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Diagnostic criteria in Pai syndrome: results of a case series and a literature review

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Abstract. Pai syndrome 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 with the full triad, and most exhibit a wide spectrum of phenotypic variability. The aim of this study was to phenotypically delineate Pai syndrome and to propose new criteria to facilitate a clinical diagnosis in the future. The study cohort consisted of seven case patients and an additional 60 cases diagnosed with Pai syndrome identified in a literature review. Only 23 of 67 patients presented the full triad as historically described by Pai et al. (1987). A congenital facial midline skin mass was always encountered, particularly affecting the nasal structures (60/67). A midline facial cleft was reported in 45 of 67 patients and a pericallosal lipoma in 42 of 67 patients. The proposed definition of Pai syndrome is the association of (1) a congenital nasal and/or mediofrontal skin mass and/or a mid-anterior alveolar process polyp as a mandatory criterion, and at least one of the following criteria: (2) midline cleft lip and/or midline alveolar cleft, and/or (3) a pericallosal lipoma or interhemispheric lipoma in the case of corpus callosum dysgenesis.

Key words: Pai syndrome; midline cleft lip; skin tag; pericallosal lipoma; frontonasal dysplasia.

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Pai syndrome is a rare congenital craniofacial malformation involving the midline cranial and facial structures. According to the literature, Pai syndrome is phenotypically highly variable and overlaps with frontonasal dysplasia spectrum in some cases[1–3]. Most of the cases of Pai syndrome described in the literature do not meet all criteria as initially defined by Pai et al., i.e., (1) a midline cleft lip, (2) midline nasal and facial polyps, and (3) lipoma of the central nervous system[4]. Less stringent diagnostic criteria have been proposed, including the presence of at least (1) a midline cleft lip, and (2) one hamartomatous nasal polyp and/or mid-anterior alveolar process polyp[5], or the association of a congenital nasal polyp and one of the three following criteria: (1) midline cleft lip, (2) mid-anterior alveolar process congenital polyp, or (3) a pericallosal lipoma[3].

Most cases are sporadic, and although an autosomal dominant inheritance has been suggested, the aetiology remains unknown[2,6]. Establishing homogeneous study cohorts in the future may help to elucidate the aetiology of Pai syndrome. Thus, there is the need for a consensus definition of Pai syndrome.

This article describes a series of seven additional patients diagnosed with Pai syndrome and provides a review of cases reported in the literature according to the three current clinical diagnostic criteria. The aim of this study was first to describe the phenotype spectrum of reported cases of Pai syndrome and to determine whether these cases are consistent with the existing definitions of Pai syndrome. The second aim was to propose more appropriate diagnostic criteria and systematic investigations, based on these findings.

Patients and methods

Patients

A retrospective study was conducted in the Rare Diseases Reference Centre for Cleft Lip and Palate and Facial Malformations at Hôpital Trousseau and Hôpital Universitaire Necker-Enfants Malades, Paris, France, covering the years 2008 to 2018. Using the CEMARA database (Banque Nationale de Données Maladies Rares), seven patients diagnosed with Pai syndrome were identified. These patients presented at least two criteria of the triad as defined by Pai et al.[4], with a midline facial congenital skin mass as a mandatory criterion. The following information was collected from a chart review: sex, birth parameters, location of the congenital facial skin mass, description of the facial cleft and additional abnormalities, neuropsychological development, and results of genetic investigations. Cerebral magnetic resonance imaging (MRI) scans were reviewed to determine the type of pericallosal lipoma and any additional central nervous system malformations.

Literature review

The review of the literature was conducted by screening the PubMed database using the terms ''Pai syndrome'' and/or ''midline lip cleft'' and/or ''facial skin mass'' and/or ''cutaneous polyps'' and/or ''lipoma of the corpus callosum''. This analysis included case reports and series of Pai syndrome, as well as literature reviews published since 1965.

