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Clinico-radiological correlation of pituitary stalk interruption syndrome in children with growth hormone deficiency

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Abstract

Purpose To analyze the clinical, hormonal, and radiological characteristics of Pituitary stalk interruption syndrome (PSIS) in children with growth hormone deficiency (GHD).

Methods This is a prospective cross-sectional study, conducted over a period of three years in a short stature clinic of tertiary care referral hospital. 57 severe short stature children with proven GHD were included in the study.

Results Among 57 children with GHD, 14 (24%) were diagnosed as PSIS. The mean age at diagnosis was 11.8 ± 2.6years. The male to female ratio was 2.5:1. Nine (64%) children had multiple pituitary hormone deficiency (MPHD) and 5 (36%) had isolated growth hormone deficiency (IGHD). In spite of absent or ectopic posterior pituitary (EPP)in Magnetic Resonance Imaging (MRI) of PSIS cohorts, only one had Arginine vasopressin (AVP) deficiency. EPP was seen near median eminence in 6 (44%), elsewhere in 4 (28%), and absent in 4 (28%)children. The height gain following growth hormone therapy was better in PSIS cohorts as compared to non-PSIS.

Conclusion Male gender, breech presentation, external congenital anomalies like cryptorchidism, midline defects and nystagmus were more common in children with PSIS. MPHD were more frequently seen in PSIS whereas IGHD in non-PSIS cohort. AVP deficiency is very rare in PSIS despite of absent or ectopic posterior pituitary in MRI. High index of clinical suspicion in all severe short stature may lead to early diagnosis and prompt initiation of growth hormone treatment for better outcome.

Keywords Pituitary stalk interruption syndrome · Short stature · Growth hormone deficiency · Multiple pituitary hormone deficiency · MPHD · Combined pituitary hormone deficiency · CPHD · IGF-1 · India

Introduction

Pituitary stalk interruption syndrome (PSIS) is a rare, clinically heterogeneous congenital disorder with an incidence of 5 in 1,000,000 live births [1]. PSIS is characterized by a triad of thin, interrupted, or absent pituitary stalk, hypoplastic or aplastic anterior pituitary, and an absent or ectopic posterior pituitary (EPP) in magnetic resonance imaging (MRI) [2]. The term PSIS also includes patients with one single entity such as EPP or interrupted stalk [2]. The clinical manifestations of PSIS are highly variable depends upon the age at presentation. Patients with more severe pituitary hormonal deficiency may present in the neonatal period with hypoglycemia, prolonged jaundice, micropenis, and cryptorchidism. During childhood, they may present with either isolated growth hormone deficiency (IGHD) or multiple pituitary hormone deficiency (MPHD) [3]. Extra-pituitary malformations (EPM) may be associated with PSIS

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[4, 5] and the diagnosis of PSIS is classically established by magnetic resonance imaging (MRI) [6]. To the best of our knowledge, very limited studies are published in this regard from the Indian subcontinent [7–9]. In this study, we described the clinical, hormonal, and radiological characteristics of PSIS in children with growth hormone deficiency (GHD) and compared these characteristics with non-PSIS children of GHD.

Materials and methods

This prospective cross-sectional study was conducted in a short stature clinic of department of Endocrinology at 3100 bedded multi-specialty hospital in South Tamil Nadu. The Institutional Ethics Committee approval was obtained before conduction of the study. 130 severe short stature children with suspected GHD between January 2020 and January 2023 were evaluated. Short stature is defined as a height less than 2 SD below the mean or less than 3rd percentile according to WHO 2006 & IAP 2015 growth chart. Other causes of short stature like pituitary neoplasms, radiation exposure, malnutrition, chronic systemic diseases, Turner syndrome, Noonan syndrome, Prader-Willi syndrome (PWS), familial short stature, and skeletal dysplasia were excluded.

The clinical history including the gestational age at birth, mode of delivery and presentation like breech or vertex, birth weight, perinatal complications like birth asphyxia, neonatal hypoglycemia, and neonatal jaundice were asked. The detailed clinical evaluation which includemicropenis, cryptorchidism, midline congenital anomalieslike cleft lip, cleft palate, single central incisor, and ophthalmic anomalies like squint, nystagmus were noted. The pubertal status, patient's height, height standard deviation score (SDS), target height (TH), TH-SDS, weight, weight-SDS, body mass index (BMI), and BMI-SDS were calculated.

