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Microphthalmia with Linear Skin Defects (MLS) Syndrome: A Rare Condition Case Report and Review

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ABSTRACT

The Microphthalmia with Linear Skin Defects (MLS) syndrome, also known as Microphthalmia, Dermal Aplasia and Sclerocornea (MIDAS) syndrome is a rare genetic neurodevelopmental condition that is presented in females at birth. We describe a case of a newborn daughter of a healthy non-consanguinous couple with ophthalmological, neurological, dermatological and cardiological findings that suggested the condition, which was genetically proved by her DNA analysis.

KEYWORDS: *Michophthalmia, Skin defectcs, Sclerocornea, Genetics*

INTRODUCTION

Microphthalmia with Linear Skin Defects (MLS) syndrome, also named as Microphthalmia, Dermal Aplasia and Sclerocornea (MIDAS) syndrome is an extremely rare genetic entity presented with unilateral or bilateral microphthalmia and/or anophthalmia and linear skin defects. These skin variations normally involve the face and neck, are present at the childbirth and improve with age, leaving hyperpigmented streaks. Alteration in other organs can happen, which gives the importance of general health examination at birth.

CASE REPORT

We describe the case of a newborn girl, first child of a non-consanguineous healthy couple (32 year-old mother and 34-year old father). During pregnancy, her mother was treated for hypertension with oral Methyldopa, hypothyroidism with oral Levothyroxine and a urinary tract infection with a course of Nitrofurantoin.

She was born at 35 weeks and 5 days via caesarean section, as the rupture of the membranes three days prior did not progress to vaginal delivery. At birth, she presented with an Apgar Index of 9/10 and weighing 2.100kg.

On examination, she was diagnosed with low cervical limited dorsal myeloschisis (abnormality of corpus callosum), hypertrophic cardiomyopathy, suspected Peters anomaly in the right eye, left microphthalmia, linear pigmentary anomaly of skin following Blaschko lines in the face and suspected Incontinentia Pigmenti.

Skin Findings

Linear hyperpigmentation following Blaschko lines were present on her face (Figure 1).

Figure 1. Blaschko lines in the face

Ocular Findings

At one day old, Retcam (Clarity Medical System) and wide angular lens imaging of her right eye showed corneal opacification secondary to leucoma with only a small central area of transparency, but with apparent normal diameter. The corneal opacity prevented intraocular examination (Figure 2).

On left eye examination, there was narrowing of the interpalpebral fissure and severe microphthalmia with corneal opacity (Figure 3).

