Case Report
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Management Challenges of an Infant with Multiple Endocrinopathies with Mc Cune Albright Syndrome: A Case Report

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Abstract

Introduction:

McCune Albright syndrome (MAS) is a rare genetic disorder characterized by a triad of hyperpigmentation, endocrinopathies, and fibrous dysplasia (FD), caused by post-zygotic somatic mutations. Hyperthyroidism is the second most common endocrinopathy in MAS and poses significant management challenges in infants.

Case Description:

A 7-month-old girl, born to unrelated parents, presented with vaginal bleeding, breast development, excessive sweating, rapid weight gain, and height acceleration over the past 2-3 months. She had café-au-lait spots, tachycardia, and high blood pressure. She was started on carbimazole following that developed neutropenia, needed temporary cessation of carbimazole. After short course of Lugol's iodine carbimazole restarted and thyrotoxicosis was successfully managed medically.

Conclusion:

It is a challenge managing the early onset endocrinopathies. Early-onset hyperthyroidism in MAS often needs surgical intervention by experienced surgeons. This case highlights the successful management of thyrotoxicosis in an infant with high doses of carbimazole, avoiding immediate surgery, though future surgical intervention might still be needed.

Keywords: McCune Albright syndrome (MAS)

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Introduction

McCune Albright syndrome (MAS) is a rare genetic disorder characterized by a triad of hyperpigmentation, endocrinopathies, and fibrous dysplasia, caused by postzygotic somatic mutations [1]. The disorder is caused by a mutation in the gene for the alpha subunit of the stimulatory G-protein, resulting in permanent activation of tissues that are stimulated via receptors linked to the G-protein-cAMP protein-kinase A dependent pathway [2]. The clinical picture varies extremely among affected individuals. Hyper-functioning endocrinopathies are a key feature of MAS. The most common endocrinopathy is gonadotropin-independent sex steroid production, which affects ~85% of girls with MAS [3]. Hyperthyroidism is the second most common endocrinopathy in MAS and poses significant management challenges in infants. Activation of G protein coupled GNAS in thyroid gland is responsible for thyroid gland hyperplasia. Which leads to thyroid hormone overproduction and increase conversion from T4 to T3. Clinically, this presents with hyperthyroidism, goiter, and/or thyroid nodules [4].

The management of hyperthyroidism in children typically involves one of three strategies: anti-thyroid medication (such as carbimazole), radioactive iodine ablation or thyroidectomy. Despite these established approaches, specific guidelines for managing hyperthyroidism in children with MAS are lacking [5]. While most children respond well to anti-thyroid medications, recurrence of hyperthyroidism is common once the medication is stopped. However, this case demonstrates adequate control of

thyrotoxicosis with higher doses of carbimazole in an infant, without the need for immediate surgery.

Case Presentation

A 7-month-old infant girl, born to non-consanguineous parents, presented with per vaginal bleeding. On questioning, her mother reported noting breast development for 2 months of age. She exhibited excessive sweating since birth, along with rapid weight gain and height acceleration over the past 2-3 months. Physical examination revealed extensive café-au-lait spots not crossing the midline (Figure 1), tachycardia, and elevated blood pressure. Skeletal deformities not noted at initial presentation. Head circumference was normal with open anterior fontanel, while height and weight were crossing centiles (Figure 2). There was round face without fascial plethora and a few acne lesions were noted on the face. Pubertal examination indicated stage 2 breast development without axillary or pubic hair.

Investigations confirmed gonadotrophin-independent puberty and thyrotoxicosis (Table 1), with high levels of 8 am cortisol and ACTH following overnight dexamethasone suppression test (ODST). Her estradiol was 7719.9 pmol/L with suppressed LH (<0.216U/L) and FSH (<0.66U/L). USS revealed a bulging uterus for the age, measuring 3.2*1.6*5 cm, with endometrial echo, right ovarian cyst measuring 4.1*3.8cm with thin separation, and prominent follicle in left ovary, measuring 1.7 cm. There were no supra renal masses.

Gonadotropin-independent precocious puberty was treated with the aromatase inhibitor letrozole. Hyperthyroidism was treated with carbimazole (0.75 mg/kg/day), led to neutropenia, necessitating a switch to Lugol's iodine, which successfully resolved the thyrotoxicosis and neutropenia within 10 days (Table 2). High level of ACTH and cortisol during ODST prompted the diagnosis of Cushing Disease. MRI brain and pituitary revealed a normal-sized pituitary for age (3mm) with normal contrast enhancement. Posterior pituitary bright spot was normal in position. Clivus and sphenoid bone showed minimal expansion with signal heterogenicity, suggesting the possibility of fibrous dysplasia.

