes in either Ht-SDS or height- velocity was observed in 6 cases (out of 10, 60%, F:M –2:4); among them, 4 had known variants of

TABLE 4 | Comparison of cases of MGS with and without favourable response to growth hormone (GH) therapy*#.

	Significant response to GH ($n = 6$)	No/inadequate response to GH ($n = 4$)	OR (C.I.)
Delayed bone age	5 (83.33%)	2 (50%)	5 (0.34 to 84.39)
Low stimulated GH levels	4 (66.67%)	0	—
Low IGF-1 for age	2/4 (50%)	1/2 (50%)	1 (0.04 – 27.69)
Median age of GH initiation	3.5 [2.75,6.89]	4.5 [2.6,8]	
Genes mutated	*ORC4* = 1 *ORC1* = 1 *CDT1* = 1 *GMNN* = 1 Not found = 0	*ORC1* = 1 *CDC6* = 1 *GINS3* = 1 Not found = 1	

Note: *Favorable response to GH was defined as improvement in Height-SDS > 1 SD and/or height velocity > 50th centile for age and gender on standard height velocity charts. #The study is underpowered for this comparison and hypothesis-generating.

ORC4, *ORC1*, *CDT1*, and *GMNN* genes, and 5 had delayed bone age. On comparing those with ($n = 6$) and without ($n = 4$) height improvement for whom data regarding the GH-IGF-1 axes were available, we found that $n = 4$ (out of 6, 66.7%) in the former group had documented evidence of GHD on stimulation tests versus none in the latter group. Delay in bone age was found in 5 (out of 6, 83.3%) of those with good response to GH therapy than those without ($n = 2$ out of 4, 50%). The study was underpowered for this comparison and hypothesis generating. The differences were not statistically significant but, due to very small numbers, statistical interference becomes difficult and subject to inaccuracies. There were no notable differences in the prevalence of low IGF-1 for age between the two groups (50% in both), age of initiation of GH, or genetic mutations (Table 4).

3.2.8 | *Other Endocrinopathies and Response to Hormonal Supplementation/Replacement*

Apart from disorders of the GH-IGF1 axis, primary hypothyroidism was reported in $n = 2$ cases. One of the cases had a possible Addisonian crisis with low cortisol and elevated ACTH. The same patient also had lipodystrophy and hypertriglyceridemia but low LDL and HDL cholesterol. The patient was initiated on both hydrocortisone and fludrocortisone but developed hypertension for which the latter had to be stopped, suggesting a form of mineralocorticoid-sparing primary adrenal insufficiency. Another case had congenital primary hypothyroidism. Two cases had subclinical hypothyroidism, including our female case. Two patients had diabetes; the elderly female of 65 years had been taking oral antidiabetic agents for 6 years. Though she had a family history of diabetes, attempts had been made to rule out type 1 diabetes in her. The other obese male, aged 30 years, had diabetes, probably due to exogenous glucocorticoid use (indication unknown), as mentioned by the authors. One female received a Lucrin depot (GnRH agonist) injection to halt her pubertal progression for possible height benefit, but the therapy had failed, and menarche had commenced. All published cases of female patients with who entered puberty had evidence of mammary hypoplasia in spite of having normal appearance of other secondary sexual characteristics and regular menstrual cycles. In $n = 2$ cases, both with documented *ORC4* variants, the mammary hypoplasia responded to exogenous estrogen with some increase in size of breasts though the percentage improvement in size was not mentioned [6, 13]. There is no report of the use of hCG or testosterone therapy in males with MGORS for cryptorchidism and/or micropenis.

4 | Discussion

MGORS is a microcephalic primordial dwarfism which has a triad of short stature, microtia and patellar hypoplasia/aplasia, most common findings among the triad being microtia and patellar hypoplasia or aplasia [5, 6]. Impaired DNA replication results in impaired cellular hyperplasia and hypertrophy. Defects in 13 different genes, which encode DNA replication proteins, have been associated with MGORS, namely *ORC1, ORC4, ORC6, CDT1, CDC6, GMNN, MCM3, MCM5, MCM7, CDC45, GINS2, GINS3*, and *DONSON* [7, 13–33] (Supporting Information S1: Table 2).

