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CASE REPORT

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Pai syndrome: From the womb until 19 months of age, a neurological development success story

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Abstract

A prenatal and postnatal follow-up of a child with Pai syndrome, especially till toddler age, allows a better understanding of the evolution of this syndrome. This offers insight on possible outcomes especially in what concerns the neurodevelopment.

KEYWORDS

corpus callosum, prenatal diagnosis, syndrome, ultrasound

Nasal polyps, pericallosal lipoma, and corpus callosum hypoplasia are known pathologies but have rarely been observed as a combination in a single patient being visualized pre- and postnatally.[1] One of the syndromes addressing such pathologies is Pai syndrome. This latter was originally described as the association of a midline cleft lip, midline facial polyps, and lipoma of the central nervous system. However, only a few patients present the full triad, and most exhibit a wide spectrum of phenotypic variability.[2] In 1987, Dr G.S. Pai and his colleagues, a group of pediatricians and radiologists, offered a postnatal description for what will be known as Pai syndrome in the American Journal of Medical Genetics. They actually reported the case of a newborn with an unusual combination of three rare developmental anomalies: complete median cleft lip, cutaneous polyps, and midline lipomas of the central nervous system.[3] We present the case of a patient with prenatally diagnosed Pai syndrome and the postpartum fetal follow-up.

Our patient was a healthy 26-year-old lady, G1P0 with a spontaneous pregnancy and a healthy non-consanguineous partner. She was addressed after her 2nd trimester morphological scan to the center of prenatal diagnosis at the René Dubos Hospital (RDH) for an unusual morphology of the face.

A morphological ultrasound was performed at 22 weeks and 6 days by one of our referral maternal-fetal specialists that described a mobile non-vascularized polypoid structure of 8 × 7 mm at the level of the left nostril and an arched corpus callosum of 21.7 mm. A follow-up ultrasound at 27 weeks and 6 days showed the polypoid structure with no sign of jeopardized flow or obstructed choanae. The corpus callosum was measured at 28.3 mm (3rd percentile Achiron), and an associated curvilinear image evoking a lipoma was seen (Figures 1 and 2). Explanations were given to the patient, and she opted for an amniocentesis. It was performed at 28 weeks and 2 days showing a karyotype of 46, XY, a negative CMV PCR and a normal CGH array.

A fetal MRI at 32 weeks showed a nodular structure in the left nasal fossa, a corpus callosum at the inferior limit of the normal with an associated hyperintense signal on T1 over the anterior 2/3rd of the corpus callosum which was compatible with a pericallosal lipoma. The association between the findings was suggestive of Pai syndrome.

At 34 weeks, a suspicion of a secondary cleft palate of 7.4 × 7.4 mm was evoked.

The patient had a premature rupture of membranes at 37 weeks and 1 day leading to a normal vaginal delivery of a baby boy of 2854 g, 48 cm. The pediatric examination at birth confirmed the presence of the previously diagnosed nasal polyp; however, no cleft palate was found. The pericallosal lipoma was later confirmed on imaging.

A transfontanellar ultrasound at day 5 of life documented the presence of the pericallosal lipoma covering the anterior 3/4th of the corpus callosum.

The prenatally diagnosed polyp was resected on day 6 of life after being ligated 48 h earlier. On day 8 of life, an ophthalmologic examination was performed and facing doubts on a left eye abnormality, a specialized consultation at Rothschild institution in Paris was organized. The examination showed an ascended left pupil with posterior synechiae and lens opacities as well as an abnormal fundal examination. Hence, congenital left eye glaucoma was diagnosed necessitating surgery and ablation of the lens and iris that were replaced by an implant.