Ten days after controlling the thyrotoxicosis, cortisol day curve revealed normal cortisol day profile. Carbimazole was then reintroduced at a dose of 0.75 mg/kg/day and gradually increased to 1 mg/kg/day to normalize the thyroid functions. She didn't developed neutropenia during follow up. Patient is currently showing normal development with normal thyroid function tests on a reduced dose (0.5 mg/kg/day) of carbimazole.

Figure 1: Extensive café-au-lait spots & blood-stained nappy

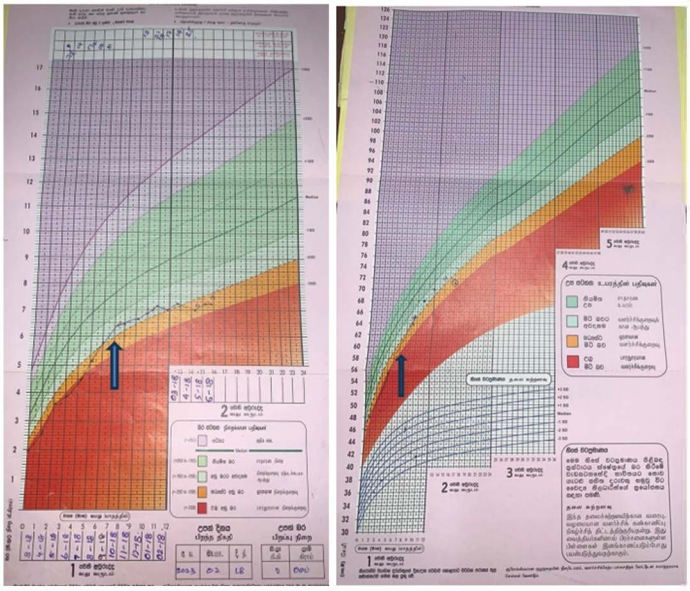

Figure 2: Height and Weight crossing the midline at presentation (Arrow), which is stabilizing during follow up

Table 1: Summary of biochemical investigations

	11/10/2023
LH (0.03-3.9)mLU/L	<0.216
FSH(0.3-5) mLU/L	<0.66
S.Testosterone(<0.69)nmol/L	0.6nmol/L
Estradiol (<92) pmol/L	7719.19
Prolactin (3.6-12)ng/mL Female Tanner stage 1	49.3
IGF 1 (8-131)ng/mL	163.1

Table 2: Timeline of thyrotoxicosis and it's management
Treatment with carbimazole (0.75 mg/kg/day) initially led to neutropenia, necessitating a switch to Lugol's iodine, which successfully resolved the thyrotoxicosis and neutropenia within 10 days.

	fT3 pg/ml (1.21 - 4.18)	fT4 pg/ml (8.9 - 17.2)	TSH mlU/L (0.3 - 4.5)	FBC 10^9/L		Treatment
13/10/2023	12.77	63.9	<0.0015	WBC	13.3	Carbimazole 5mg/ daily propranolol 3mg TDS
				Neutrophil	2.54	
				Lymphocytes	10.32	
				Hb	10.5	
20/10/2023	12.58	57.4		WBC	12.8	Stopped Carbimazole (Neutropenia)
			0.001	Neutrophil	0.67	
			0.34	Lymphocytes	11.02	Lugo's' Iodine 0.3 ml TDS
				Hb	9.5	
23/10/2023	6.79	23.64				
26/10/2023	6.8	21.74				Stopped Logo's Iodine Restarted Carbimazole 5 mg daily (0.75 mg/kg/day)
30/10/2023	5.69	19				
03/11/2023	5.443	17.5		WBC	14.4	Carbimazole 5 mg/2.5 mg (1.1 mg/kg)
				Neutrophil	5.53	
				Hb		
05/04/2024	4.95pmol/L (3.1-6.8)	13.86pmol/L (12-22)		WBC	14.92	Carbimazole 2.5 mg BD(0.7 mg/kg/day)
				Neutrophil	3.93	
				Hb	11.3	

Discussion

In this child, dermatological manifestations (café-au-lait spots), hyperthyroidism and precocious puberty, favored a direct clinical diagnosis of McCune Albright syndrome.

