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CASE REPORT

Case Report: Hyperprolactinemia and growth hormone deficiency associated with Morning Glory Syndrome; with a review of the literature [version 1; peer review: 1 approved, 1 not approved]

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V1 First published: 18 Sep 2017, 6:1702
<https://doi.org/10.12688/f1000research.12655.1>
 Latest published: 18 Sep 2017, 6:1702
<https://doi.org/10.12688/f1000research.12655.1>

Abstract

Morning Glory Syndrome (MGS) is a rare congenital malformation of the optic nerve that is caused by a failure of the closure of the choroidal embryonic fissure *in utero*. The syndrome is usually seen in association with midline cranial defects, such as transsphenoidal and basal encephaloceles. Although MGS usually presents as an isolated ocular finding, it can be associated with endocrinological abnormalities. We report a case of a 32 year old female with MGS with hyperprolactinemia and growth hormone (GH) deficiency. She was diagnosed with MGS at the age of three and her past medical history was significant for left eye blindness, hyperprolactinemia and GH deficiency. She has received GH replacement and oral contraceptive pills in the past. Our investigations revealed elevated prolactin levels (63mg/l) and borderline low GH levels. Magnetic resonance imaging revealed an abnormality involving the optic chiasm, left optic nerve and compression of the pituitary gland by a basal encephalocele. Genetic studies were positive for a mutation in Paired box 6 gene (*PAX6*). She is being currently treated with cabergoline for her hyperprolactinemia. Our aims of this report are to highlight the hormonal manifestations of MGS and to review the etiopathogenesis of this rare disorder.

Keywords

morning glory syndrome, hyperprolactinemia, growth hormone deficiency, basal encephalocele

Open Peer Review

Approval Status

	1	2
version 1
18 Sep 2017	view	view

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Any reports and responses or comments on the article can be found at the end of the article.

This article is included in the **Eye Health** gateway.

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Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Bhavsar R, Pavlovic M, Razavi A *et al.* **Case Report: Hyperprolactinemia and growth hormone deficiency associated with Morning Glory Syndrome; with a review of the literature [version 1; peer review: 1 approved, 1 not approved]** F1000Research 2017, 6:1702 <https://doi.org/10.12688/f1000research.12655.1>

First published: 18 Sep 2017, 6:1702 <https://doi.org/10.12688/f1000research.12655.1>

Introduction

Morning Glory Syndrome (MGS) was first reported in German literature in 1929, but has been more frequently reported since Kindler named it in 1970¹. The name was based on the condition's resemblance to the funnel-shaped excavation of the posterior fundus incorporating the optic nerve to a tropical morning glory flower¹. It is a rare congenital malformation of the optic nerve that is caused by a failure of the closure of the choroidal embryonic fissure *in utero*. We report a unique case of a 32 year old female with MGS with hyperprolactinemia and growth hormone (GH) deficiency. Our case highlights the various endocrinological presentations that can present concomitantly with this rare syndrome.

Case report

A 32 year old woman came to our clinic for the evaluation of amenorrhea and hyperprolactinemia. She was diagnosed with MGS at the age of 3 and at the age of 17 she was diagnosed with hyperprolactinemia and GH deficiency causing her to have a short stature (4ft 1 inch). She had no family history of similar or related issues. She was treated with GH replacement in the past, which led to an increase in her height (5ft) and she received oral contraceptives until the age of 28. Due to hyperprolactinemia and anovulatory cycles, she was treated with cabergoline. At the age of 31, she delivered a healthy baby via *in vitro* fertilization.

Her most recent physical and vital parameters were under normal limits (blood pressure: 110/70 mmHg; pulse: 72 per minute; height: five feet; weight: 126 pounds). Visual acuity to finger counting was 20/20 in the right eye and 20/200 in the left eye. She had hypertelorism and strabismus of the left eye. Laboratory investigations revealed: fasting glucose levels: 87 mg/dl (65–99); Prolactin: 62 mg/l (2–14); GH: 0.2 ng/ml (0.0–10.0); GH arginine stimulation test: <2ng/ml; Insulin-like growth factor 1: 22ng/ml (71–241); luteinizing hormone: 1.3 mIU/ml (0.0–4.0); follicle stimulating hormone: 5.0 mIU/ml (0.0–5.0); Estradiol: 8.6 pg/ml (12.5–166.0); Dehydroepiandrosterone: 323 ng/dl (31–701); adrenocorticotrophic hormone: 33.1 pg/ml (7.2–63.3); thyroid stimulating hormone: 1.48 mIU/L (0.45–4.5); free T4: 1.2 ng/dl (0.58–1.6).