Results

Case series (Table 1, Figs. 1–3)

Seven patients were included in this study, five female and two male, with a median age of 1 month (range 0.25–5 months) at initial examination and a median follow-up of 9 years (range 0.5–19 years). For all patients, family history was unremarkable, and the patient's parents were not consanguineous. Patients 5 and 7 each had a non-affected dizygotic twin. Cleft lip was diagnosed prenatally in two patients (patients 2 and 7).

Among the seven patients, four presented with the full triad (patients 1–4) as described by Pai et al.[4], whereas three patients presented two criteria (patients 5–7; Table 1; Fig. 1). A midline nasal skin mass was present in all cases, a midline facial cleft was observed in six of seven cases, and a pericallosal lipoma was seen in five of seven cases (Fig. 3). Multiple congenital skin tags were present in three of seven patients (Table 1; Fig. 2).

Ophthalmological abnormalities were diagnosed in two patients, including a hyperpigmented spot of the iris and a limbal dermoid. Intracranial abnormalities were also detected, including partial agenesis of the corpus callosum, short corpus callosum, choroid cyst, and agenesis of the olfactory bulbs. Hypertelorism, bifid nose, and down-slanting palpebral fissures were noted in patient 3 (Fig. 1). Two patients presented a bifid midline frenum of the upper lip (Fig. 2). Neuropsychological development was considered in the normal range for all patients.

Literature review

Fifty articles matched the research criteria, including 46 case reports and four case series (from two to seven patients per series). Among these case reports and series, nine included a review of the literature[3,5,7–13].

In total, 60 cases of Pai syndrome have been described to date. Nineteen patients met the three clinical criteria as defined by Pai et al.[4] (**Supplementary Material**, Table S1). Thirty-six patients presented two of the three criteria: 14 patients had at least one nasal skin mass and a midline cleft of the upper lip, 15 patients had at least one congenital nasal skin mass and a pericallosal lipoma, and seven patients presented with a paramedian cleft lip or midline alveolar cleft without cleft lip, associated with midline facial polyps and/or a pericallosal lipoma (**Supplementary Material**, Table S2). Forty-two cases featured additional abnormalities, with multiple congenital facial skin masses (40/60), hypertelorism (19/60), and ophthalmological anomalies (19/60) being the most frequently observed (see **Supplementary Material**, Tables S1 and S2). Five patients presented one criterion only (i.e., nasal congenital skin mass).

Discussion

The phenotypic spectrum of the reported cases of Pai syndrome is heterogeneous[2], as are the diagnostic criteria[3–5], which was confirmed by the present review. This study first described the phenotype of seven additional cases of Pai syndrome and then compared them with 60 cases of Pai syndrome reported in the literature to date, in order to determine whether these cases are consistent with the existing definitions of Pai syndrome. The second aim was to critically analyse the three definitions of Pai syndrome and, on the basis of the results, to propose new diagnostic criteria as well as systematic investigations.

Almost all cases reported in the literature, as well as the cases in the series presented herein, harboured a facial midline hamartoma (57/60 cases in the literature and 6/7 cases in this series). Castori et al. have previously noted that this is the most frequently encountered feature[5]. These congenital skin masses affected the nasal structures in 53 of 60 cases reported in the literature, particularly the nostrils, and this was also seen in the present case series. In a few cases, examination of the skin masses revealed a lipoma or a myolipoma[14–19] or a dermoid cyst[6], as in two patients in the case series (see Table 1).

Midline cleft lip is rare and represents 0.43% to 0.73% of cases of cleft lip and palate[9,20]. In the literature, midline clefts were reported in 39 of 60 patients with Pai syndrome (65%), with a wide range of severity exhibited (**Supplementary Material**, Tables S1 and S2). In the case series, six of seven patients had a midline cleft lip, and one patient presented with a paramedian cleft lip, a median notch of the upper lip, and a midline alveolar cleft (see Table 1). In the literature, three patients with Pai syndrome presented with uni- or bilateral paramedian lip clefts[2,21,22]. In four cases, a midline alveolar cleft without cleft lip was reported[3].

Intracranial lipomas represent less than 0.1% of intracranial anomalies. They are mostly located in the midline[22,23]. Anterior lipomas of the corpus callosum are mostly of tubulonodular type and frequently associated with hypoplasia or

Table 1. Clinical, radiological, and pathological characteristics of the patients diagnosed with Pai syndrome included in the current series.

