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Case Report

Pituitary Stalk Interruption with Varied Presentation: A Case Duplet

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Case Report

Pituitary Stalk Interruption Syndrome (PSIS) is characterized by association of an absent or thin pituitary stalk, an absent or hypoplastic anterior pituitary lobe and/or an ectopic posterior pituitary lobe [1]. This syndrome belongs to the spectrum of midline abnormalities and is often associated with other midline extra-pituitary malformations [2]. The importance of its diagnosis lies on the basis that it leads to complete and permanent form of anterior pituitary hormone deficiency which occurs in varied fashion. We present to you a case duplet of PSIS with two different forms of presentation and pituitary morphology.

Case 1

5 year 3 month old boy, only child born of non-consanguineous marriage, presented to our OPD with complaints of noticing the child not growing well from the age of three. The advice was sought only when in play school the parents noticed the child to be the shortest in class. He was born but normal vaginal delivery, vertex presentation and had no asphyxia, however was noticed to have pallor and decreased activity at 48 hours of life with documented blood glucose of 32 mg/dl requiring intravenous dextrose. After stabilisation of blood glucose values child was discharged on day seven of life. However he had a second episode of hypoglycaemia at 14th day of life requiring IV dextrose. No record of evaluation for hypoglycaemia was available. Mild delay in attainment of gross motor milestones was present. On examination he weighed 14 kg {Weight Age (WA)=2.9yrs (z score:-1.79)} and was 94 cm tall {Height Age (HA)=2.8 years (z score:-3.42 SD) Refer figure 1}. He had a normal arm span and was proportionately short. He had infantile facies, maxillary protrusion, overcrowding of teeth, protuberant belly, small hands and feet and thin upper lip. He was prepubertal and had a normal sized penis. On investigation he had a normal hemogram and celiac screen with normal liver and renal function tests. His TSH was 3.49 mIU/ml (0.7-6.4), free T4:1.03 ng/dl (0.8-2), serum Cortisol 8 am:173 nmol/l (83-583). IGF-1 was low for age and sex:25 ng/ml (52-297), IGFBP3 was 1.54 mcg/ml (1.4-6.1). Bone Age (BA) by Radius Ulna Staging Tanner White III (RUS TW III) was 2 years and 2 months at Chronological Age (CA) 5 years and 3 months (Figure 2).

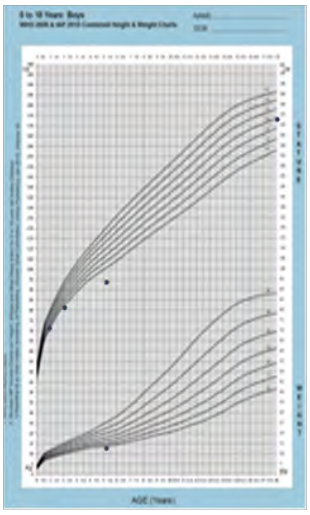

Figure 1: Growth chart of case 1.

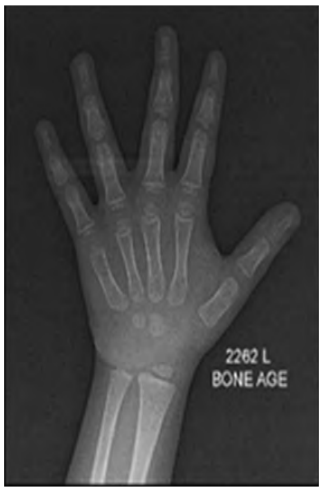

Figure 2: Left hand and wrist X-ray of case 1 showing a delayed bone age. CA=5 years 3 months. BA=2 years 2 months.

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Growth Hormone (GHST) stimulation test with clonidine at 0,30,60,90,120 min revealed Growth Hormone (GH) value of 2.25,1.30,1.19,1.81,2.11 ng/ml respectively. In view of GH Deficiency (GHD), MRI brain (Figures 3a & 3b) revealed the classical triad of absent anterior pituitary, absent infundibulum and ectopic posterior pituitary with absent septum pellucidum. Complete ophthalmic examination revealed a normal optic nerve. Hence the diagnosis of pituitary stalk interruption syndrome was made.

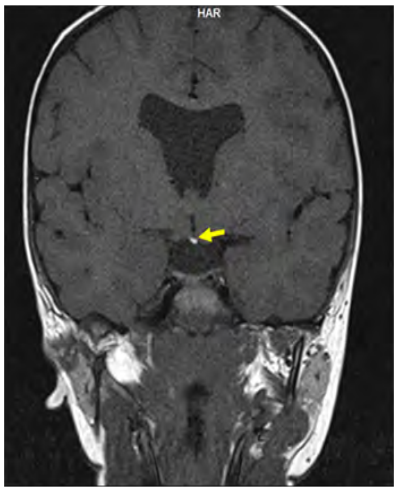

Figure 3a: T1 weighted MRI brain plain (Coronal section) of case 1 showing hypoplastic anterior pituitary, absent septum pellucidum and stalk and ectopic posterior pituitary (arrow head).