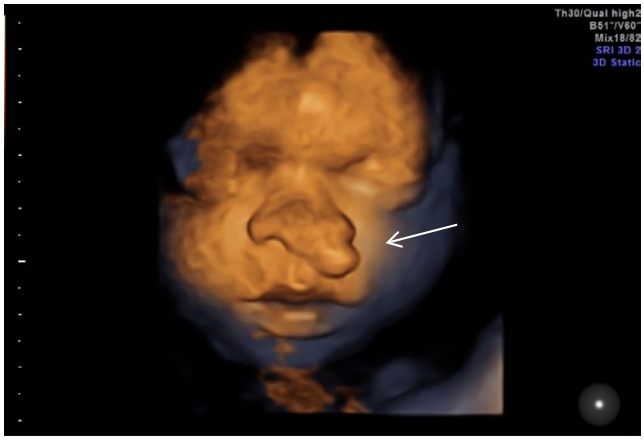

FIGURE 1 Prenatal 3D ultrasound showing the nasal polyp (arrow)

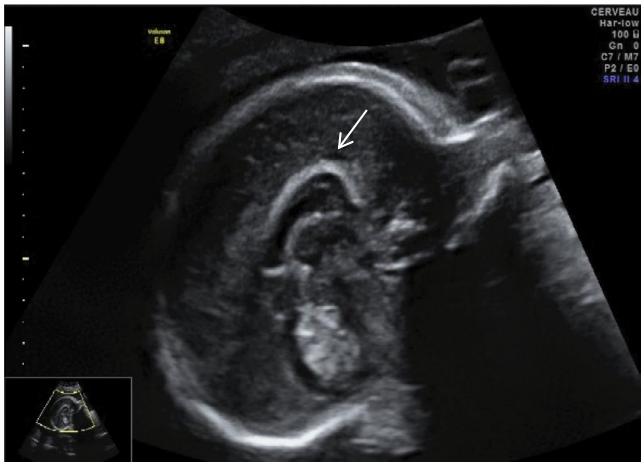

FIGURE 2 Prenatal ultrasound showing the pericallosal lipoma (arrow)

An MRI was performed at 3 months of age showing the persistence of the pericallosal lipoma without any other associated abnormality (Figure 3). Ever since, the baby has had a regular neuropediatric follow-up that has been normal. He has an adequate acquisition of neurodevelopmental milestones such as standing and walking without assistance and babbling words, despite some described temper abnormalities reported by the mother. Today, he is 19 months old and is still followed closely by a multidisciplinary team with no ENT (Ear/Nose/throat) or neurological deficits. In what concerns his ophthalmologic follow-up, he has been prescribed adapted glasses and the necessity of a left eye patch has been recommended.

Till this day, there has been no consensus regarding the diagnostic criteria of Pai syndrome. In a recent attempt to propose a diagnostic strategy for Pai syndrome, Morice et al. presented in their work published in 2018, a flowchart of new criteria. Accordingly, the diagnosis of Pai syndrome necessitated (1) a congenital nasal or mediofrontal skin mass and/or a mid-anterior alveolar process polyp (regardless of the pathological diagnosis, that is, hamartoma, dermoid cyst, and/or lipoma) as an obligatory criterion, and at least one of the following criteria: (2) midline cleft of the upper lip and/or midline alveolar cleft and/or (3) a pericallosal lipoma or interhemispheric lipoma in the case of corpus callosum dysgenesis.[2]

Regarding etiology, several hypotheses behind the genetic background have been made; however, there are not enough data yet to elucidate this point.[4] In the literature, a family with five generations affected by midline cleft lips and nasal dermoids was described, possibly supporting the autosomal dominant inheritance pattern theory.[4] Pai syndrome has also been hypothesized to have an X-linked recessive inheritance.[4] A 'de novo' reciprocal translocation 46,X,t(X;16)