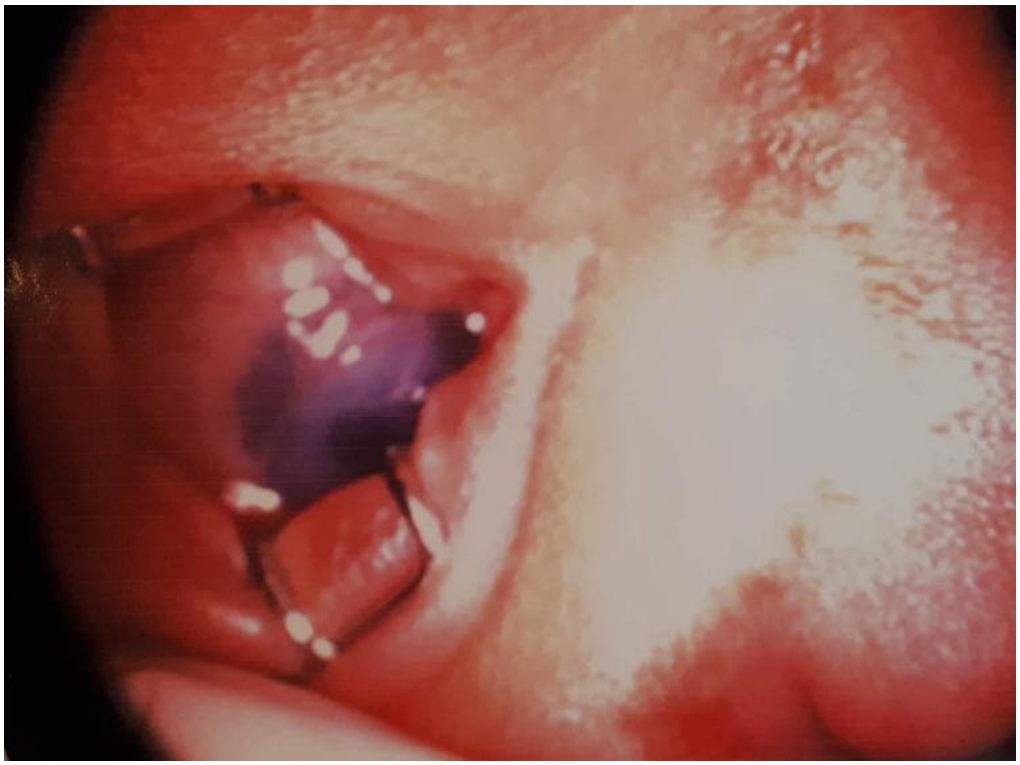

Figure 2. Right eye corneal leucoma

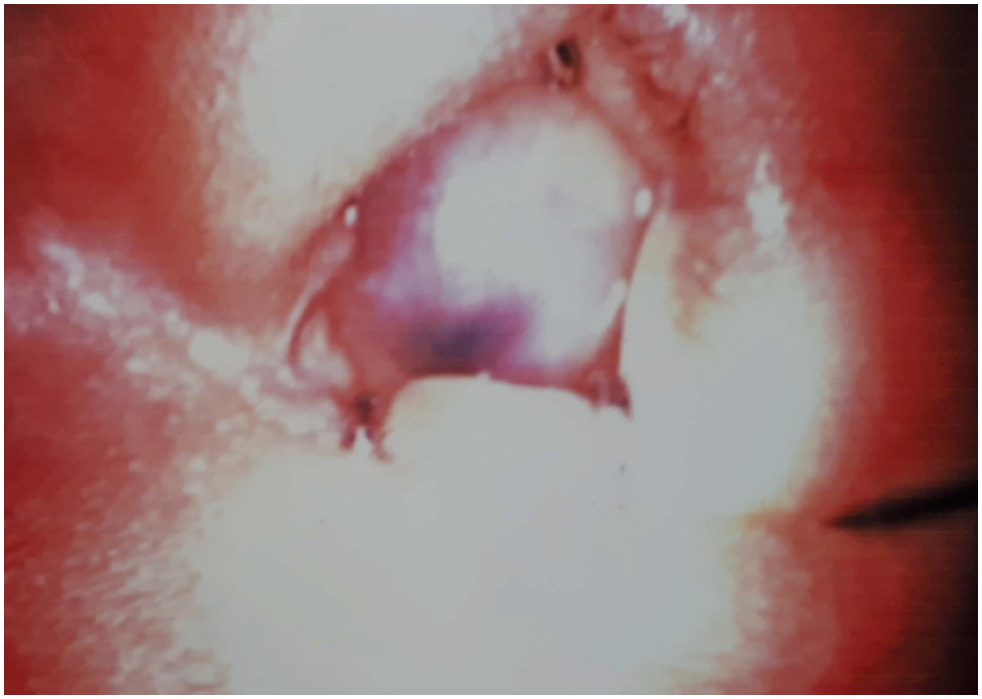

Figure 3. Left microphthalmia

At three days old, ultrasound of the right eye showed preserved anteroposterior diameter, correctly placed crystalline lens, well-formed and anechoic vitreal chamber and flat retina (Figure 4a).

Ultrasound of the left eye showed significant microphthalmia, formed vitreal chamber and a flat retina (Figure 4b).

