International Journal of Pediatrics & Neonatal Care

Research Article Open Access

Special Issue: Perinatal Management of Congenital Anomalies

Congenital Hypopituitarism in Saudi Arabia: Is it That Rare?

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Abstract

Background: Congenital hypopituitarism is a clinical syndrome of deficiency in pituitary hormones production. Panhypopituitarism refers to involvement of more than one pituitary hormone while involvement of one hormone refers to partial hypopituitarism It is an uncommon disorder of the hypophyseal system but could be life threatening, however, it is treatable if the diagnosis is made early.

Design and setting: A retrospective hospital based study was conducted at Pediatric endocrine service, King Khalid University Hospital (KKUH) Riyadh, Saudi Arabia during the period of January 1990 and December 2017.

Material and Methods: The medical records of patients with the diagnosis of hypopituitarism were retrospectively reviewed. Data included age, sex, clinical presentation, and results of relevant laboratory investigations and radiological imaging.

Results: During the period under review, a total of 177 patients were diagnosed with possible congenital hypopituitarism. The mean age was 6.5 years range 0-18 years. Seventy-five percent were having isolated hormone deficiency; Growth hormone 117 (87.9%), gonadotrophic hormone 8 (6.0%), central hypothyroidism 5 (3.8%) and adrenocorticotrophic hormone 3 (2.3%). In twenty- five percent of patients the diagnosis was multiple pituitary hormone deficiency (MPHD), in which septo-optic dysplasia and other midline defects, constitute the majority (56.8%). Diabetes Insipidus was found in association in five (2.5%) patients.

Conclusion: Congenital hypopituitarism in not that rare in Saudi Arabia. An early diagnosis can be obtained with high accuracy based on a high clinical suspicion index. Imaging abnormalities are frequent and associated with the clinical and biochemical phenotypes. It had variable presentations, such as hypoglycemia, micro phallus in boys and neonatal cholestasis, or in association with midline defects. There is a need to compliment hormonal and radiological investigations with gene study.

Publication History:

Received: October 25, 2018
Accepted: December 05, 2018
Published: December 07, 2018

Keywords:

Congenital, Hypopituitarism, Partial, Complete, Association, Magnetic resonance imaging (MRI), Saudi Arabia

Introduction

Congenital hypopituitarism is a clinical syndrome of deficiency in pituitary hormones production. Panhypopituitarism refers to involvement of more than one pituitary hormone while involvement of one hormone refers to partial hypopituitarism It is an uncommon disorder of the hypophyseal system but could be life threatening, however, it is treatable if the diagnosis is made early [1-4].

Congenital hypopituitarism is associated with possible serious complications and long-term neurological sequelae, Neonates with congenital hypopituitarism may present with or without associated developmental defects, such as ocular, midline, and genital abnormalities. They may also present with nonspecific symptoms, including hypoglycemia, lethargy, apnea, hemodynamic instability, jitteriness, seizures, poor weight gain, failure to thrive, temperature instability, recurrent sepsis and neonatal cholestasis. It is typically detected shortly after birth, but it may occur several weeks after the neonatal period. The cholestatic jaundice most commonly associated with neonatal hypopituitarism manifests as conjugated hyperbilirubinemia with elevated alkaline phosphatase. The cholestasis resolves after replacement of glucocorticoids or growth hormone, suggesting a role of these hormones in biliary excretory function. Furthermore genetic mutations in transcription factors gene involved in the embryogenesis of the pituitary gland such as HESX-1, PROP -1 and PIT-1 were reported and implicated in the pathogenesis of congenital hypopituitarism [5-10].

This article reports on the clinical experience of congenital hypopituitarism from the pediatric endocrine service, King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia over more than two decades, January 1990 to December 2017. KKUH is the major hospital of King Saud University and provide primary, secondary and tertiary health care service to the local population and also receives patients' referral from all over the country.