MAS is characterized by ligand-independent signaling through the LH, FSH, TSH, GHRH, and ACTH receptors resulting in hyper-functioning endocrinopathies. Activation of the stimulatory G protein is responsible for increased production of T3 which eventually gives rise to hyperthyroidism, which can manifest as excessive sweating, weight loss and tachycardia [4]. In this case, however, weight loss was not evident and conversely, rapid weight gain was noted, which could possibly be due to co-existing hypercortisolism, which could also explain the round face, acne and elevated blood pressure present in this child. Hyperthyroidism can lead to reduced cortisol binding globulin, leading to increased free cortisol which can possibly lead to the above clinical picture, which in this case, settled with the control of hyperthyroidism [4]. Hypercortisolism is one of the rarest and most serious complication of MAS. Transient hyper-secretion of ACTH and cortisol is also possible in the context of MAS [6]. Acute onset of pubertal features is due to the GNAS activation in ovarian tissue, resulting in recurrent estrogen-producing cysts, which was evident in the ultrasound scan of the pelvis in this child, leading to oestrogenization of uterus and breast development. Cyst resolution causes acute drop in estradiol, which triggers vaginal bleeding. In girls this is treated with the aromatase inhibitors letrozole or anastrozole. If not responding, estrogen-receptor blocker tamoxifen or selective estrogen receptor modulator fulvestrant can be tried. In boys, precocious puberty is treated with aromatase inhibitors together with spironolactone, an androgen receptor blocker [5].

Height acceleration in children with MAS can occur due to thyrotoxicosis, precocious puberty and/or growth hormone (GH) excess. In this child, IGF-1 level was high during the initial presentation and normalized during follow up. During initial presentation prolactin was high, but normalized later. Excess pituitary production of GH, ACTH and prolactin can occur in MAS. GH excess can be treated with somatostatin analogs, and prolactin excess treated with dopamine agonist [5]. Failure of medical management may require surgical interventions for the management of severe endocrinopathies.

Minority of patients with MAS develop Cushing syndrome. It has a heterogeneous natural history, ranging from spontaneous resolution to need for adrenalectomy or even death [7]. Up to 7.1% of patients with MAS will develop Cushing syndrome and may be characterized by low birth weight or failure to thrive, as well as more classic features of

cortisol excess [8]. High levels of ACTH and cortisol during ODST prompted the diagnosis of Cushing Disease in our patient which normalized with control of hyperthyroidism.

Fibrous dysplasia (FD) is characterized by replacement of the hematopoietic and adipose bone marrow with fibrous stroma. This fibrous tissue consists of a mix of mutant and wild-type (WT) bone marrow stromal cells (BMSCs) that develop an abnormal fibroblastic phenotype due to Gαs activation. The proliferation of these abnormal BMSCs result in the formation and expansion of FD lesions [8]. Fibrous dysplasia can affect any region of the craniofacial, axial, or appendicular skeleton. The condition can vary significantly, from a single, symptomless monostotic lesion found incidentally to a severe, debilitating polyostotic disease. In the latter case, it can involve nearly the entire skeleton, resulting in progressive scoliosis, facial deformities, and the potential loss of mobility, vision, and hearing [3]. Measures such as management of FGF-23 induced renal phosphate wasting, management of scoliosis and management of bone pain could be useful in the treatment of FD in MAS [5].
In this child, minimal expansion of clivus and sphenoid bone with signal heterogenicity in MRI brain and pituitary reveals possible involvement of clivus and sphenoid bones with fibrous dysplasia, and she could develop extensive fibrous dysplasia later with complications like bony deformity, compression of nerves leading to hearing and vision impairment and hypophosphatemic rickets in later life.

Early recognition and control of hyperthyroidism is crucial in preventing complications including advanced bone age and premature growth plate fusion, and rare but life-threatening conditions like arrhythmia and thyroid storm. Early-onset hyperthyroidism in MAS typically requires surgical intervention by experienced surgeons. However, our case demonstrates successful management with higher doses of carbimazole in an infant, with close observation for side effects like neutropenia, which is a life-threatening condition associated with carbimazole. This approach-controlled thyrotoxicosis without the need for immediate surgery, which is challenging in infants. Nevertheless, definitive surgical intervention may still be necessary in the future. As this is an inherent somatic gene mutation leading to endocrine hyperactivity, spontaneous remission can sometimes occur. If medical management fails, definitive surgical treatment may be needed in the future.

A multidisciplinary approach in the management of MAS is necessary as it involves multiple bodily systems and the parents need to be educated about the complex nature of the disease. Providing sufficient information about the disease to patients and families is of utmost importance for this rare condition.

Conclusion

Management of multiple endocrinopathies of MAS in an infant is challenging and needs close observation for side effects of the treatment and meticulous management for optimum control of the syndrome and prevention of complications of the syndrome involving multiple bodily systems. Shifting from currently accepted and widely used methods of treating may be needed for the individual patients, depending on their clinical outcomes.

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