PEDIATRIC ENDOCRINOLOGY- A TROPICAL PERSPECTIVE

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ABSTRACT

Pediatric endocrine disorders are frequently seen in tropical countries. While broadly the spectrum of pediatric endocrine disorders in the tropics is not entirely different from that seen in other parts of the world, some aspects of these disorders are unique to the tropics. Many pediatric endocrine disorders are underreported from the tropics, presumably because of limited access to medical care in terms of both diagnostic and therapeutic facilities. Lack of formal training of pediatricians and physicians in pediatric endocrinology may be a contributor. Some conditions such as exogenous Cushing syndrome are seen very frequently in tropics because of easy access and unrestrained use of glucocorticoids by quacks/ faith healers. Malnutrition is an important contributor to short stature in many tropical countries where a large section of the population is living in abject poverty. Iodine deficiency disorders are seen in many countries despite iodine fortification of salt or other edible items. Lack of universal screening for congenital hypothyroidism often leads to late detection of this disorders contributing to significant morbidity and mortality. Vitamin D deficiency and nutritional rickets is rampant even in areas where sunlight is abundant year around. Since most of the pediatric endocrine disorders are easily treatable and can have severe consequences when diagnosis or treatment is delayed, increasing the awareness of these disorders in the healthcare workers in the tropics is necessary.

PITUITARY DISEASE

The common pituitary disorders reported from the tropics include craniopharyngiomas, growth hormone deficiency, pituitary adenomas (including prolactinomas), and Cushing's disease.

Craniopharyngiomas

Craniopharyngiomas are common suprasellar tumors in childhood. A retrospective analysis of 62 pediatric (onset <18 years) craniopharyngiomas was reported from a tertiary care hospital from India. The presenting features included central diabetes insipidus (6.5%), central hypothyroidism (43.5%), secondary adrenal insufficiency (32%), and delayed puberty (24%). On follow up 90% had some form of anterior pituitary deficiency and 22.6% developed obesity. GH therapy was given to 14% of cases. Incomplete surgical removal was frequent and radiotherapy was used in many cases (1). Another study from Egypt reported

137 patients with pediatric craniopharyngiomas. They were treated with surgery alone (65), radiotherapy after surgery (71), or surgery for Ommaya insertion with intracystic interferon injection (1). Subtotal resection was seen in 58 patients (42.33%) while 48 cases (35.04%) had gross total resection/near total resection. The 5-year progression-free survival (PFS) was 52.3%, (surgery alone 34.49% and radiotherapy after surgery 72.25%) (2). Both craniopharyngiomas and gliomas were most common supratentorial pediatric brain tumors in Nigeria (3). In a study of 37 pediatric craniopharyngiomas who underwent surgery, gross total resection was possible in 43.2%, near total resection in six patients 16.2%. and subtotal resection (STR) in 40.5%. The recurrence-free survival rate was 81.1% and 70.3% at 5- and 10-year follow-up, respectively. Diabetes insipidus, anterior pituitary hormone deficits, and obesity were common in follow up (4). In a study from Pakistan, craniopharyngiomas were 14.3% of the reported pediatric intracranial tumors (5). Another study from Pakistan has reported the use of gamma knife radiosurgery in craniopharyngiomas. The patients included 17 children. Nearly 80% of the patients achieved tumor control with gamma knife (6). An uncommon variant called papillary craniopharyngiomas has been reported in 13 cases from Pakistan (7).

Growth Hormone Deficiency And Related Disorders

Isolated growth hormone deficiency (IGHD) and combined pituitary hormone deficiency (CPHD) are the two presentations of growth hormone (GH) deficiency. The mutations involved in IGHD are GH*1* and *GHRHR* while CPHD is associated with mutations in transcription factor genes *PROP1*, *POU1F1*, and *HESX1.* Genetic analysis performed in 51 patients with CPHD at a tertiary care center in India reported that 10 (20%) patients had POU*1F1* and *PROP1* mutations and of these 5 were novel and 2 previously reported. No mutations were identified in *HESX1* (8).

A study of growth hormone deficient patients from South India reported that smaller pituitary size was associated with worse height deficits and bone age delays. However, they had a better response to GH therapy (9).