We report a series of two cases of MGORS, both of which have unique features. Case 1 is the third reported case of MGORS due to *CDC6* variant, and the first pubertal-age *CDC6*-variant associated MGORS case with profound mammary hypoplasia. Our case 2 was unique in possessing a novel GMNN variant with evidence of GHD, and responded to rhGH with remarkable improvement in height SDS. Upon review of the literature, we found MGORS to be a very rare syndrome with fewer than 150 cases reported to date, with a dearth of data regarding multiple aspects, especially hormonal evaluation and gross heterogeneity of presentation. It can affect both genders and all ethnicities. A history of consanguinity has been reported in upto 48% of the reported cases, underscoring the autosomal recessive mode of its transmission.

MGORS can mimic many common endocrinopathies that present with short stature, absence of breast development, and skeletal dysmorphism. However, the presence of the triad of MGORS and the absence of biochemical evidence of hormone deficiencies point towards the possibility of MGORS, which needs to be confirmed with genetic testing through next-generation sequencing [5, 6, 16]. We found, however, that all three classic manifestations of MGORS may not be universally present [22–24]. Around one-fifth might have the presence of patellae. Thus, it is important to have a high index for suspicion in the presence of one or multiple features of the triad.

Among the reported cases of MGORS who had anthropometric data, almost all had short stature at the time of presentation with a median *Z* score of −4.4 (in region-specific growth charts), except one male with the *MCM7* variant [23]. Among cases with available birth anthropometry, most had prenatal growth restriction with a median birth weight *Z* score of −3.15 (as per regional growth charts). Causes of short stature in MGORS can be multifactorial, including defects in genes responsible for proliferation leading to primordial dwarfism, skeletal deformities, poor feeding due to hypoplastic stomach, seizure disorders, cardiac and other organ dysfunctions [7, 16]. However, unlike what's expected for primordial short stature/intrinsic short stature, upto 70% of the cases which published data regarding bone age were found to have had delayed bone age.

Serum levels of IGF-1 are frequently used as screening tests for children with short stature. Though predominantly affected by GHD resulting from disorders due to hypothalamo-pituitary region, it is not specific for GHDy. Several conditions affect IGF-1 secretion and action including chronic illnesses, malnutrition, hepatic failure, systemic inflammation, presence of other hormonal deficiency like hypothyroidism, and assay variability and even in certain syndrome causing intrinsic short stature even when they are not classically associated with GHD [1]. Therefore, the results of IGF-1 should be interpreted with caution. To establish the presence of GHD, it requires additional GH stimulation tests, especially in the absence of structural defects of the pituitary or concomitant other hormonal deficits. Low IGF-1 for age was seen in upto 6 out of 14 cases and 6 out of 17 cases had documented GHD, including the index male case. Untreated hypothyroidism, anatomical or functional defects in the gastrointestinal tract and resultant malnutrition, as well as chronic hypoxia due to cardiac/pulmonary etiologies, might contribute to the dysfunction in the GH-IGF-1 axis, but cases with documented GHD did not typically report having a serious underlying organ disorder or systemic illness. Whether a hypoplastic hypothalamo-pituitary region could account for the GHD remains to be explored. The index male case had a normal-sized pituitary. Other cases have reported cortical dysplasia and pachygyria on MRI brain, but data regarding pituitary abnormalities are not available.

Certain syndromes like Turner syndrome, Noonan syndrome and Prader-Willi syndrome are well-established indications for GH therapy following results of randomized trials and long-term cohort studies that demonstrated clear auxologic, body-composition and metabolic benefits from GH therapy in them [34–37]. Although both GHD and insensitivity have been reported in these syndromes, certain studies claim better results with GH among candidates with Noonan syndrome who have defects in GH secretion [36, 38, 39]. Also, GH therapy is fraught with unique adverse effects in some of these syndromes, like worsening of scoliosis or dysglycemia in TS, worsening of OSA and even sudden deaths in PWS or risk of tumorigenesis in Noonan syndrome [37, 40]. Since GH is indicated in significant growth delay due to “idiopathic” short stature, it is often prescribed routinely in syndromic short stature where the etiology is not clear. However, given the cost of therapy, the burden of daily injections, the uncertainty of its benefits in different syndromes as well as the risk of adverse effects, it is important to identify candidates of different syndromes who might benefit best from GH therapy. Data on GH replacement therapy is limited in MGORS. A prior article on MGORS suggests the possibility of better results with GH among those with certain variants, while others suggest good results in MGORS with low IGF-1 [5, 7]. The male case in our series received GH for 2 years during which his height velocity increased by 15 cm, which is similar to the height velocity seen in cases with pituitary or hypothalamic causes of GHD. Reports from other authors suggest up to 40% of MGORS cases receiving GH might have improvement in height SDS with GH therapy [5, 7]. Apparently, from available data, it appears that those with evidence of GHD and delayed bone age might be more likely to benefit from GH therapy than those without GHD and with bone age corresponding to chronologic age [5]. Relationship with underlying genotype is controversial, although reported from a prior study [7]. However, paucity of data, heterogeneity of reported results and very small numbers limit statistical inferences. Further data is needed to know regarding the best dose, initiation, and duration of therapy with GH. Evaluation of the GH-IGF1 axis may be prudent before initiation of GH replacement.