GHD was diagnosed based on peak GH level of <8 ng/ml after both the clonidine stimulation test (CST) as well as glucagon stimulation test (GST), which were done on two separate days with one week apart. The serum insulin-like growth factor 1 (IGF-1) level was estimated and interpreted according to age and sex-matched reference range [10, 11]. For the clonidine stimulation test (CST), clonidine tablet was given at a dose of 5 mcg/kg. Blood samples were drawn at baseline, 30, 60, 90, and 120 min. For glucagon stimulation test (GST), glucagon was administered intramuscularly at a dose of 30 mcg/kg, up to a maximum of 1 mg.GH samples were drawn at baseline, 30, 60, 90, 120, 150, and 180 min following glucagon administration. All peri-pubertal male and female children of more than 10 years were primed with oral estradiol valerate of 2 mg for 3 days before GH provocative tests [12].

Multiple pituitary hormone deficiency (MPHD) is defined as the presence of GHD along with deficiency of one or more anterior pituitary hormones. In patients with polyuria, Arginine vasopressin (AVP) deficiency (central diabetes insipidus) is diagnosed when serum osmolality of greater than 300 mosm/l and/or urine osmolality less than 300 mosm/l. Water deprivation test was done in equivocal cases. Hormonal assays like Thyroid stimulating hormone (TSH), Free Thyroxine level (FT4), Prolactin (PRL), Cortisol, Luteinizing hormone (LH), Follicle stimulating hormone (FSH), Testosterone, and Estradiol were performed using an electrochemiluminescence immune assay (ECLIA) (Roche Diagnostics – Cobas e411 analyzer, Germany).

Bone age was assessed with Greulich and Pyle method using X-ray of nondominant hand with wrist anteroposterior (AP) view. Pituitary MRI with or without gadolinium contrast was performed in all patients. AllMRI reports were reported by two independent radiologists. The radiological findings were described as anterior pituitary—normal, hypoplastic or aplastic, pituitary stalk (PS)—normal, thin, interrupted or not visualized, posterior pituitary—eutopic or ectopic (EPP). Any extra pituitary malformations (EPM) such as corpus callosum a genesis, optic nerve hypoplasia, absent septum pellucidum, holoprosencephaly, and Chiari I malformations were noted. All GHD children were received recombinant Growth hormone therapy in a dose of 0.034 mg/kg/day and height gain were monitored at regular intervals during the treatment period.

Statistical analysis

All categorical variables were expressed in actual numbers and percentages and the continuous variables as mean ± standard deviation. The categorical variables were compared using the $\chi 2$ test,and the Kruskal-Wallis test, whereas continuous variables were compared using independent t-test in normally distributed data and Mann–Whitney U tests in non-normally distributed data. A p-value of less than 0.05 was considered significant. All statistical analyses were done with SPSS version 29.0.

Results

Clinical, radiological, and biochemical characteristics of PSIS children

GHD was diagnosed in 57 children of severe short stature after excluding other causes. Among the 57 children, 14 (24%) were diagnosed as PSIS. The male to female ratio was 2.5:1. The mean age at diagnosis was 11.8 ± 2.6 years (IQR = 8.8–16.2). The mean birth weight was 2.9 ± 0.4 kg (IQR = 2.5–3.5). Three (21%) children had breech

presentation. Among the perinatal complications, 4 (28%) had birth asphyxia, one (7%) had micropenis, hypoglycemia with bilateral cryptorchidism. One (7%) child had midline congenital anomalies like cleft lip and cleft palate. Two (14%) children had bilateral convergent squint with nystagmusand seizure disorder. Despite all of them had GHD, thyroid and cortisol axis were affected only in five (36%) of them. Among the nine peri-pubertal children where the gonadal axis were assessed, six (66%) had hypogonadotropic hypogonadism. Of the 14 PSIS cohort, five (36%) children had IGHD, and 9 (64%) had MPHD. Among nine MPHD children, only one had posterior pituitary involvement in the form of AVP deficiency. In MRI pituitary, all PSIS children had either thin, interrupted (Fig. 1a) or non-visualized pituitary stalk (Fig. 1b) with hypoplastic pituitary (Fig. 1b). EPP was seen near median eminence (Fig. 1c) in 6 (42%), elsewhere along the stalk (Fig. 1d), over the optic chiasma (Fig. 1e), near floor of third ventricle (Fig. 1f), in 4 (29%) and absent (Fig. 1g) in 4 (29%) children.