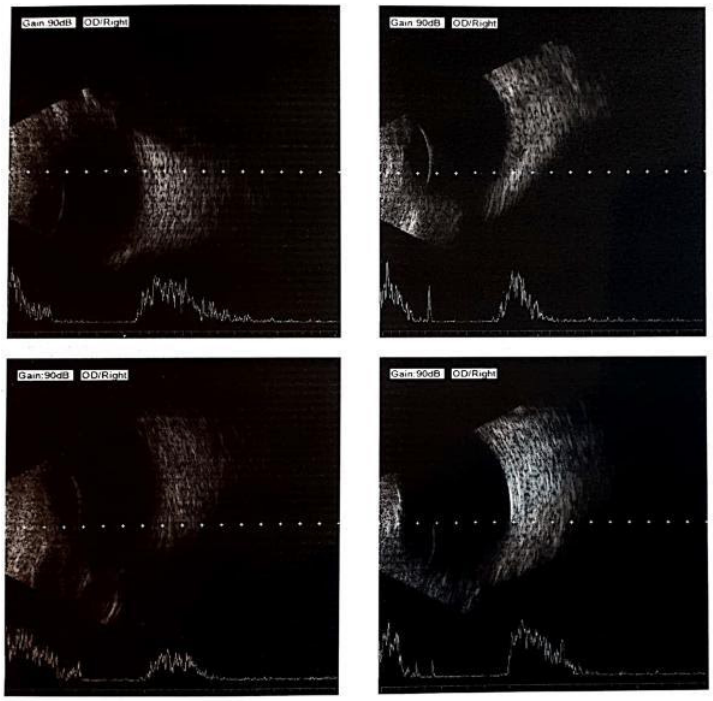

Figure 4a. Right eye ultrasound.

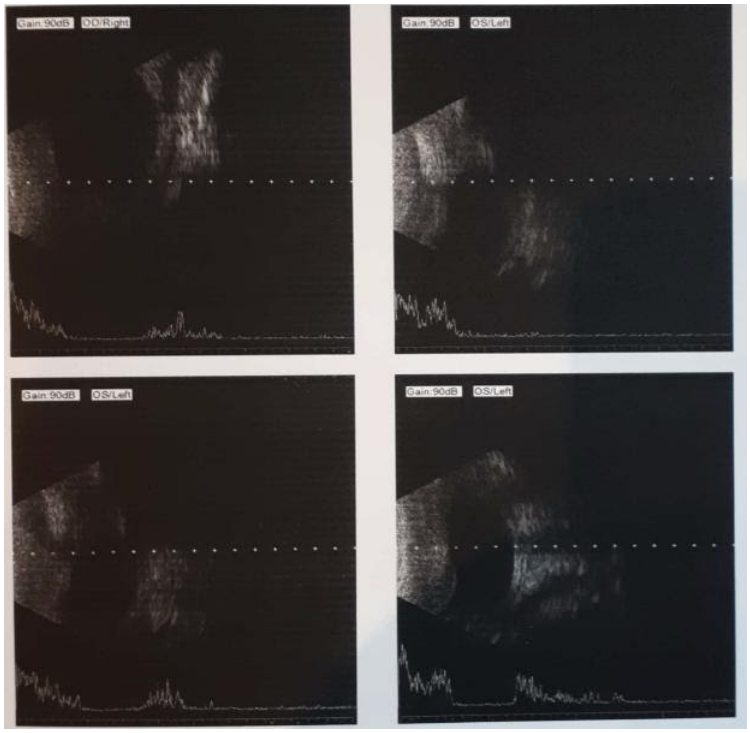

Figure 4b. Left eye ultrasound.

At seventeen days after birth, the right eye biomicroscopy showed corneal opacification, less dense in periphery through which a shallow anterior chamber, increased iris vascularisation and signs of cataract were seen. Furthermore, mild thinning of the cornea was suspected.

On the left eye, its biomicroscopy showed significant microphthalmia with corneal diameter less than 5mm and corneal opacity.

At four months and twenty-five days after birth, biomicroscopic ultrasound of the right eye demonstrated: (Figure 5a)

1. Generalized corneal hyper-reflectivity, central and paracentral corneal posterior face defect, with temporal paracentral superior decreased thickness (360 micra).
2. Anterior chamber depth shallow compared to normal for age;
3. Angular closure between 10/11 and 1/2 o'clock, compatible with iridocorneal angle malformation;

4. Iridocorneal adhesion at the posterior corneal defect in all meridians, except at 9 o'clock;
5. Phakic, correctly located crystalline lens, with localized anterior and paracentral hyper-reflectivity and thin corneal- lenticular adhesion membrane.

The left eye biomicroscopic ultrasound (Figure 5b) showed corneal generalized hyper-reflectivity, with central thickness of 410 micra, approximately, area of irido-corneal adhesion superiorly. The image attenuation did not allow identifying the lens.