Overt manifestations of hypogonadism are not classically seen, but cryptorchidism in males and hypoplastic labia and clitoromegaly in females have been reported in MGORS. Short course of testosterone or orchidopexy early in life for cryptorchidism may be attempted as for other etiologies of cryptorchidism. Data regarding gonadal hormones is limited but has mostly been reported to be normal. All reported cases of post-pubertal females till date had mammary hypoplasia but available data on the effect of estrogen for hypoplastic mammary glands or labia is variable and the role of estrogen therapy for breast development in MGORS remains debatable. The chance of ovulation and conception is expected to be normal, but possibly due to a hypoplastic uterus, pregnancy leads to early premature deliveries and runs a high risk of abortion or stillbirth [34].

Hypothyroidism may be seen in MGORS [27, 28, 30]. There is no data on thyroid volume, and most of the hypothyroidism has been of adult onset. The case with congenital hypothyroidism also did not report having agenesis or hypoplasia of the thyroid gland [30]. Available reports do not establish an increased risk of thyroid disease in MGORS; however, thyroid function testing is clinically reasonable as part of the assessment of short stature and before GH therapy. Primary adrenal insufficiency presenting with adrenal crisis has been reported in one case, while lipodystrophy with progeroid appearance has been reported in two cases, though one of the two has not been included in analysis of results [23].

The study had several limitations. Data on endocrine evaluation published till date is very scarce, making statistical interferences impossible. Since our search strategy did not include subscription-based databases like Embase or Scopus, some studies might have been omitted, though that is unlikely given that the topic is a niche paediatric endocrine disease. Parental testing for the presence of the genetic variants and Sanger sequencing could not be done. While we analysed height velocity based on standard growth charts and height-velocity charts, it is important to note that height velocity in syndromic short stature require careful contextualisation and depends on

multiple factors including age, sex, pubertal stage and the underlying disease. In many of the cases, factors like access to health-care facilities, type of the caring physicians and local/regional medical practices might decide the line of investigations and the therapy provided rather than the type of genetic defect or phenotypic manifestation alone. There is an ardent need to collect cross-sectional as well as longitudinal data on heights of children with MGORS at different ages in order to formulate a syndrome-specific growth chart for MGORS in the future.

Pediatricians and endocrinologists need to keep in mind the possibility of MGORS for all cases presenting with proportional short stature with facial dysmorphism and lack of breast development, even when features of the classic triad of MGORS are not present. Genetic testing should be done to confirm the diagnosis. Although MGORS is a known cause for intrinsic short stature, children with MGORS with poor growth trajectory and/or low IGF-1, delayed bone age or clinical suspicion of GHD should also be considered for evaluation of the GH-IGF-1 axis prior to trial of rhGH therapy. Families need to be counselled however, regarding the uncertain benefit of GH specially with regard to adult height. Estrogen therapy for hypoplastic breasts do not seem to hold much promise but needs more data. Further systematic studies are required to find the best-suited dose and duration of GH therapy in MGORS and the need to screen for other endocrinopathies in them.

Author Contributions

Authors Kumar Swapnil and Roohi Nanda were involved in the acquisition of data from the index cases. Author Rajdeep Basu, S.M. and S.o.M. did systematic review of published literature while critically analysing it and formulating the initial draft. Author SM formulated the concept and design of this project. Authors Arjun Baidya, Nilanjan Sengupta and Soumik Goswami edited the draft incorporating important intellectual content. All the authors approved the final version of the manuscript. Authors Kumar Swapnil and Rajdeep Basu contributed equally to the manuscript and should be regarded as joint first authors.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The raw data file and analysed datasets can be available from the corresponding author on reasonable request by e-mail to sunetra59@gmail.com.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Figure S1: PRISMA diagram for literature search strategy.

Table S1: Biochemical and hormonal tests of the two index cases with reference ranges.

Table S2: Summary of the genes known to be implicated in the pathogenesis Meier-Gorlin Syndrome with characteristic phenotypic manifestations.

Table S3: Baseline demographic, birth details, and anthropometric data of reported cases in literature and the two index cases.