Magnetic resonance imaging (MRI) performed at this time revealed an abnormality involving the optic chiasm, left optic nerve and mild compression of the pituitary gland by a basal encephalocele (BE), with a normal sized pituitary gland. Genetic studies were positive for a mutation in Paired box 6 gene (*PAX6*). She continues to receive 0.5 mg of cabergoline once daily in view of her elevated prolactin levels. Our patient does not have any other symptoms and is being followed up regularly at our clinic.

Discussion

MGS is a rare congenital malformation of the optic nerve that is caused by a failure of the closure of the choroidal embryonic fissure *in utero*. It is characterized by an enlarged, funnel shaped optic disk with a central mass of white glial tissue, surrounded by a raised pigmented chorioretinal ring. MGS usually presents as a unilateral malformation without gender predisposition with a median diagnosis of two years. The pathogenesis of MGS is relatively unknown

and studies are currently being done to understand the syndrome clearly.

MGS usually presents as an isolated ocular manifestation with decreased visual acuity, strabismus, myopia and astigmatism. The most common visual field defect is a central scotoma² and MGS is also commonly associated with midline cranial defects, such as transsphenoidal and basal encephaloceles. Transsphenoidal encephalocele or BE have been largely associated with MGS, with 67% of people with BE also having MGS³.

Cranial defects may present with wide heads, flat noses, cleft lip/palate, hypertelorism, agenesis of the corpus callosum, hypopituitarism, posterior pituitary ectopia, basal and transsphenoidal encephaloceles. BE is a herniation of tissue through the sphenoid bone or cribriform plate of the ethmoid bone⁴. BE may present as a mass in the pharynx, nasal cavity and orbits⁴. Literature suggests that the association of MGS with craniofacial abnormalities may be linked to an embryogenic effect. Kissel *et al.* theorized that defects in neural crest cells are responsible for the craniofacial malformations⁵. This is the most probable mechanism by which BE occurs, due to the failure of closure of the anterior neuropore, which normally occurs by 4 weeks *in utero*⁵. The embryological findings support the neurologic and craniofacial manifestations seen with MGS.

Hormonal dysfunctions are seen with approximately 50–60% of BE patients. GH deficiency (66.7%), hypogonadotropic hypogonadism, hypothyroidism, hyperprolactinemia (13.3%) and diabetes insipidus are the most common hormonal disorders reported³. Eustis *et al.* postulated that the dysplastic optic discs in association with endocrine abnormalities are products of reduced trophic stimulation of the pituitary gland caused by abnormal hypothalamic control or an abnormal portal hypophyseal system⁶. Table 1 lists several cases of MGS associated with endocrinopathies that have been reported in literature.

Studies by Asakura *et al.* suggest that MGS may be associated with a heterozygous Prokineticin receptor 2 (*PROKR2*) gene mutation⁷. The *PROKR2* pathway plays a vital role in early pituitary development and the development of gonadotropin releasing hormone neurons. This could possibly explain the pituitary malformation and the hormonal imbalance seen in our case report. Hormonal disorders are common in patients with BE induced MGS, possibly due to malformed cranial structures, which exert pressure on the pituitary gland causing gland compression, thereby restricting production of hormones, such as GH and prolactin at healthy rates.

Genetic studies performed on our patient revealed a mutation in the *PAX6* gene. *PAX6* gene mutations are commonly implicated in congenital ocular malformations. *PAX6* gene is responsible for activating genes involved in the formation of the eyes, brain, spinal cord, and pancreas during embryonic development⁸. As far as MGS is concerned, the *PAX6* protein is an excellent resource to study in patients, as it is responsible for ocular embryogenesis and regulating the expression of other genes involved in the other structures of the eye.

Table 1. Cases of Morning. Glory Syndrome associated with different endocrinopathies that have been reported in the literature. Abbreviations: M: Male, F: Female, ADH: Anti-Diuretic Hormone, GH: Growth Hormone, TSH: Thyroid Stimulating Hormone, PRL: Prolactin, LH: Luteinizing Hormone, NP: Not Performed.