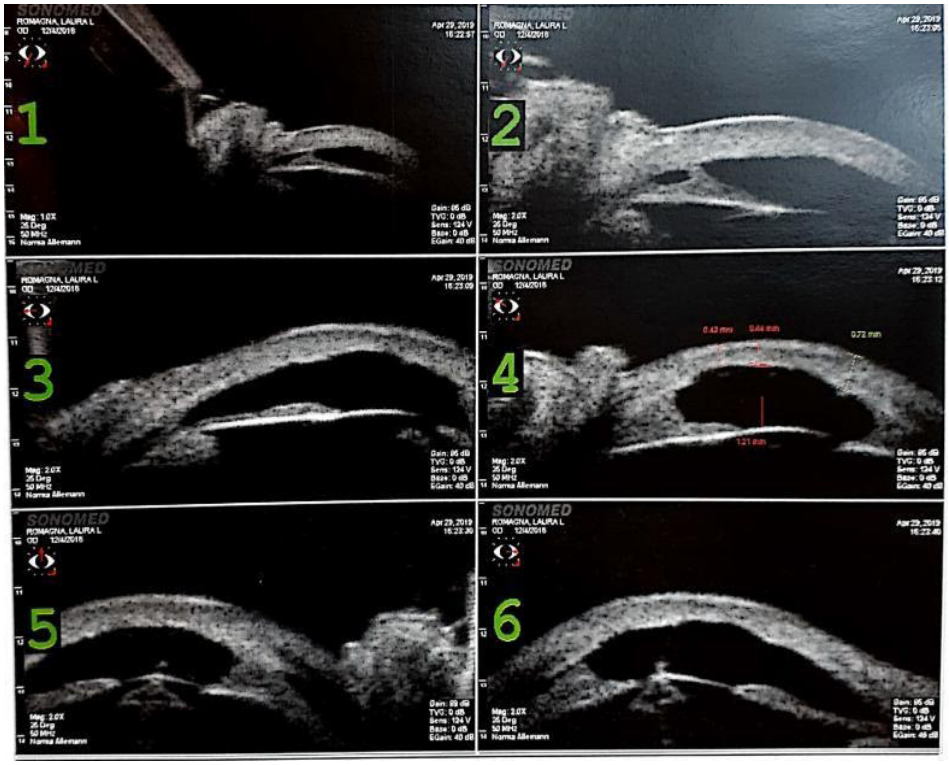

Figure 5a. Right Biomicroscopic Ultrasound

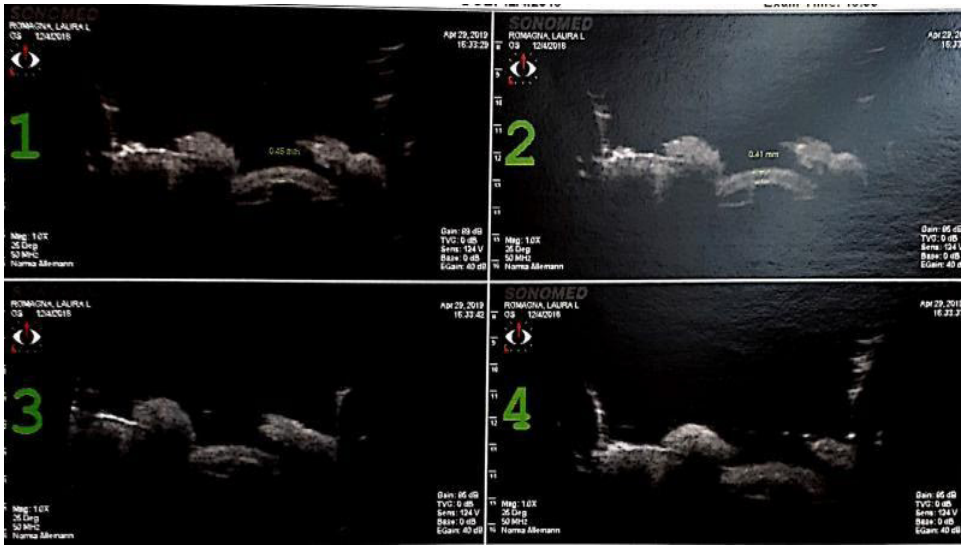

Figure 5b. Left Biomicroscopic Ultrasound

She was reviewed by an ophthalmologist at eight months old.