Material and Methods

The medical records of patients who diagnosed to have congenital hypopituitarism (aquired causes has been excluded) were retrospectively reviewed. Data included were age, sex, clinical presentation, and results of the relevant laboratory investigations and radiological images; where Magnetic resonance imaging (MRI) scan was done. The diagnoses of congenital hypopituitarism were based on clinical suspicion supported by appropriate hormonal testing. The diagnoses of congenital growth hormone deficiency

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Citation: Al-Jurayyan RN, Al-Issa SD, AlKhalifah RA, Al-Otaibi HM, Al-Jurayyan NA, et al. (2018) Congenital Hypopituitarism in Saudi Arabia: Is it That Rare?. Int J Pediatr Neonat Care 4: 145. doi: https://doi.org/10.15344/2455-2364/2018/145

were made by performing one physical (sleep) and two biochemical tests, using sex hormone priming when indicated. The various hormonal testing to assess both the anterior and posterior pituitary gland functions, were performed following the specific protocol [11]. Unfortunately, no genetic studies were done in any of our patients.

Results

During the period under review, a total of 177 patients were diagnosed with possible congenital hypopituitarism. The mean age was 6.5 years range 0-18 years. Majority of patients with congenital growth hormone deficiency was diagnosed at a later age because of late referral. Seventy-five percent were having isolated hormone deficiency; Growth hormone 117 (87.9%), Gonadotrophic hormone 8 (6.0%), central hypothyroidism 5 (3.8%) and Adrenocorticotrophic hormone 3 (2.3%). In twenty- five percent of patients the diagnosis was multiple pituitary hormone deficiency (MPHD), in which septo-optic dysplasia and other midline defects, constitute the majority (56.8%). Magnetic resonance imaging (MRI) results in 177 patients with congenital hypopituitarism revealed the majority (86.5%) of patients with isolated hormonal deficiency (IHD) were normal, while the majority (95.5%) of patients with multiple pituitary hormonal deficiency (MPHD) were abnormal. Diabetes Insipidus was found in association in five (2.5%) patients.

Discussion

Congenital hypopituitarism is a clinical syndrome characterized by deficiency of pituitary hormones production. This may result from peri-natal or birth asphyxia or congenital defects of the hypothalamus, pituitary gland or surrounding structures, of which septo-optic dysplasia and other midline defects constitute the majority. However, in rare occasions a genetic basis involving the pituitary transcription factors that regulate the formation of the gland. It could be partial, involving the deficiency of one hormone, or complete (pan) involving the deficiency of more than one hormone with estimated incidence between 1:3000 and 4000 births [1-5]. Onset can be at any time of life, it might be lethal if not diagnosed and treated early. It is reported in association with other diseases like Shaw Ashman-Diamond syndrome, hyperemia and slipped capital femoral epiphysis [12-14]. Jain et al [15] reported the adverse on the heart. Also, Brown et al [16] reported that in children with congenital hypopituitarism have an IQ that is below average when compared to the normal population and a reduced performance IQ when compared to sibling control, which may reflect abnormal brain development or could be linked to the impact of hypoglycemia or low thyroxine concentration in early life. In Saudi Arabia, there are no precise data on the prevalence of the disorder, however, there is an impression fostered by clinical experience and scant published data, that this is not that rare disease. [17-21]

The presentation is variable. The most important presenting feature, and perhaps most common feature, of congenital hypopituitarism is hypoglycemia [22]. This occurs secondary to the presence of GH deficiency with or without associated ACTH deficiency. The majority of patients were GH deficient in our series [23-26].

Another unique feature of congenital hypopituitarism is the presence at birth of a microphallus (small penis). This is a result of gonadotrophic hormone deficiency [27-28]. Noninfectious form of hepatitis developed in our series, the condition is suspected as liver