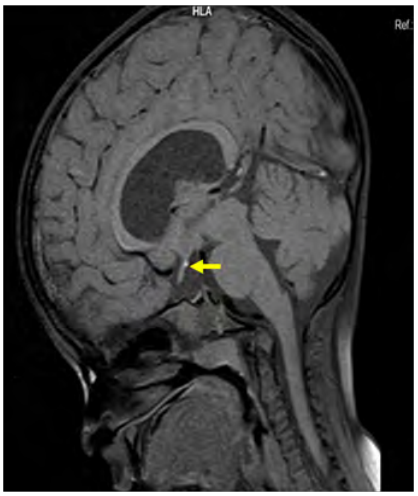

Figure 3b: T1 weighted MRI brain plain (Sagittal section) of case 1 showing hypoplastic anterior pituitary with absent septum pellucidum and stalk with ectopic posterior pituitary (arrow head).

Case 2

9 years 10 month old boy, born to a non consanguineous couple by normal vaginal delivery (birth weight of 2.8 kg, vertex presentation and uneventful neonatal period) presented to us with short stature noticed over the last 2-3 years. He was diagnosed and treated as primary hypothyroidism at his hometown (Table 1). His height was 104 cm (Height Age {HA}: 4 year 3 months, < 3rd centile; z score:-4.70); Weight was 19.4 kg (WA: 5 year 3 months, 3rd centile; z score:-2.51) at initial presentation. BA was 3.5 years at a CA of 8 years and 4 months. Annual Growth Velocity (GV)=4 cm (same height centile). On examination he had a narrow forehead, infantile facies, thin upper lip and protuberant belly. His height was 112 cm (HA: 5 years 6 months, z score:-4.14) and weight was 21 kg (WA: 6 years 3 months, z score:-2.69 (Figure 4)}. He was prepubertal and had normal stretched penile length. Investigations revealed a normal liver and renal function test with a negative celiac screen. His hemogram showed microcytic hypochromic anemia, TSH:2.8 mIU/ml (0.7-6.4), free T4:0.84 ng/dl (0.8-2.2), serum cortisol 8 am:280 nmol/l (83-583), IGF-1 and IGFBP3 was low for age and sex i.e. 25 ng/ml (52-297) and 0.79 mcg/ml (1.4-6.1) respectively. BA (RUS TWIII) was 6 years 8 months at CA of 9 years and 10 months (Figure 5).

Trend of Thyroid Profile	8 year 4 Months	8 year 7 Months	9 year 1 Months	9 year 10 Months
TSH (mIU/ml)	9.68	0.24	14	1.33
Free T4 (ng/dl)	Not done	2.97	Not done	1.04
Treatment (Levothyroxine in mcg/day)	25	12.5	20	25
Anti-Thyroid Peroxidase Anti-Thyroglobulin Antibodies	Trend of thyroid profile at the patients' hometown.			

Table 1: Trend of the Thyroid functions of the patient.

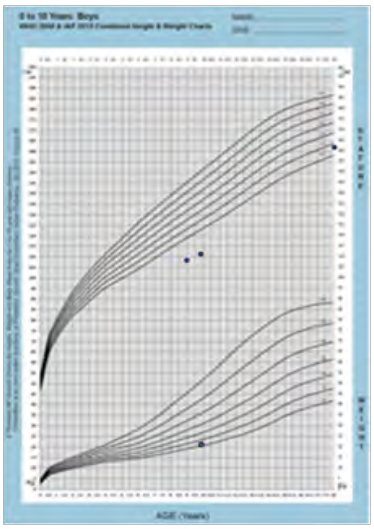

Figure 4: Growth chart of case 2.

His GHST at 0 min/30 min/60 min/90 min/120 min revealed GH deficiency with GH values of 0.11/0.03/0.05/0.15/0.18 ng/ml respectively. MRI brain (Figure 6) showed ectopic posterior pituitary and hypoplastic anterior pituitary with absent pituitary stalk, suggestive of PSIS also known as "PickardtFahlbusch Syndrome". Both the patients were started on GH therapy with close monitoring and regular follow up and are growing well.

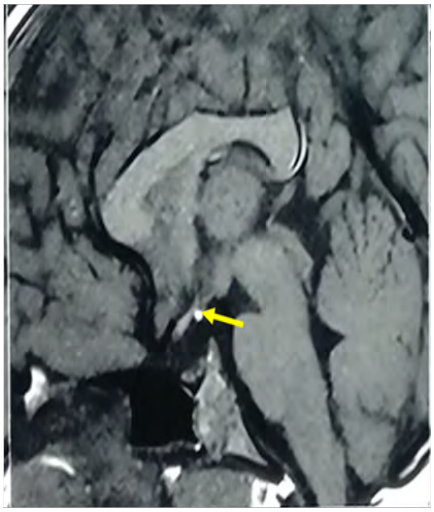

Figure 5: Left hand and wrist X-ray of case 2 showing a delayed bone age. CA=9 years 10 months. BA=6 years 8 months.