Children with IGHD had several biochemical and cardiac parameters that may be associated with an increased CVD risk in later life. This included higher waist-hip-ratio, total cholesterol, non-high-density lipoprotein-cholesterol, serum homocysteine, C-reactive protein (CRP), and pro-brain natriuretic peptide (pro-BNP). Left ventricular mass (LVM) and interventricular septal thickness were significantly lower (10).

A novel POU*1F1* c.605delC mutation in combined pituitary hormone deficiency (CPHD) was identified by Sanger sequencing carried out in 160 trios and 100 controls. In vitro studies showed that the this mutation codes for a truncated protein with reduced transactivation capacity on downstream targets like growth hormone (*GH*) and prolactin (*PRL*) (11).

Laron dwarfism first reported among Israeli Jewish children is a rare disorder characterized by low IGF-1 and high GH levels. A case series of nine such cases (6 male, 3 female) was reported from South India. The short stature was extreme with a mean height Z score of 7.7 (SD 0.8). Clinical features included characteristic facial features, microcephaly, micropenis and developmental delay. All children had typical hormonal profile of low IGF-1 and elevated GH (12). Laron syndrome has been reported from Africa and South America (13)(14)(15).

Pituitary Adenomas

While adult pituitary tumors are relatively common, pediatric pituitary adenomas (PPA) are less common. A retrospective study of 74 cases of PPA was published from a center in North India. The median age was 15 years and 42 % were females. Headache and menstrual abnormalities were common

presentations. Corticotroph adenomas (32.4%) and somatotropinomas (25.7%) were among the common types. TSHoma and pituitary blastomas were very few. In 81% cases, transsphenoidal surgery was performed while adjuvant medical management and radiotherapy was required in 25% and 18% respectively. Remission rates in Cushing's and acromegaly were 62.5% and 57.8%, respectively, and post operative hormone deficits were seen in 33% (16).

Giant prolactinoma (GP) are rare pituitary tumors in childhood and adolescence. A series of 18 cases of GP has been reported from India. GP constituted 20% of pediatric prolactinomas at this center. The authors conducted a systematic review including these 18 and 77 other cases from the literature. They found a male predominance with pubertal arrest/delay. Dopamine agonist (DA) monotherapy showed good results as monotherapy (17).

Cushing's Disease

Cushing's disease is an important cause of hypercortisolism in children. It is caused by an ACTH secreting pituitary adenoma. A retrospective study of 48 pediatric cases of Cushing's disease who underwent transsphenoidal adenectomy between 1998 and 2008 was published from India. Weight gain, round facies, and short stature were the most common clinical manifestations. Low dose dexamethasone suppression test and midnight cortisol showed 100% sensitivity for establishing hypercortisolism, while midnight ACTH had 100% sensitivity for confirming ACTH dependence. Magnetic resonance imaging and unstimulated BIPSS were used to confirm Cushing's disease. Post surgical remission was 56% after first transsphenoidal adenectomy with higher remission rate of 75% in those with microadenoma. Eight patients were given radiotherapy and four of these achieved remission (18).

GROWTH AND PUBERTAL DISORDERS

Short stature and delayed puberty are commonly seen in children visiting pediatric endocrine clinics in the tropics.

Short Stature

Malnutrition, systemic illnesses, endocrine disorders, and syndromic disorders are among the major causes of short stature in the tropics.

MALNUTRITION

Malnutrition in early childhood is an important cause of short stature in tropical counties. The role of early childhood undernutrition on physical growth and cognitive achievement was assessed in a nationwide population-based cohort study in India. Data on undernutrition was taken from Human Development Survey (IHDS) in 2004 to 2005 while the outcomes on physical and cognitive outcomes during preadolescent (8 to 11 years) years was assessed in 2011 to 2012. The study assessed 7868 children and 4334 were undernourished. Undernourished children had 1.73 times increased odds of short stature. It was associated with decreased odds of achieving a higher reading and arithmetic outcomes. The findings were worse in female children.(19)