Comparison of clinical, hormonal, and radiological characteristics of patients with PSIS and non-PSIS

The male to female ratio in PSIS and non-PSIS were 2.5:1 vs. 1.2:1 respectively. The mean age at diagnosis is late in PSIS cohort as compared to non-PSIS cohort with no statistical difference (11.8 ± 4.9 vs. 9.6 ± 3.9 years, P = 0.08). When the mode of delivery was taken into account, the lower segment cesarean section was similar in both groups (21% vs. 23%, P = 0.874). Breech presentation was noted only in PSIS cohorts (21% vs. 0%, P = 0.002). The frequency of birth asphyxia had no significant difference (28% vs. 16%, P = 0.324) between these groups. There was no family history of GHD in PSIS cohort whereas three children had positive family history of GHD in non- PSIS cohort and all of them were on GH therapy. Cleft lip and cleft palate were noted among one in each cohort (7% vs. 2%, P = 0.362). Seizures were noted in two children of PSIS cohort and none in non-PSIS cohort (14% vs. 0%, P = 0.013). The birth weight, height SDS, weight SDS, BMI SDS, TH SDS, BA, and BA/CA ratio were not statistically significant between these cohorts. The mean stimulated peak growth hormone level were low in both the cohorts and no statistically significant difference was noted between the groups (1.07 ± 0.94 vs. 2.37 ± 2.78 ng/ml, P = 0.09).Table 1 summarizes the difference between clinical, hormonal profile, and radiological characteristics of patients with PSIS and Non-PSIS.

Among the total 57 children of GHD included in the study, isolated GHD (IGHD) was seen 5/14 (36%) in PSIS cohort, whereas 36/43 (84%) in non-PSIS cohort. MPHD was more