Author, year	Age (year)	Sex	Endocrine abnormalities		Optic abnormalities	Reference
			First exam	Follow up		
Pollock JA, 1968	21m	M	ADH	NP	+	9
Pollock JA, 1968	12	M	GH, TSH (10)	GH, TSH PRL (12)	+	9
Pollock JA, 1968	20	F	GH, ADH, gonadotropin (20)	NP	+	9
Pollock JA, 1968	48	M	ADH(8)	ADH, TSH (48)	+	9
Wiese GM <i>et al</i> , 1972	28	M	GH, gonadotropin (20)	GH gonadotropin, PRL (28)	-	10
Manelfe C <i>et al</i> , 1968	57	M	TSH (57)	NP	+	11
Larsen JL <i>et al</i> , 1979	16	F	GH, ADH (16)	NP	-	12
Ellyin F <i>et al</i> , 1982	12	M	GH, PRL ↑ (12)	NP	-	13
Ellyin F <i>et al</i> , 1982	16	F	PRL ↑	NP	-	13
Nishi Y <i>et al</i> , 1982	12	M	GH (9)	GH, ADH, gonadotropin (12)	+	14
Takezawa N <i>et al</i> , 1986	7	M	GH (4)	GH (4)	+	15
Durham <i>et al</i> , 1988	33	M	Gonadotropin, cortisol (18)	Gonadotropin, cortisol, TSH, ADH (33)	+	16
Rice JF <i>et al</i> , 1989	15	F	GH, gonadotropin (15)	NP	-	17
Kobayashi <i>et al</i> , 1990	6	M	GH (3)	GH (6)	+	18
Morioka <i>et al</i> , 1995	11	F	GH, ADH (9)	GH, ADH, gonadotropin, PRL (11)	+	19
Eustis <i>et al</i> , 1994	4 months	F	NP	GH, TSH	+	6
Eustis <i>et al</i> , 1994	3 months	M	NP	GH, gonadotropin	+	6
Present case	17	F	GH,PRL	GH,PRL,LH		

MGS is a complex disease, but can be diagnosed best through a fundus examination and radiological studies, such as CT scans and cranial MRI scans. The white glial tissue mass in the malformation causes the pupil to look a whitish-color (leukokoria), which is a classic and telling symptom. The diagnostic measures should be accompanied by a complete physical and ophthalmological examination and appropriate laboratory investigations to rule out hormonal dysfunction.

There are still under 100 cases of MGS reported worldwide. It is still a very rare medical anomaly that has not been greatly researched until more recent decades. Treatments are directed towards preventing and treating possible existing complications associated with the syndrome such as hormone replacement for hormonal imbalance and suitable correction lenses for myopia and astigmatism.

Conclusion

Our case aims to highlight the endocrinological manifestations of MGS. Although the association of MGS with pituitary hormonal imbalance is relatively well known, the diagnosis was

established much later in our case. Early recognition of these features through physical examination and lab investigations should prompt appropriate intervention.

Consent statement

Written informed consent was obtained from the patient for the publication of the patient's details.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

Acknowledgements

Our team presented this case as an abstract (#1349) at the American Association of Clinical Endocrinologists meeting in 2014. The considerable interest received regarding the case promoted the authors to write this article.

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Current Peer Review Status:

Version 1

Reviewer Report 03 January 2018

<https://doi.org/10.5256/f1000research.13701.r27942>

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Pamela Garcia-Filion

The Vision Center at Children's Hospital Los Angeles, Los Angeles, CA, USA

1. Is the background of the case's history and progression described in sufficient detail?
Partly

Comment: The background fails to describe the ophthalmic diagnostic characteristics of Morning Glory Syndrome.

2. Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?
No

Comment: Case describes only a patient with decreased visual acuity, and nothing specific to Morning Glory. Authors don't provide information about the clinical eye exam to establish the 3 defining clinical features: i.e., enlarged disc, chorioretinal pigmentary changes around the optic disc, a glial tuft overlying the disc. Decreased visual acuity is insufficient to establish diagnosis. There is no ophthalmoscopic findings, no funduscopy findings. The MR findings don't match those of Morning Glory. Additionally, the MR details don't mention whether the scan involved orbital cuts.

3. Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?
Yes

Comment: The discussion is the best part of the case report. The relevance is questionable since the case is unlikely to be Morning Glory Syndrome.

4. Is the case presented with sufficient detail to be useful for other practitioners?

No

Commentary: Detail is insufficient and this case absolutely shouldn't be available to clinicians.

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

No

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

No

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 10 October 2017

<https://doi.org/10.5256/f1000research.13701.r26768>

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Thiago Gonçalves dos Santos Martins

Departamento de Oftalmologia, Universidade Federal de São Paulo, São Paulo, Brazil

The background of the case's history and progression is described in sufficient detail. The case is presented with sufficient detail

The authors should consider a differential diagnosis. The coloboma of optic disk, which is a differential diagnosis, is characterized as excavation, normally in inferior part, without glial tissue typically present in Morning Glory syndrome. Coloboma of the optic nerve is a [congenital anomaly](#) of the [optic disc](#) in which there is a defect of the inferior aspect of the optic nerve. The issue stems from incomplete closure of the embryonic fissure while in utero. A varying amount of glial tissue typically fills the defect, manifests as a white mass. Although both optic nerve colobomas and [morning glory disc anomaly](#) (MGDA) involve mutations of the PAX6 gene, these two separate

diseases represent two distinct causes. An optic nerve coloboma is easily differentiated from morning glory anomaly. Colobomas affect only the inferior aspect of the nerve as it represents an incomplete closure of the embryonic fissure, whereas MGDA encompasses all aspects of the nerve and represents more generally a **dysgenesis** of the mesoderm.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Ophthalmology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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