SYNDROMIC SHORT STATURE AND OTHER CAUSES

Noonan syndrome (NS), an autosomal dominant disorder, is caused by mutations in genes associated with the RAS / mitogen-activated protein kinase (MAPK) pathway. A large series of 363 patients with Noonan' syndrome was published from India. The exons of PTPN11 gene were sequenced in all patients. Congenital cardiac anomalies (mostly right sided defects) were present in 84% of patients. The downward-slanting palpebral fissures, hypertelorism, low-set posteriorly rotated ears, short stature, pectus

excavatum, and unilateral or bilateral cryptorchidism were common clinical findings. The most common variants in this series were in exon 8 (c.922A > G, c.923A > G), observed in 22 of the affected. Thirty-two previously described pathogenic variants in eight different exons in PTPN11 gene were detected in 107 patients (20). Similar findings were reported from a study in Morocco (21). Noonan syndrome has been described in Latin America, Africa and other countries in Asia. The facial characteristics of Noonan syndrome cases worldwide were similar to those of European descent (22).

Achondroplasia is a skeletal dysplasia that is a common cause of disproportionate short stature. In a study of forty cases with disproportionate short stature from India , achondroplasia was the most common skeletal dysplasia with c. 1138 G>A, p. Gly380Arg mutation seen in all cases (23). Achondroplasia has been reported from Pakistan and Africa also (24,25).

Idiopathic short stature (ISS)refers to the short stature where all the conventional clinical and biochemical work up is normal. Genetic studies in 61 patients with ISS in India showed that four patients had a heterozygous variant in SHOX gene while two had novel, likely pathogenic variants, in the IGFALS gene (26).

Thalassemia is a frequent cause of short stature and pubertal delay. Inadequate chelation therapy and lack of awareness among treating physicians on endocrine complications lead to higher prevalence of undiagnosed endocrine issues in these children. In a study from central India, short stature (88%), delayed puberty (71.7%), hypothyroidism (16%), and diabetes mellitus (10%), were reported in children with thalassemia (88).

Puberty

Pubertal disorders can be broadly classified as delayed puberty and early (precocious puberty). Secular trends of gradual reduction in the age of puberty have started becoming apparent in tropics.

SECULAR TRENDS IN PUBERTY

The age of normal puberty has shown a decline in many tropical countries- a trend which mimics that witnessed in the developed world decades earlier. Data regarding normal puberty from Egypt suggests that in girls with BMI ≥85th percentile all pubertal stages started earlier as compare to girls with BMI less than 85th centile. No such association between BMI and pubertal stage was noticed in males (27). A decline in the age of pubertal maturation of girls in Nigeria was also reported. The median age at beginning of breast maturation (B2) and menarche were 9 and 12 years respectively. The age at menarche was significantly associated with overweight/obesity and high social class (28). Similar findings have been reported from India where a study of 2010 school girls reported that median age of thelarche and menarche was 10.8 and 12.4 years with obese girls showing a six month earlier onset of thelarche and menarche when compared to those with normal BMI (29). Similar findings were reported from Western India (30). School girls in Riyadh, Saudi Arabia also had earlier onset of puberty similar to that seen developed countries (31).

DELAYED PUBERTY

Delayed puberty is a common pubertal disorder. It may be a normal variant such as constitutional delay in growth and puberty or represent a pathology. Pathological causes are classified as hypogonadotropic or hypergonadotropic hypogonadism. In a retrospective study of 136 patients with delayed puberty from Sudan, permanent or functional hypogonadotropic hypogonadism was seen in 37.5 and 36% while hypergonadotropic hypogonadism was seen in 11.7%. Constitutional delay in growth and puberty was present in 14.7%. Type 1 diabetes and celiac disease were common

systemic illnesses (32). A study of 42 cases of delayed puberty from India (19 boys, 23 girls) underlying systemic illnesses were the dominant cause of pubertal delay in girls (11/23) while the major cause in boys were endocrinopathies (6/19). Malnutrition, chronic infections, and anemia were common systemic illnesses (33).

An unusual association of hypopituitarism along with Turner syndrome was reported in six Tunisian patients (34). A study of 11 Turner syndrome patients was reported from Cameroon, seven had monosomy while four had mosaic Turner syndrome. Most of these had presented with delayed puberty or short stature. Other clinical features were short neck, forearm carrying-angle deformity, a low hairline, and a webbed neck. Horse shoe kidney was found in two cases but none had cardiac abnormalities. The average age at diagnosis was 18.4 years indicating a delay in the diagnosis (35).