On the right eye examination, there was a corneal clouding in the centre and the intraocular pressure measured 20mmHg using the 'iCare' tonometer. A good right red reflex could be seen on dilated pupil examination and daily pupil dilation with Tropicamide was advised with the option of surgical optical iridectomy to try and enhance the vision through the peripheral cornea.

The left eye was microphthalmic and a referral for consideration of prosthesis was recommended to encourage socket development in light of the degree of microphthalmia (Figure 6).

Figure 6. Right eye corneal opacity and left microphthalmia.

Neurological Findings

Neurological report (no date) showed that the child was born with limited dorsal myeloschisis (LDM) in the cervical region, which originates from undisfjointed neural and cutaneous ectoderms during neurulation, causing spinal cord tethering.

Neurological examination was normal. In the posterior cervical region, a bulging of the skin could be seen and was caused by the malformation of the nervous tissue. The magnetic resonance imaging (MRI) scan showed the LDM tethering the cervical spinal cord and the proposed treatment was surgery.

A cervical laminotomy was at seven months of age and the fibroneural stalk causing tethering on the dorsal spinal cord was resected and the spinal cord anchorage was released. The dura mater was sutured to prevent cerebrospinal leakage. The glioneural tissue under the skin was also removed.

Cardiac Findings

Cardiac report at 9 months of age was diagnostic of hypertrophic cardiomyopathy with moderate degree at the moment and mild left ventricle dysfunction (Ejection Fraction 56%). There were no signs of left ventricular outflow tract obstruction or heart failure.

Cytogenetics

DNA analysis showed a heterozygous nonsense mutation Holocytochrome C Synthase (HCCS) gene, c.789G>A p.(TRP263*). The HCCS nonsense variant was not detected in her parents. (here we need to talk about the literature and mutations in existing literature)

The test methodology used was "Trio exome sequence analysis of the coding region and conserved splice sites of 23,244 genes by next generation sequencing (Twist Core Human Exome/Illumina NextSeq). Copy Number Variations (CNVs) can be detected but this assay does not detect balanced rearrangements and cannot exclude the presence of a CNV. The sensitivity for detecting small variants (SNVs and indels) is 99% at a read depth of ≥ 20, although a mosaic variant allele may not be detected." The analysis does not exclude the possibility of a disorder inherited from a mildly affected mosaic or non-penetrant heterozygous parent.

REVIEW OF THE SYNDROME

Microphthalmia with Linear Skin (MLS) syndrome, also known as Microphthalmia, Dermal Aplasia and Sclerocornea (MIDAS) syndrome, a term created by Happle at al (1993) to describe a rare genetic neurodevelopmental condition presented at birth in females. It was first described by al-Gazali et al (1990), and was initially known as Gazali-Temple syndrome.[1]

MLS syndrome is characterized by unilateral or bilateral microphthalmia and/or anophthalmia and linear skin defects, usually involving the face and neck. Acute weeping linear lesions are present at birth and improve with age, leaving hyperpigmented streaks. The cutaneous findings typically follow the lines of Blaschko corresponding to cell migration pathways evident during embryonic and fetal skin development, which (unlike dermatomes) do not correspond to innervation patterns. The restriction to the head and neck is thought to result from involvement of neural crest cells.[2]

Other ocular abnormalities may include orbital cysts, eyelid fissures, corneal anomalies (microcornea, corneal leukoma, sclerocornea), anterior chamber anomalies (iridocorneal adhesion (Peter's anomaly), aniridia, congenital glaucoma with total/ peripheral anterior synechiae), cataracts, a remnant of the anterior hyaloid artery, vitreous opacity, hypopigmented areas of the retinal pigment epithelium. [2]

Clinical examination may also reveal a central nervous system involvement, for example, structural anomalies, developmental delay and infantile seizures; cardiac distresses, including hypertrophic or oncocytic cardiomyopathy, atrial or ventricular septal defects and arrhythmias; short stature; diaphragmatic hernia; nail dystrophy; hearing impairment and genitourinary malformations.[2]