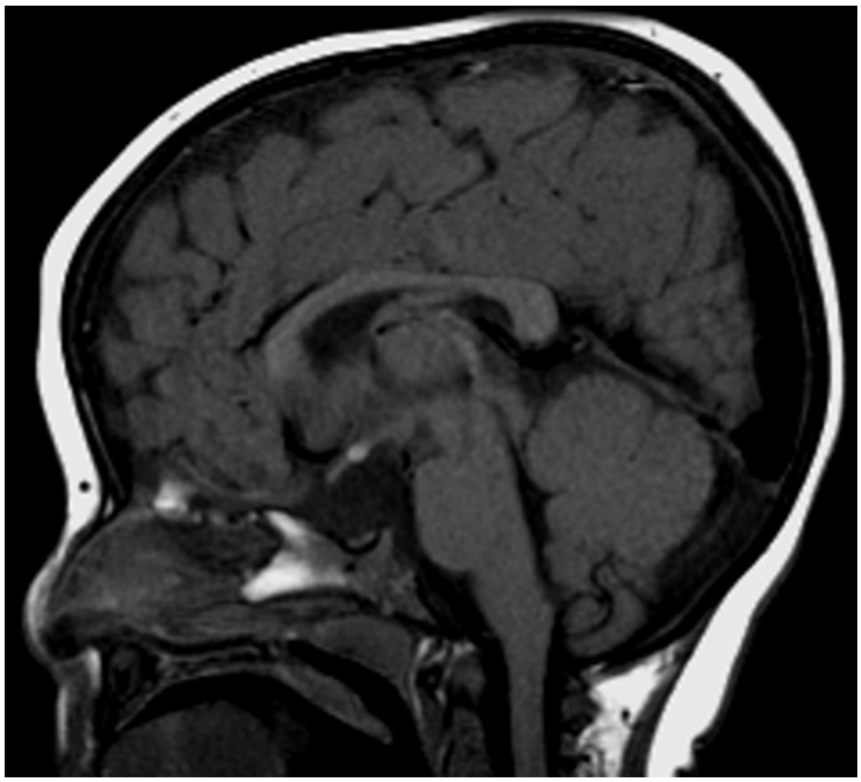

Figure 1: Sagittal T1 weighted Magnetic resonance imaging showing a small anterior pituitary, absent stalk, and normally located posterior pituitary.

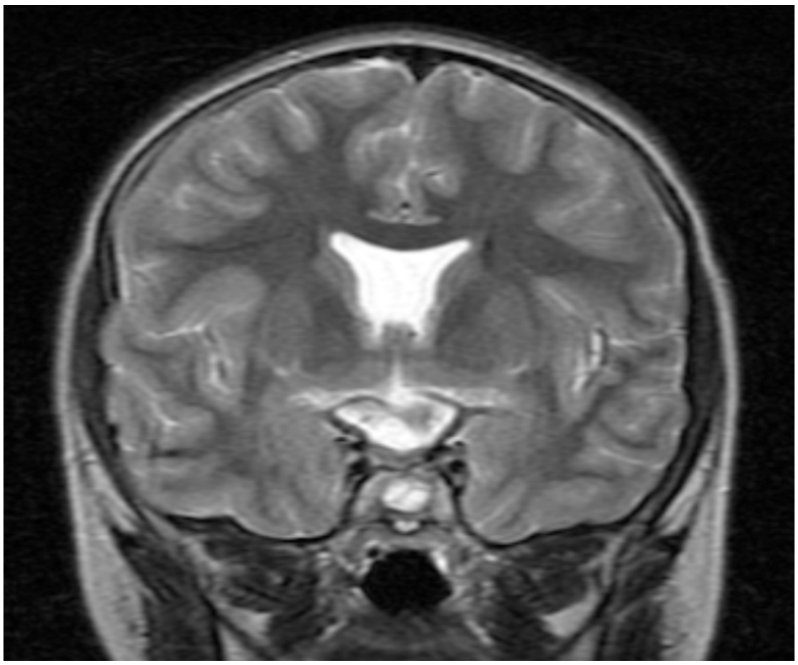

Figure 2: Coronal T2W image of the brain demonstrating absence of the septum pellucidum in septo-optic dysplasia.

enlarged with abnormal liver function tests [18,20,29-32]. The diagnosis of central hypothyroidism should not be over looked. Five (5.6%) patients, in our series were diagnosed to have isolated thyroid stimulating hormone (TSH) deficiency with low free thyroxine (FT4) [3,33,34]. Furthermore, three (1.7%) patients were diagnosed with isolated adrenocorticotrophic hormone (ACTH) deficiency at variable ages, Takagi et al described in a cohort of Japanese patients, the gradual loss of ACTH in patients carrying an LHX4 mutation [35-37].