Differentiation between CDGP and hypogonadotropic hypogonadism is challenging in tropical countries. Most patients do not have regular height measurements and estimation of growth velocity in the years preceding to the presentation is often not possible. GnRH stimulation test has been employed but has limited utility because of significant overlap in the hormonal levels between the two groups. GnRHa-stimulated inhibin B (GnRH-iB) has been developed as a convenient test to differentiate between CDGP and hypogonadotropic hypogonadism. A cut-off value of 113.5 pg/ml in boys and 72.6 pg/ml in girls could predict spontaneous pubertal onset with 100% sensitivity and specificity (36).

PRECOCIOUS PUBERTY

Precocious puberty is a common pubertal disorder. It is classified as central precocious puberty (caused by premature activation of the hypothalamic-pituitary-gonadal axis) or peripheral precocious puberty (due to secretion of gonadal steroids from other causes without activation of the hypothalamic-pituitary-gonadal axis).

A retrospective analysis of 55 children (36 girls) with precocious puberty was reported from India. Central precocious puberty occurred in 62% (34 cases, out of which 19 were idiopathic) while peripheral precocious puberty was found in 14 children. The commonest cause of peripheral precocious puberty was congenital adrenal hyperplasia (46%) (37). A rare case of precocious pseudopuberty due to a virilizing adrenocortical carcinoma progressing to central precocious puberty after surgery has also been reported (38). Idiopathic precocious puberty responds well to GnRH analogue therapy as reported from a series for India (39).

There appears to be an increase in the incidence of central precocious puberty especially in girls in the COVID-19 lockdown in India as compared to the pre-lockdown period (40).

DISORDERS OF BONE AND MINERAL METABOLISM

Vitamin D deficiency and nutritional rickets are very common in tropics. Primary hyperparathyroidism and less common forms of rickets like vitamin D resistant and hypophosphatemic rickets also occur.

Vitamin D Deficiency And Nutritional Rickets

Tropical countries have high prevalence of nutritional rickets. The human body can generate vitamin D in the skin from sunlight. Although tropical countries get abundant sunlight, vitamin D deficiency (VDD) is common. Harsh summers limit sunlight exposure in many tropical countries. Adequate sunlight exposure was found in only 27 % neonates in Ethiopia (41). In some countries, atmospheric pollutions limits sunlight penetration in winters (42). Darker skin color with high melanin content, different socio-cultural factors, and genetic variation also contribute to vitamin D deficiency. Infants are at a high risk of vitamin D deficiency which could be due to low vitamin D content in breastmilk, and inadequate vitamin D content of complementary foods and maternal vitamin D

deficiency. Routine vitamin D supplementation at a dose of 400 IU per day till 12 months of age in breastfed infants has been recommended in India (43). Oral vitamin D supplementation of mothers during lactation has been shown to reduce risk of vitamin D deficiency in infants at 6 months of age by almost 95% (44). Nationwide data from India suggests that prevalence of vitamin D deficiency defined as serum 25OHD <12 ng/ml was 14% (1-4 years), 18% (5- 9 years), and 24% (10-19 years) (43). However, VDD prevalence ranging from 60-87 % has been reported in low birth weight infants and 71-88% in normal birth weight infants in Delhi, India (45) (46). In Uganda, a study found that prevalence of VDD in LBW infants was 12.1 % but most of these had received supplemental vitamin D (47). A larger study including five countries from sub-Saharan Africa, showed that prevalence of vitamin D deficiency in children aged 0-8 years was 7.8% (48). Countries closed to the Equator had less VDD. In India, a study from the state of Kerala reported a VDD prevalence of 11.1%. The reasons implicated for this relatively lower prevalence were latitude and fish intake in the diet (49). Data suggests that in several African countries nutritional rickets is common although VDD prevalence is not high. Children requiring surgical correction of deformities resulting from rickets in Malawi, Africa had lower dietary calcium intake but VDD was uncommon (50). Low dietary calcium intake has been implicated as a causative factor for rickets in Studies from Nigeria and Bangladesh (51,52). Serum alkaline phosphatase has been explored as a low-cost biochemical test to screen for nutritional rickets in children in Nigeria. A cut off of ALP > 350 U/L has been proposed in one study (53). Severe vitamin D deficiency can present as osteomalacic myopathy in children and adolescents (54).