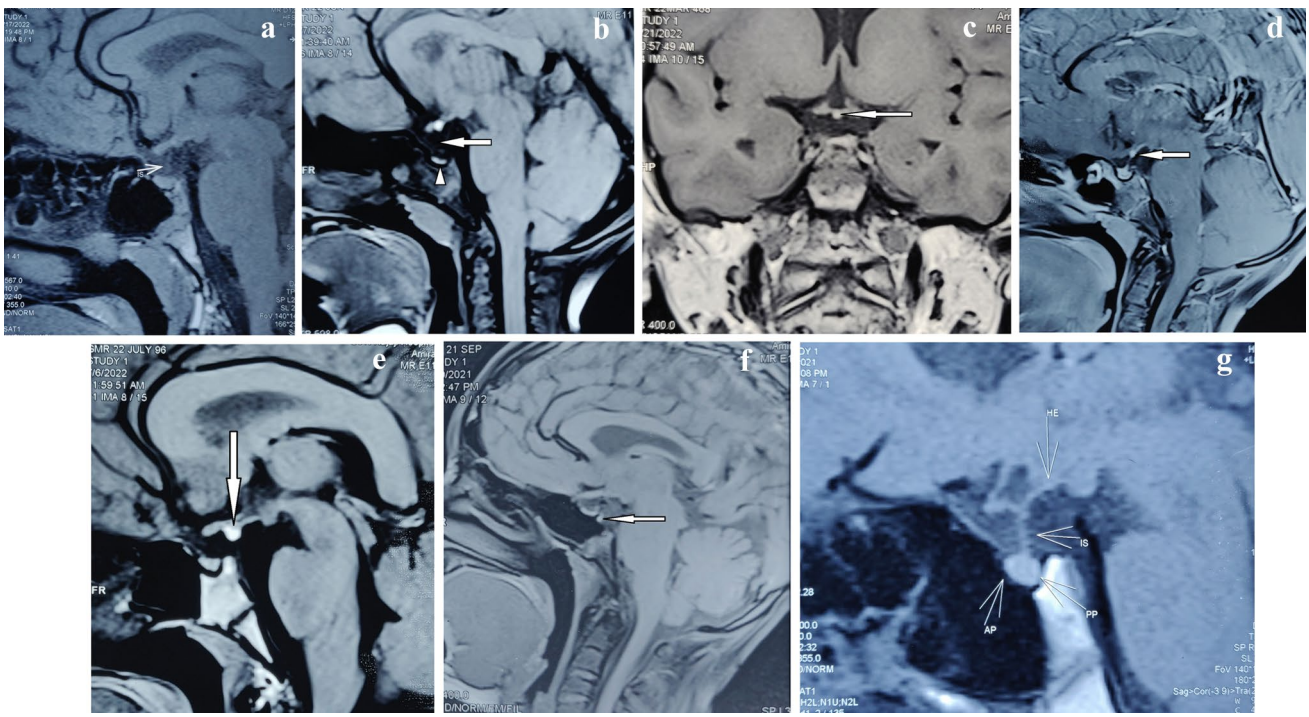

Fig. 1 Radiological characteristics of PSIS children in MRI pituitary. **a** Interrupted pituitary stalk (White Arrow), **b** Hypoplastic anterior pituitary (White arrow) with absent pituitary stalk (White Arrow Head), **c** EPP in median eminence (White Arrow), **d** EPP in superior aspect of stalk (White Arrow), **e** EPP in Optic chiasma (White Arrow), **f** EPP near infundibular recess of floor of III ventricle (White Arrow), **g** Interrupted pituitary stalk with Absent posterior pituitary bright spot (White Arrow)

Table 1 Comparison of clinical, hormonal profile, and radiological characteristics of children with PSIS and non-PSIS cohort

Parameters	PSIS	Non-PSIS	P Value
Number	14 (24%)	43 (76%)	0.005*
Sex (Male vs. Female)	10 (71%) vs. 4 (29%)	24 (56%) vs. 19 (44%)	0.324
Age (Mean ± SD) ; (IQR), years	11.8 ± 4.9; 8.8–16.2	9.6 ± 3.9; 7–12.7	0.08
Breech presentation	3 (21%)	0	0.002*
Cesarean section vs. Normal vaginal delivery	3 (21%) vs. 11(79%)	10 (23%) vs. 33 (77%)	0.874
Family history	0	3 (7%)	0.313
Seizures	2 (14%)	0	0.013*
Midline congenital anomalies	1 (7%)	1 (2%)	0.362
Height SDS	− 4.28 ± 1.12	− 4.5 ± 1.27	0.56
Weight SDS	− 3.48 ± 0.92	− 3.57 ± 1.16	0.79
BMI SDS	− 1.41 ± 1.18	− 1.3 ± 1.09	0.75
TH SDS	− 1.24 ± 0.87	− 0.93 ± 1.07	0.33
BA, years	7.43 ± 4.29	5.78 ± 3.23	0.13
BA/CA ratio	0.58 ± 0.16	0.57 ± 0.16	0.84
IGF-1 SDS	− 3.4 ± 0.92	− 3.0 ± 0.62	0.06
Mean peak GH level, ng/ml	1.07 ± 0.94	2.37 ± 2.78	0.09
MPHD vs. IGHD	9 (64%) vs. 5 (36%)	7 (16%) vs. 36 (84%)	0.006*
AVP deficiency	1 (7%)	0	0.082
EPP in ME/Elsewhere/Absent	6 (43)/4 (28%)/4 (28%)	Not applicable	–
EPM	2 (14%)	1 (2%)	0.075
Height gained in 1st year, cm	11.3 ± 1.9	9.6 ± 2.1	0.008*
Height gained in 2nd year, cm	9.8 ± 1.7	7.0 ± 1.7	< 0.0001*
Height gained in 3rd year, cm	9.3 ± 3.5	6.3 ± 1.0	< 0.0001*

MPHD Multiple pituitary hormone deficiency; *IGHD* Isolated Growth hormone deficiency; *AVP* Arginine Vasopressin; *EPP* Ectopic posterior pituitary; *ME* Median eminence; *EPM* Extra pituitary malformations.