Prenatal, during pregnancy, and birth asphyxia are important contributing factors for etiology. Nine (7.7%) patients of the isolated growth hormone deficiency (GH) group, (five-breech delivery, and four with birth asphyxia with low Apgar scores) had history suggestive of birth asphyxia [38]. Furthermore, severe midline defects, such as septo-optic dysplasia which include absence of the septum pellucidum, underdevelopment of the optic nerve, associated with variable degrees of impaired vision. Also, cleft lip and/or palate, choanal atresia, anomalies or absent vascular supply to the central nervous system, and encephaloceles. In this series, they constitute a majority [5,6,19,21,39-43], similar to previously reported [44]. Rarely, it might result in genetic mutations like transcription factors, involved in the regulation of the pituitary gland and its function [1,3,45]. Unfortunately, the service is not available to us.

Magnetic resonance imaging (MRI) scan remains the modality of choice assessing the hypothalamic pituitary region in patient with congenital hypopituitarism. MRI scan precisely diagnose abnormality of the adenohypophysis and neurohypophysis usually the stalk, and correlate well with the clinical presentation. In a normal head magnetic resonance imaging (MRI) scan, the anterior pituitary, on T1-weighted imaging, appears dark and equal in intensity to gray matter, while the posterior pituitary gland appears white and is referred to, radiologically, as the posterior "bright spot" (Figure 1). In Septo-optic dysplasia the absence of the septum pellucidum (Figure 2) is a constant finding in our series, similar to what have been reported [46-50].

Conclusion

Congenital hypopituitarism in not that rare in Saudi Arabia. An early diagnosis can be obtained with high accuracy based on a high clinical suspicion index. Imaging abnormalities are frequent and associated with the clinical and biochemical phenotypes. It had variable presentations, such as hypoglycemia, micro phallus in boys and neonatal cholestasis, or in association with midline deficits. There is a need to compliment hormonal and radiological investigations with gene study.

Acknowledgement

The authors would like to thank Mr. Abdulrahman AL Jurayyan for his help in preparing the manuscript .

Conflict of Interests

The authors have no conflict of interests to declare.

Reference

1. Geffner ME (2002) Hypopituitarism in childhood. Cancer Control 9: 213-222.
2. Kim SY (2015) Diagnosis and tretment of hypopituitarism. Endocrinol Metab 30: 443-455.
3. Schoenmakers N, Alatzoglou KS, Chatterjee VK, Dattani MT (2015) Recent advances in central congenital hypothyroidism. J Endocrinol 227: R51-R71.
4. Higham CE, Johannsson G, Shalet SM (2016) Hypopituitarism. Lancet 388: 2403-2415.
5. Akin MA, Kurtoğlu S, Sarici D, Akin L, Hatipoğlu N, et al. (2014) Endocrine abnormalities of the patients with cleft lip and/or cleft palate during the neonatal. Period Turk J Med Sci 44: 696-702.