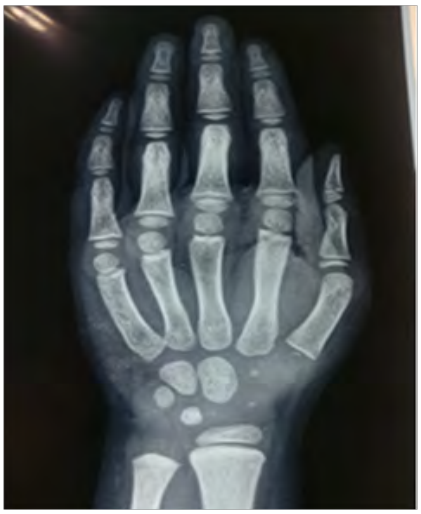

Figure 6: MRI brain plain (Sagittal section) of case 2 showing hypoplastic anterior pituitary (pituitary height 1.5 mm) with absent infundibulum and ectopic posterior pituitary (arrow head).

Discussion

PickardtFahlbusch Syndrome/PSIS has an incidence of 0.5 per 100000 births with male predominance [3]. The theories of pathogenesis responsible for this entity is vague and attributed to multiple factors including defects in embryogenesis of the hypophysis secondary to mutations in transcription factors and genes (PROP-1, HESX1, LHX4, OTX2, SOX3 and PROKR2) and defective induction of mediobasal structures of the brain during embryogenesis (accounting for the other midline defects along with PSIS). The traumatic hypothesis involves transaction of the stalk (breech delivery/asphyxia) and the proximal hypertrophy of the neurons leading to ectopic posterior pituitary. However, there are many cases reported without any genetic mutation or history of traumatic delivery still having PSIS [3,4]. The clinical and biological presentations of patients with PSIS vary with precocity and type of presenting symptom, isolated or multiple nature of the hypothalamo-pituitary deficiency and hypothalamic or pituitary origin of the deficiency [5]. Panhypopituitarism presents as early as in the neonatal period [6] and short stature with primary infertility presents as late as in adulthood [7]. The prevalence of deficiency in growth hormone is the most, followed by gonadotropins, thyrotropin and corticotrophin [8]. 70% patients are brought to medical attention as children with growth retardation [9]. The median age at diagnosis of these patients is 4 years [10]. Regular follow-up of growth if done helps in earlier diagnosis. Features suggestive of neonatal growth hormonal deficiency (hypoglycaemia, jaundice and micropenis/cryptorchidism in males) if seen should prompt earlier evaluation of pituitary anatomy and function [4]. Most patients diagnosed on growth retardation have isolated GHD at diagnosis. This could cause moderate and spontaneously reversible hypoglycaemia during the neonatal period [11]. Hypoplasia of the pituitary gland, infundibulum, septum pellucidum, corpus callosum and optic nerve(s) may be seen in an isolated fashion or in combination with one another. These related midline developmental anomalies are thought to represent a spectrum of congenital and developmental conditions with varying degrees of penetrance, including holoprosencephaly and/or septo-optic dysplasia [12]. The cases described here tell us how the cause of short stature has been elucidated. The first case had a typical GH deficiency history whereas the second case in view of elevated TSH and low-normal free T4 was considered primary hypothyroidism and treated accordingly. Importantly, a low-normal to low free T4 with low/normal or high TSH (not more than 20 usually) needs a neuroimaging for evaluation of pituitary gland. High TSH in central hypothyroidism is due to lack of metabolism of circulating TSH in the absence of thyrotropin-releasing-hormone action and pituitary TSH reserve is infrequently depleted and the anterior pituitary can secrete the immunoreactive TSH without full biological activity [13].

	Case 1	Case 2
Presenting complaints	Poor growth velocity	Poor growth velocity and deranged thyroid profile.
Clinical features	Infantile facies	Infantile facies
Birth history **Mode of delivery** **Breech/vertex** **Hypoglycaemia** **Jaundice** **Microphallus**	No asphyxia Spontaneous vaginal Vertex Yes No No	No asphyxia Spontaneous vaginal Vertex No No No
Milestones	Gross motor delay	Normal
Anterior pituitary hormones	GH deficiency (after GH stimulation testing with clonidine) Other hormones normal.	Central hypothyroidism with GH deficiency (after GH stimulation testing with clonidine).
Post pituitary hormones	Normal	Normal
Neuroimaging	Adenohypophysis, pituitary stalk and septum pellucidum not visualised. Ectopic posterior pituitary. No evidence of optic atrophy.	Hypoplastic adenohypophysis, absent stalk and ectopic posterior pituitary.

Conclusion

Neonatal hypoglycaemia, hyperbilirubinemia and microphallus needs close follow up to see whether they develop GHD later. History of traumatic delivery is not a mandatory phenomenon. Any child with

short stature and deranged thyroid profile especially in the setting of a low normal free T4 with a normal to marginally high TSH in absence of thyroid antibodies needs a neuroimaging to delineate the anatomy of the pituitary.

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