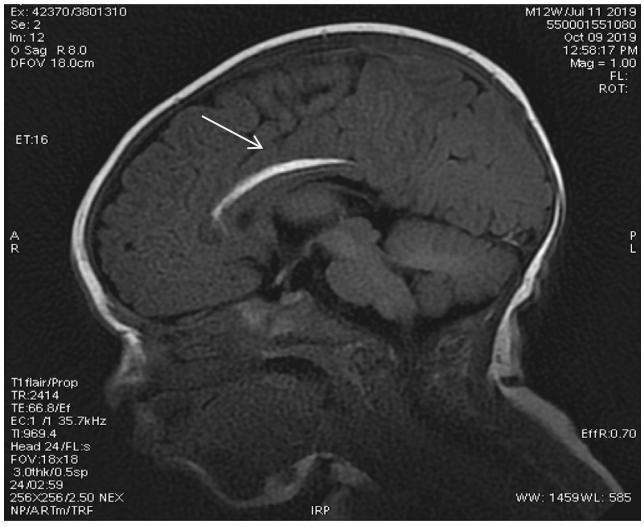

FIGURE 3 Postnatal fetal MRI showing the pericallosal lipoma (arrow)

(q28,q11.2) hypothesized to be candidate regions for median cleft of the upper lip and pedunculated facial skin masses was reported in a 13-year-old Japanese girl with clinical features of Pai syndrome.[4] This latter finding overlaps with frontonasal dysplasia (FND), as it is often observed in Pai syndrome. Also, when chromosomal analysis was performed, it has been shown to be normal in some previous case reports of Pai syndrome; however, in patients with additional features, chromosomal abnormalities might be present.[4] In fact, cytogenetic studies might have a role in evaluating patients with the characteristics attributed to Pai syndrome, ours included, which would definitely add more insight into the pathogenesis of this pathology.

We presented a case of Pai syndrome with a pericallosal lipoma and nasal polyp without the association of a midline cleft.

In fact, CNS lipomas are rare and account for less than 0.4% of all CNS masses.[5] One of the accepted etiological hypotheses is the persistence of primitive meninges into mature adipose tissue.[6] Patients with CNS lipomas usually present with seizures, but those with Pai syndrome or frontonasal dysplasia associated with CNS lipomas do not.[7] The authors suggest that isolated CNS lipomas have a different embryological origin compared with those occurring in association with midfacial clefting; this is a 'positive prognostic factor' regarding seizure occurrence and overall clinical behavior.[7] Our case being a validating example of this suggestion.

As for mental development, cognitive functions in the Pai syndrome have not been fully understood because a short follow-up period is not enough to notice the cognitive disabilities that might occur with one case report of ADHD at the age of 8 years having been documented in 2018.[8] The features related to the suspicious temper of our toddler might or not be a consequence of the Pai syndrome, and such conclusions will not be valid until further follow-up with time.

On the other hand, our newborn was diagnosed with a left eye glaucoma with the previously mentioned description of an ascended pupil, posterior synechiae, and lens opacities. In a literature review conducted in 2017 by the journal of ophthalmic genetics, the search yielded 32 case reports of diagnosed Pai syndrome. However, only 17 of these cases fulfilled the classic clinical triad consisting of midline orofacial cleft, cutaneous facial polyp, and pericallosal lipoma.[9] Furthermore, only nine of these case discussions described ocular manifestations of the disease, including hypopigmented fundi, peripapillary pigmentation, hypopigmented macula, hypertelorism, epicanthus, persistent pupillary membrane, conjunctival lipoma, and mesodermal dysgenesis of the anterior segment of the eye.[8–10] In the extensive literature review we had conducted writing this article, no association of Pai syndrome with glaucoma was reported. This might be a coincidence of incidence; however, it could also be regarded as an ocular manifestation within the vast spectrum of ophthalmological pathologies associated with this syndrome.

Pai syndrome remains a condition that needs an improved awareness, which could help in diagnosing the condition and performing the necessary investigations. This diagnosis should be generally easy when the awareness toward its typical features becomes a prerequisite to diagnostic ultrasound performers.

A long-term follow-up of the babies born with this syndrome is highly essential to draw conclusions regarding its multisystem prognosis, especially when mild cases with positive prospects like ours do exist and present a hopeful outlook to expecting couples. Lastly, the efforts of a multidisciplinary approach to the management remain the cornerstone in welcoming and helping these newborns to have the best outcomes.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

All authors have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ETHICAL APPROVAL

The approval of the ethical committee at the René Dubos Hospital (RDH) had been granted.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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