Patient Birth term (weeks) Birth weight (g) Birth height (cm)	Sex	Cutaneous facial polyps (localization, number, and histopathological diagnosis)	Orofacial cleft	Pericallosal lipoma	Additional findings	Genetic investigations
Patient 1 37 weeks + 5 days 3070 g 48.5 cm (Figs. 1–3)	Female	Polypoid mass attached to the right nasal septum (1) (hamartoma) Nasal skin lesion of the nasal tip (1) (dermoid cyst)	Midline cleft of the upper lip[a] (microform) Median alveolar cleft of premaxilla	Tubulonodular pericallosal lipoma	Bifid frenum of the upper lip	Not performed
Patient 2 40 weeks 2640 g 47.5 cm (Figs. 1, 2)	Female	Diverticula of the nasal dorsum (1) (hamartoma) Pedunculated skin mass pedicled on columella (1) (hamartoma) Diverticula of the upper gingiva (1) (hamartoma) Three left pre-auricular pedunculated masses (one fibrochondroma and two lipofibromas)	Complete midline cleft lip and palate	Tubulonodular pericallosal lipoma Short corpus callosum	Bilateral ear deformities Agenesis of the olfactive bulb Left ocular dermoid	46 XX Comparative genomic hybridization array: normal (holoprosencephaly excluded)
Patient 3 38 weeks 2850 g 48 cm (Fig. 1)	Female	Skin mass of the right nostril (1) (hamartoma)	Complete midline cleft of the upper lip	Tubulonodular pericallosal lipoma Partial agenesis of the corpus callosum	Hypertelorism Bifid nose Median fistula (columella) Down-slanting palpebral fissures	Not performed
Patient 4 41 weeks + 5 days 2980 g 49 cm (Figs. 2, 3)	Female	Pedunculated skin mass on the nasal tip (1) (hamartoma)	Midline cleft of the upper lip[a] (microform) Median alveolar cleft of premaxilla	Curvilinear lipoma of corpus callosum	Bifid frenum of the upper lip High arched palate Small left choroid plexus cyst Hyperpigmented spot in the left iris	46 XX
Patient 5 38 weeks 2950 g 48 cm (Fig. 1)	Male	Pedunculated skin mass of the right nostril (pedicled on the nasal septum) (1) (hamartoma) Skin mass of the alveolar cleft arising in the midline cleft lip (hamartoma) (1)	Incomplete midline cleft of the upper lip and alveolus	None	None	Not performed
Patient 6 40 weeks 2950 g 48 cm (Fig. 1)	Female	Nasal skin mass (columella extending to the right alar dome) (dermoid cyst) (1)	None	Tubulonodular pericallosal lipoma	None	Exome sequencing: no abnormalities
Patient 7 38 weeks 2800 g 48 cm (Fig. 1)	Male	Pedunculated skin mass of the cleft lip, with extension into the right nostril (1) (hamartoma)	Complete paramedian cleft lip and palate (right side) Midline alveolar cleft	None	Congenital stenosis of the right lacrimal duct Duplication of the vomerian bone	Exome sequencing: no abnormalities

[a] Characterized by disrupted vermilion–cutaneous junction, hypoplastic mucosal free margin, and notching of the vermilion.