For the treatment of rickets and vitamin D deficiency, oral cholecalciferol in a daily dosing schedule (2000 IU below 1 year of age and 3000 IU in older children) for 12 weeks has been recommended by some Indian guidelines (43). However, compliance issues are common in underprivileged populations. When compliance to daily dosing cannot be ensured, this guideline has suggested intermittent regimen provided the child is above 6 months of age. Sunlight exposure was shown to be inferior to oral vitamin supplementation (400IU/day) in preventing rickets or vitamin D deficiency in infants in India (55). A single intramuscular dose of 600,000 IU of vitamin D has shown to be safe and effective for treatment of nutritional rickets in India (56).

Primary Hyperparathyroidism

Pediatric primary hyperparathyroidism (PHPT)has been reported in two studies from India. George et al performed a retrospective analysis of 15 children and adolescents with PHPT (age <20 yr.) between 1993 and 2006. The mean age was 17.7 (range 13-20 years) with 80% of patients being female. Clinical features included bone pain, proximal myopathy, bony deformities, fractures, palpable osteitis fibrosa cystica, nephrolithiasis, and acute pancreatitis. No cases had evidence of multiple endocrine neoplasia. Nearly a third of the cases developed post-operative hungry bone syndrome occurred in 33.3%. Histology was suggestive of parathyroid adenoma in all cases (57). Sharanappa et al reported retrospective data (September 1989-August 2019) of 35 pediatric PHPT patients (< 18 years) who underwent parathyroidectomy. The mean age was 15.2±2.9 years and with male to female ratio of 1:1.9. Skeletal manifestations were seen in 83% while renal manifestations occurred in 29%. Parathyroid adenoma was present in 91.4% patients, whereas the remaining had hyperplasia. Except one patients all others had hungry bone syndrome in postoperative period (58). Adolescent PHPT can present as posterior reversible encephalopathy syndrome (59). Neonatal severe hyperparathyroidism is a rare disorder. One such case has been reported from India (60).

Other Forms Of Rickets

A case series of 36 patients with refractory rickets published from India reports that renal tubular acidosis (63%), vitamin D dependent rickets (14 %) (VDDR I in 2 and VDDR II in 3 patients), chronic renal failure (11%), hypophosphatemic rickets (6 %), and chronic liver disease (6%) were common causes (61). Pseudohypoparathyroidism may also present with bony deformities resembling rickets (62). Hereditary vitamin-D resistant rickets was reported in eight patients in Tunisia. Two mutations in vitamin D receptor gene were found: p.K45E (5 patients with alopecia) and a novel p.T415R mutation located in the ligand-binding domain.

X linked hypophosphatemic rickets is the most common cause of phosphopenic rickets. It can be caused by loss of function mutations in the PHEX gene which leads to an increase in the phosphaturic hormone fibroblast growth factor-23 (FGF-23). Two novel mutations in the PHEX gene has been reported from two families from India (63). A family suffering from XLH has been reported from Pakistan (64). Idiopathic tumoral calcinosis (ITC) refers to the deposition of calcium hydroxyapatite crystals or amorphous calcium usually in juxta-articular tissue in a tumor-like fashion. ITC has been reported in an 8-year-old child who had the symptoms at 4 years of age (65).

THYROID

Common thyroid disorders in pediatric age group include hypothyroidism, iodine deficiency disorders, thyroiditis, and thyroid cancer

Congenital Hypothyroidism

Congenital hypothyroidism can be a devastating disease if not diagnosed and treated on time. Congenital hypothyroidism is much more common in tropical countries as compared to developed world. The prevalence in India is estimated to be one in 1000-1500 births (66). The Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) has published guidelines on screening, diagnosis, and management of congenital hypothyroidism (66,67). High prevalence of CH has been reported from Sri Lanka as well as Iran (68,69). A cut off of ≥20 mIU/L for capillary TSH screening for CH beyond 24 hours of life has been proposed in the India for deciding on recalling the patient for further workup while a repeat capillary sample was advised for TSH values between 10 and 20 mIU/L (70).

Despite the above research, most tropical countries do not have universal screening for CH. This contributes to significant morbidity due to this potentially treatable condition.