The underlying defect in MIDAS syndrome is due to a deletion at Xp22.3. The disease is believed to be transmitted as an X-linked dominant trait that is lethal in the male hemizygous state. The few reported cases of males with MIDAS syndrome had 46,XX karyotypes with a deletion of the Xp22.3 region due to an X/Y translocation. Although these patients were genotypically female, they were phenotypically male. One case was reported of identical twin boys demonstrating

identical genetic deletions at the Xp22.3 locus with different phenotypical features.[3] Women who are affected or have MIDAS syndrome-associated pathogenic variant have a 50% chance of passing the genetic alteration to each offspring.[3] Familial example has been described, with both mother and daughter having an identical terminal deletion of X, with the break point at Xp22.2. This case documented that the abnormalities in the child were more severe than those described previously, causing death of the infant, whereas the mother had minimal manifestations.[4]

The diagnosis of MLS is established when two major criteria (microphthalmia and/or anophthalmia and linear skin defects) are present and confirmed by identification of a pathogenic variant in COX7B, HCCS, or NDUFB11.[2]

MLS syndrome is likely to be diagnosed by chromosome microarray (CMA), which is the best first test when multiple congenital abnormalities are present. If CMA is not diagnostic, additional genomic testing is indicated, such as exome sequencing or genome sequencing.[2]

To establish the extent of disease and needs in an individual diagnosed with MLS syndrome, the following evaluations are recommended:

- Ophthalmologic examination
- Dermatologic evaluation for skin lesions
- Brain MRI for corpus callosum dysgenesis and other neurologic abnormalities
- Developmental assessment, with further evaluation if significant delays are identified
- Cardiac evaluation
- Hearing evaluation
- Consideration of abdominal MRI and standard protocols for management of diaphragmatic hernia
- Consultation with a clinical geneticist and/or genetic counselor

Treatment plan should be individually aimed at presenting symptoms and clinical findings and may include the following:

- Oculoplastics input: use of a prosthesis in severe microphthalmia and anophthalmia
- Dermatologist: regular care for individuals with significant skin lesions
- Paediatric neurologist: evaluation and treatment of microcephaly, seizures, and/or other neurologic abnormalities if present
- Appropriate developmental therapies and special education as indicated for developmental delay and intellectual disability
- Cardiology: standard care for cardiac concerns and other malformations, when present.[2]

The differential diagnosis of MLS includes the syndromes of IP and Goltz which are both multisystem disorders affecting structures of ectodermal and mesodermal origin; other differentials are oculocerebrocutaneous syndrome and Aicardi syndrome.

Symptoms of IP (incontinentia pigmenti) include bullae, present at birth or soon after, to verrucous eruptions and later hyperpigmented whorls. The abnormal eye findings usually involve the posterior chamber and resemble chorioretinitis or retrolental fibroplasia. Anterior chamber anomalies are rare in this condition. Other systemic features are cleft lip and palate, alopecia, syndactyly, 0% CNS abnormalities, seizures, MR, hydrocephalus.[5]

Goltz syndrome (focal dermal hypoplasia) often presents with linear areas of dermal hypoplasia, which may be associated with areas of fat herniation and abnormal pigmentation. Ocular signs include anterior chamber defects, microphthalmia, coloboma of iris. Patients may also present with diaphragmatic hernia, exomphalos, syndactyly/ oligodactyly, angiofibromata. Occasionally there is mental retardation.[5]

Oculocerebrocutaneous syndrome (OCCS) is described with focal skin defects, anophthalmia/ microphthalmia. Other features include brain malformation, psychomotor impairment and episodes of seizures. It is more prevalently observed in males.[2]

In Aicardi syndrome, there is agenesis of the corpus callosum and distinctive chorioretinal lacunae. Infantile spasms, microphthalmia, pigmentary lesions of the skin are often observed.[2]

CONCLUSION

MLS syndrome is a very rare condition that can be present with different phenotypes. With the advance of the new genetic technologies, rare conditions are being recognized and diagnosed in a better time manner, which can add information to the treatment plan, that should be individually aimed at presenting symptoms and clinical findings.

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Dr. Rodolfo Alves Paulo de Souza did the ocular ultrasound at three days old, which is demonstrated at Figures 4a and 4b.

The ophthalmologic examination when the patient was seventeen days old was completed by Dr. Cassiano Rodrigues Isaac.

Dr. Norma Allemann performed the four months and twenty-five days after birth biomicroscopic ultrasound of the eyes and Figures 5a and Figures 5b.

Mr John L. Brookes preformed ophthalmological examination when she was eight months old.

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The cardiac findings were described by Dr. Mauricio Jaramillo Hincapie

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