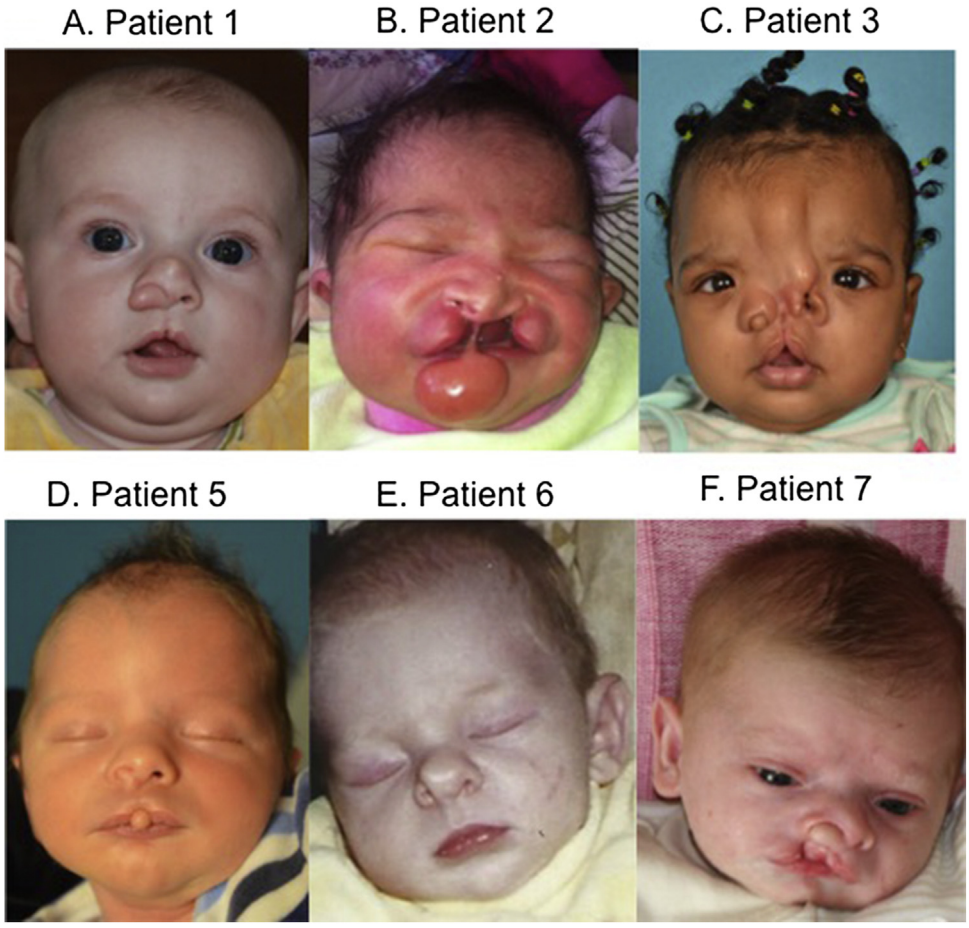

Fig. 1. Frontal views of the patients in this series. (A) Patient 1 at the age of 1 year, showing the midline cleft lip and polypoid mass attached to the right side of the nasal septum. (B) Patient 2 at the age of 8 days, showing a large midline cleft lip and a pedunculated skin mass attached to the columella. (C) Patient 3 at the age of 5 months, showing a midline cleft lip, a bifid nose, hypertelorism, wide forehead, down-slanting palpebral fissures, and a pedunculated skin mass attached to the right nostril. (D) Patient 5 at the age of 1 month, showing a midline cleft lip, a skin mass of the alveolar cleft arising in the midline lip cleft, and a pedunculated skin mass of the right nostril (pedicled on the nasal septum). (E) Patient 6 at the age of 1 week showing the deformity of the right nostril linked to the nasal dermoid cyst (of the columella extending to the right alar doma). (F) Patient 7 at the age of 1 month, showing a right paramedian cleft lip, a median notch, and a pedunculated skin mass of the cleft lip, with extension into the right nostril. Note: Informed consent for publication of the frontal photograph was not obtained for patient 4.

agenesis of the corpus callosum, frontal encephalocele, frontal lobe anomalies, and ocular anomalies. Posterior lipomas are typically described as curvilinear; they are thin and typically lie on the splenium. They are rarely associated with corpus callosum and/or encephalic anomalies[23,24]. A pericallosal lipoma or interhemispheric lipoma was identified in 37 of 60 patients with Pai syndrome; however, cerebral imaging was available for only 49 of the 60 patients. In the case series presented, five patients had a corpus callosum lipoma (tubulonodular in four cases and curvilinear type in the other). One patient with a tubulonodular pericallosal lipoma also presented partial agenesis of the corpus callosum.