Iodine Deficiency Disorder

Iodine deficiency disorders are among the top causes of thyroid disease worldwide. Several tropical countries are affected by IDD. India and Pakistan have both initiated fortification of common salt with iodine. This measure has been successful in reducing total goiter rate in children, indicating an improvement in iodine status. However, several underprivileged populations in both countries have evidence of iodine deficiency (71,72). Africa also had a high prevalence of mild to moderate iodine deficiency but several iodine fortification programs have been started which resulted in improvement in the overall iodine status. Some high risk populations such as pregnant females may still face iodine deficiency (73).

Thyroiditis

A case series of 97 children with Hashimoto's thyroiditis aged 5-12 years has been reported from India. The children were followed up for a six-month period. Goiter was seen in 89 while eight had an atrophic form. The mean age was 9.9 years and the

male to female ratio was 1:5.4. Overt hypothyroidism was present in 73.4% while hyperthyroidism was seen in 3.1%. 13.2 % were subclinical hypothyroidism and 10.3% were euthyroid. A large percentage of subclinical hypothyroid and euthyroid children developed overt hypothyroidism in the 6 month follow up. (79)

It is possible that the prevalence of autoimmune thyroiditis has increased after iodine fortification of the diet. In a case control study, 43 children with goiter and autoimmune thyroiditis were compared with 43 children with euthyroid goiter without autoimmune thyroiditis. Urinary iodine concentration (UIC) was significantly higher in children with autoimmune thyroiditis. A positive correlation between UIC and antimicrosomal antibody titers was found. A UIC ≥300 µg/L was strongly associated with autoimmune thyroiditis (80).

Hypothyroidism

Acquired hypothyroidism in most tropical countries is now predominantly autoimmune, barring those where severe iodine deficiency is still prevalent.

The control of hypothyroidism with levothyroxine therapy in children in tropical countries is often poor because of poverty, lack of proper advice, and reduced access to laboratory testing. Research work on treatment of hypothyroidism is being done. Both bedtime and early morning intake of thyroxine had equal efficacy in maintaining a normal TSH in children with hypothyroidism in a randomized controlled trial from North India (78).

Van Wyk Grumbach syndrome is a syndrome characterized by prolonged untreated hypothyroidism, short stature, and isosexual precocious puberty. This syndrome is considered to be rare with very few cases reported so far in recent times. However, many cases of Van Wyk Grumbach have been reported from tropical countries like India and Sri Lanka (74,75,76). A case series of this rare syndrome has been reported from Pakistan (77). This illustrates that availability of trained physicians as well as laboratory facilities is still a challenge in tropical countries.

Hyperthyroidism

Pediatric hyperthyroidism has been reported in the tropics. Graves' disease is the most common cause of pediatric hyperthyroidism. The factors differentiating pediatric Graves from adult disease are predominance of neuropsychiatric symptoms, gradual and often insidious onset, and absence of infiltrative ophthalmopathy.

In a seven-year period, 24 children with hyperthyroidism were reported in a study from India. Twenty of these had Graves' disease while one had toxic nodular goiter and one had neonatal Graves' disease while the remaining two were factitious. Behavioral problems, excitability, hyperkinesis, and irritability were most common symptoms. Ocular involvement was present in 85% while 30 % had cardiac involvement. Goiter was noted in 18 out of 24 cases. Carbimazole was used for treatment and remission occurred in seventeen cases (81). Neonatal thyrotoxicosis has been reported from India (82).

A case of a three and a half-year-old boy who had an autonomous functioning thyroid nodule which was cured by radioiodine ablation has been reported from India (83). Radioiodine therapy has been used for pediatric and adolescent Graves' disease. Carbimazole therapy does not appear to influence the outcome of radioiodine therapy (84). Thyroid storm precipitated by empyema thoracis has been reported in a 16 year old girl (85).

Thyroid Cancer

Thyroid cancer is not common in pediatric populations and usually occurs as papillary carcinoma (PTC). A publication from a oncology center in India reports that pediatric differentiated thyroid cancer has high rates of extrathyroidal involvement as well as lymph node and distant metastasis (86). These findings however are not unique to tropical countries as similar profile has been reported from other parts of the world. Pediatric PTC often do not have TERT promoter mutations and have a lower prevalence of BRAFV600E mutation as reported in a study from India (87). Globally, the mortality rates of pediatric PTC are similar to that of adult PTC. The data on survival in pediatric PTC from tropical countries is limited.

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