*Bold indicates significant P value, P < 0.05

frequent in PSIS cohort whereas IGHD in non-PSIS cohort (64% vs. 16%, P = 0.006, respectively).EPM was noted in two of PSIS and one of non-PSIS child in MRI. Among two PSIS children with EPM, one had bilateral parasagittal parietal polymicrogyria, hypoplasia of corpus callosum and other had absent septum pellucidum (Fig. 2a), hypoplasia of optic nerve & optic chiasma (Fig. 2b), arteriovenous malformations in pericallosal region (Fig. 2c). Tonsilar ectopia and vertical orientation of folia was noted in one of non-PSIS cohort. The mean height gain noted after the 1st, 2nd, and 3rd year of GH therapy was better in PSIS than in non–PSIS cohort andit was statistically significant between these groups. The presence of hypoplastic anterior pituitary in non-PSIS and the MRI features of PSIS are few of the better predictors of response to GH therapy. Table 2. compared the different characteristics of PSIS cohorts among the previous published studies.

Discussion

The prevalence of PSIS in the present cohort is 24% among severe short stature children with GHD which is lower when compared to the other Indian cohort by Divaker et aland higher as compared to the Italian cohorts [9, 13]. This shows that PSIS is highly heterogenous in various aspects. An increasing number of PSIS cases are diagnosed recently considering the widespread availability of neuroimaging technology like MRI. The male preponderance in the present cohort is consistent with other published studies and possible mechanisms are due to some unknown antenatal insults [9, 14–17]. No familial or inherited cases were reported in the present as well as with other studies and no specific genetic mutations were

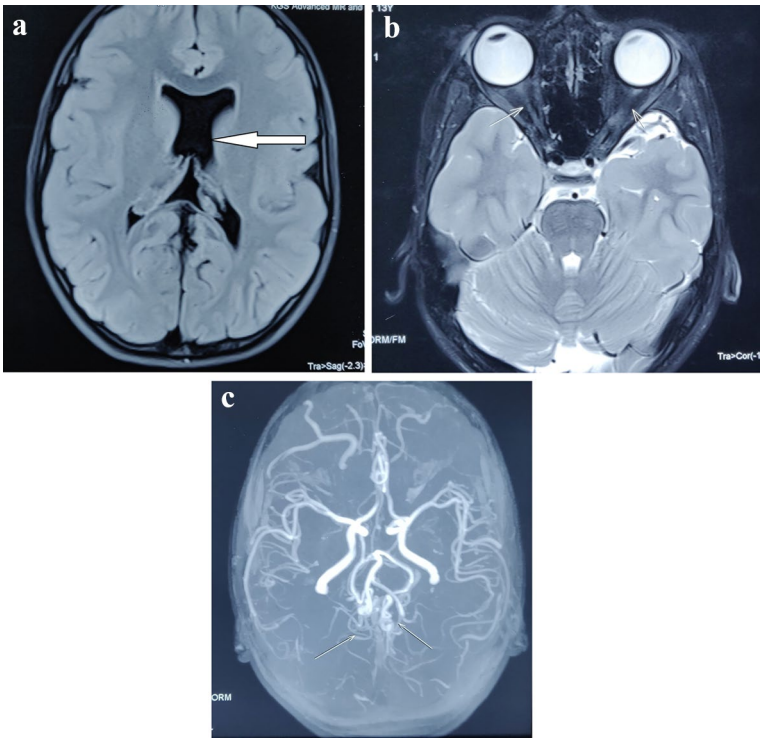

Fig. 2 Extra pituitary Malformations of PSIS children in MRI. **a** Absent Septum Pellucidum (White Arrow), **b** Hypoplasia of optic nerve (White arrow), **c** Pericallosal arteriovenous malformation (White Arrow)

Table 2. Different phenotypic characteristics of PSIS among various studies

Sr. no	Age at diagnosis (years)	Multiple hormone deficiency (%)	M:F ratio	Breech presentation (%)	Extra pituitary birth defect (%)	Familial cases (%)	Author's name and region
1	12.5 (6.3–16.7)	64.3	4.1	35.7	35.7	0	Diwaker et al., India [9]
2	Post pubertal age	54.7	1.2	21	46	–	Pham et al., France [29]
3	25 (22–28)	> 97.2	3.6	44.6	4	–	Wang et al., China [14]
4	19.7±6.7	> 95.8	6.9	88.9	9.1	0	Guo et al., China [18]
5	12.5 (9.6–17.3)	100	5.6	5	–	–	Wang et al., China [31]
6	2.5 (Range 0–16.3)	48	1.7	19	48	0	Bar et al., France [17]
7	4.8±4.1	50	1.9	–	52	8.8	Simon et al., France [22]
8	11.5±3.9 (Range 4–21.6)	81	2.3	27	18	–	Melo et al., Brazil [30]
9	9.64±5.04	> 92.5	3.7	46	–	–	Wang et al., China [15]
10	8.8–16.2	64	2.5	21	7	0	Present study Sridhar et al; India

identified since multiple factors may play a role in the pathogenesis of PSIS [9, 18].