6. Siatkowski RM, Sanchez JC, Andrade R, Alvarez A (1997) The clinical, neuroradiographic, and endocrinologic profile of patients with bilateral optic nerve hypoplasia. Ophthalmology 10: 493-496.
7. Lovinger RD, Kaplan SL, Grumbachi MM (1975) Congenital hypopituitarism associated with neonata hypoglycemia and micropenis secondary to hypothalamic hormone deficiency. J. Pediatr 87: 1171-1181.
8. Saranac L, Bjelakovic B, Djordjevic D, Novak M, Stankovic T, et al. Hypopituitarism occurring in neonatal sepsis. J Pediatr Endocrinol Metab 25: 847-848.
9. Salisbury DM, Leonard JV, Dezateux CA, Savage MO (1984) Micropenis: An important early sign of congenital hypopituitarism. Br Med J 288: 621-622.
10. Verma A, Singh K, Pannu M, Verma S, Sareen A, et al. (2014) Congenital hypopituitarism presenting like sepsis : a diagnostic challenge. Internet J of endocrinol.
11. Bertrand J, Rappaport R, Sizonenko PC (1993) Assessment of Endocrine Functions. In: Bertrand J, Rappaport R, Sizonenko PC, eds. Pediatric Endocrinology: Physiology, Pathophysiology, and Clinical Aspects. Baltimore, MD: Williams & Wilkins.
12. Jivani N, Torrado-Jule C, Vaiselbuh S, Romanos-Sirakis E (2016) A unique case of Shwachman-Diamond syndrome presenting with congenital hypopituitarism. J Pediatric Endocrinol Metab 29: 1325-1327.
13. Bowden SA, Klingele KE (2009) Chronic bilateral slipped capital femoral epiphysis as an unusual presentation of congenital panhypopituitarism due to pituitary hypoplasia in a 17 year female. Int J Pediatr Endocrinol 2009: 609131.
14. Inoue H, Ihara K, Ochiai M, Takahata Y, Kohno H, et al. (2011) Congenital multiple pituitary hormone deficiency associated with hyperammonemia: a case report with a short review of the literature. J Perinatol 31: 145.
15. Jain V, Kannan L, Kumar P (2011) Congenital hypopituitarism presenting as dilated cardiomyopathy in a child. J Pediatr Endocrinol Metab 24: 767-769.
16. Brown K, Rodgers J, Johnstone H, Adams W, Clarke M, et al. (2004) Abnormal cognitive function in treated congenital hypopituitarism. Arch Dis Child 89: 827-830.
17. Al Jurayyan NAM (2016) Congenital Hypopituitarism Variable Presentation for the Same Diagnosis. IJDR 6: 6936-6938.
18. Al Jurayyan NAM (2015) Neonatal Cholestasis: Beyond Thyroid Hormones. Basic Res J Med Ckin Sci 4: 237-239.
19. Ben Abbas BS, AL Ashwal AA, AL Alwan IA, AL Qahtani MH, AL Mutair AN, et al. The syndrome of septo-optic dysplasia in saudi children. Saudi Med J 25: 1675-1678.
20. Al Hussaini A, Al Mutairi A, Mursi A, Al Ghofely M, Asery A, et al. (2012) Isolatedcorticol deficiency. A rare cause of neonatal cholestasis. Saudi J Gastroenterology 18: 339-341.
21. Nazer NW, Al-Agha AE (2018) Hypopituitarism association with blindness in a 5 year old boy: A case report and literature review. Curr pediatr RS 22: 111-114.
22. Bell JJ, August GP, Blethen SL, Baptista J (2004) Neonatal hypoglycemia in a growth hormone registry: incidence and pathogenesis. J Pediatr Endocrinol Metab 17: 629-635.
23. Richmond EJ, Rogol AD (2008) Growth hormone deficiency in children. Pituitary 11: 115-120.
24. Lovinger RD, Kaplan SL, Grumbach MM (1975) Congenital hypopituitarism associated with neonatal hypoglycemia and microphallus: four cases secondary to hypothalamic hormone deficiencies. J Pediatr 87: 1171-1181.
25. Urzola A, Leger J, Czernichow P (1999) Three cases of congenital growth hormone deficiency with micropenis and hypospadias: what does growth hormone have to do with it? Horm Res 51: 101- 104.
26. AlJurayyan RN, AlJurayyan NA, Omer HG, Sharifah D A Alissa, Hessah M N AlOtaibi, et al. (2017) Pituitary Imaging in 129 children with growth hormone defeciency. A spectrum of finding. Sudan J Pediatr 17: 30-35.
27. Al-Jurayyan NA, Al Issa SD, Al Nemri AM, Al Otaibi HM, Babiker AM, et al. (2015) The spectrum of 46XY disorders of sex development in a University centre in Saudi Arabia. J Pediatr Endocrinol Metab 28: 1123-1127.
28. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dodé C, et al. (2015) Expert consensus document: European consensus on congenital hypogonadotropic hypogonadism-pathogenesis, diagnosis and treatment. Nat Rev Endocrinol 11: 547-564.
29. DeSalvo D, Pohl JF, Wilson DP, Bryant W, Easley D, et al. (2008) Cholestasis secondary to panhypopituitarism in an infant. J Natl Med Assoc 100: 342-344.
30. Kaufman FR, Costin G, Thomas DW, Sinatra FR, Roe TF, et al. (1984) Neonatal cholestasis and hypopituitarism. Arch Dis Child 59: 787-789.
31. Binder G, Martin DD, Kanther I, Schwarze CP, Ranke MB, et al. (2007) The course of neonatal cholestasis in congenital combined pituitary hormone deficiency. J Pediatr Endocrinol Metab 20: 695-702.
32. Spray CH, Mckiernan P, Waldron KE, Shaw N, Kirk J, et al. Investigation and outcome of neonatal hepatitis in infants with hypopituitarism. Acta Paediatr 89: 951-954.
33. Lania A, Persani L, Beck-Peccoz P (2008) Central hypothyroidism. Pituitary 11: 181-186.
34. Price A, Weetman AP (2001) Screening for central hypothyroidism is unjustified. BMJ 322: 798-801.
35. Mehta A, Hindmarsh P, Dattani MT (2005) An update on the biochemical diagnosis of congenital ACTH insufficiency. Clin Endocrinol 62: 307-314.
36. Takagi M, Ishii T, Inokuchi M, Amano N, Narumi S, et al. (2012) Gradual Loss of ACTH Due to a Novel Mutation in LHX4: Comprehensive Mutation Screening in Japanese Patients with Congenital Hypopituitarism. PLOS one 7:e 46008.
37. Couture C, Saveanu A, Barlier A, Carel JC, Fassnacht M, et al. (2012) Phenotypic homogeneity and genotypic variability in a large series of congenital isolated ACTH-deficiency patients with TPIT mutations. JClin Endocrinol Metab 97: E486 E495.
38. Craft WH, Underwoood LE, Van Wyk JJ (1980) High incidence of perinatal insult in Children with idiopathic hypopituitarism. J Pediatr 96: 397-402.
39. Triulzi F, Scotti G, di Natale B, Pellini C, Lukezic M, et al. (1994) Evidence of a midline brain anomaly in pituitary dwarfs: a magnetic resonance imaging study in 101 patients. Pediatrics 93: 409-416.
40. Brodsky MC, Phillips PH (2000) Optic nerve hypoplasia and congenital hypopituitarism. J Pediatr 136: 850.
41. Siatkowski RM, Sanchez JC, Andrade R, Alvarez A (1997) The clinical, neuroradiographic, and endocrinologic profileof patients with bilateral optic nervehypoplasia. Ophthalmology 104: 493-496.
42. Akin MA, Kurtoğlu S, Sarici D, Akin L, Hatipoğlu N, et al. (2014) Endocrine abnormalities of patients with cleft lip and/or cleft palate during the neonatal period. Turk J Med Sci 44: 696-702.
43. Phillips Plt, Brodsky MC (2003) Congenital optic nerve abnormalities in pediatric ophthalmology and strabismus 2nd edition, edited by wright KW, Springer Verlag Inc.
44. Lammoglia JJ, Eyzaguirre F, Unanue N, Román R, Codner E, et al. (2008) Congenital hypopituitarism: Report of 23 cases. Rev Med Chil 136: 996-1006.
45. Kelberman D, Dattani MT (2007) Genetics of septo-optic dysplasia. Pltuitary 10: 393-407.
46. Pressman BD (2017) Pituitary imaging. Endocrinol Metab Clin Nam 46: 713-748.
47. Scotti G, Triulzi F, Chiumello G, Dinatale B (1989) New imaging techniques in endocrinology: magnetic resonance of the pituitary gland and sella turcica. Acta Paediatr Scand 365: 5-14.
48. Di Iorgi N, Allergri AE, Napoli F, Bertelli E, Olivieri I, et al. (2012) The use of neuroimaging for assessing disorders of pituitary development. Clin Endocrinol 76: 161-176.
49. Dutta P, Bhansali A, Singh P, Rajpur R, Khandelwd N, et al. (2009) Congenital hypopituitarism clinico-radiological Correlition. J pediatr Endocrinol Metab 22: 921-928.
50. Root AW, Martinez CR (1992) Magnetic resonance imaging in patients with hypopituitarism. Trends Endocrinol Metab 3: 283-287.

This article was originally published in a special issue:

Perinatal Management of Congenital Anomalies

Handled by Editor(s):
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