Breech presentation, midline congenital anomalies and seizures are more frequent in PSIS cohorts. Though the breech presentation was most commonly associated with PSIS, its exact pathophysiological role is unknown. Defect in some unknown factor from hypothalamic pituitary axis may play a role in fetal head engagement is proposed recently [9]. Neonatal hypoglycemia, jaundice, micropenis, cryptorchidism were more frequent in PSIS cohort, and all these features favorsevere GHD and MPHD similar to other previous studies [3, 9, 15]. Micropenis and cryptorchidism are few of the predictors of adult hypogonadotropic hypogonadism. The occurrence of seizure in the present study is associated with EPM [19, 20]. The possible mechanisms of seizure in PSIS are due to hypoglycemia and/or hyponatremia as a result of

anterior pituitary deficiencies in addition to the EPM [20, 21]. Rarely it may occur as a result of hypernatremia associated with AVP deficiency. All PSIS cohorts had severe GHD but central hypothyroidism and hypocortisolism were less frequent. Hypogonadotropic hypogonadism was the second most common after GHD among the peripubertal PSIS children. The PSIS children cohorthad more frequent MPHD (57%) than IGHD (36%). This is consistent with other published literature [9, 15, 17, 18, 22]. MPHD had diverse age at presentation and progression, hence long term vigilant follow up is required in all PSIS.

AVP deficiency was uncommon in the present PSIS cohort which is consistent with other studies [9, 14, 15]. The AVP deficiency was seen only in one and associated with absent posterior pituitary as well as EPM in MRI. However none of the other children with either absent posterior pituitary or EPP had AVP deficiency. Despite absent posterior pituitary in the usual anatomical location, their function is well preserved due to their preserved posterior pituitary vascular supply. The possible mechanisms of AVP deficiency in PSIS are due to hypothalamic dysfunction and complex extra pituitary malformations like septo optic dysplasia. [23]. Hypothalamic median eminence was the most common EPP location in MRI. EPP was least commonly seen in the pituitary stalk, optic chiasma and the floor of third ventricle [19, 24, 25]. Ectopic location of posterior pituitary is due to defective neuronal migration and/or regeneration of the nerve fibers of the hypothalamo-neurohypophyseal tracts. The possible mechanisms are perinatal insults leading to traumatic ischemic injury of pituitary or genetic defects [26].

The growth hormone therapy response was better in PSIS cohort with an average of 10 cm per year when compared to non-PSIS despite of severe GHD in both the cohorts [3, 17, 27, 28]. Severe short stature at baseline and presence of severe GHD after the GH provocatice tests are few of the better predictors of growth hormone response noted in the present study [17, 28].

The main strengths are the prospective nature of study and it was done in GHD children with severe short stature. All the MRI were reviewed by two independent radiologists. This study provide better insights regarding the clinical and radiological predictors of better response to growth hormone therapy among PSIS children as well various characteristics were compared with non-PSIS children of GHD. The limitations are relatively small sample size, and lack of molecular genetic analysis.

Conclusion

Male gender, breech presentation, external congenital anomalies like cryptorchidism, midline defects and nystagmus were more common in children with PSIS. MPHD were more frequently seen in PSIS whereas IGHD in non-PSIS cohort. AVP deficiency is very rare in PSIS despite of absent or ectopic posterior pituitary in MRI. High index of clinical suspicion in all severe short stature may lead to early diagnosis and prompt initiation of growth hormone treatment for better outcome.

Author contributions SS was involved in the in the concept, design and final approval of the manuscript. BR was involved in Collection of data, statistical analysis, preparation of the manuscript for submission. RP was involved in manuscript writing SN and SS were involved in reporting of MRI NV was involved in workup of patients and management.

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Data availability Data and materials will be available on request.

Declarations

Competing interests The authors declare no competing interests.

Ethical approval Obtained and attached.

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