Intracranial lipomas are rarely symptomatic[23], and in Pai syndrome, neuropsychological development is usually normal[3], as confirmed in the case series. However, neuropsychological development is not well studied in Pai syndrome, and several conditions reported in Pai syndrome are likely to cause neuropsychological impairments. These include associated chromosomal abnormalities such as translocation q28;q11.2[25], intracranial calcifications[9,26], and corpus callosum dysgenesis[9,27] or agenesis[2,5,19]. Patients with Pai syndrome with corpus callosum dysgenesis[27], hypoplasia or agenesis[2,19], or other cerebral malformations[6,28] often present with an interhemispheric lipoma (**Supplementary Material**, Table S2). Thus, systematic cerebral imaging is recommended when a congenital midline facial skin mass and/or midline facial cleft is encountered, as there may be associated cerebral malformations[6,28]. Cerebral imaging studies are imperative, as a pericallosal lipoma may become symptomatic at a later age, with the risk of developing epilepsy, which has been reported to occur in up to 50% of patients[29].

The most frequent additional features encountered in the literature review were multiple congenital facial skin masses (66%), hypertelorism (32%), and ophthalmological anomalies (32%). In the case series, three of seven patients presented with multiple congenital facial skin masses. Two patients showed ophthalmological anomalies: a hyperpigmented spot of the iris and an ocular dermoid. The clinical spectrum of ophthalmological anomalies described in the literature is wide (**Supplementary Material**, Tables S1 and S2). However, Castori et al. suggested that they could be underestimated[5]. Thus, systematic and complete ophthalmological examination is justified when encountering Pai syndrome.

Ear anomalies are rare and these included pre-auricular skin tags and/or ear dys-

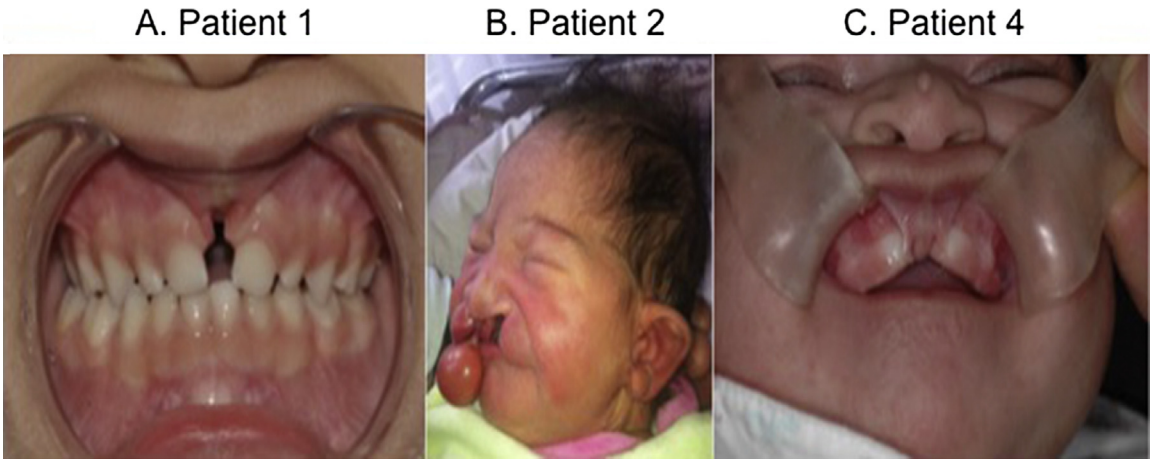

Fig. 2. Additional facial features in patients 1, 2, and 4. (A) Intraoral view of patient 1: bifid labial frenum of the maxilla and midline alveolar cleft. (B) Lateral view of patient 2 at the age of 8 days, showing pre-auricular skin tags. (C) Frontal view of patient 4 at the age of 1 month, depicting a pedunculated skin mass attached to the nasal tip and a bifid frenum.

plasia in five of 60 patients[21,30]. In the case series, one patient had three left pre-auricular skin tags and bilateral, symmetrical external ear dysplasia in addition to an ocular dermoid. The presence of ear dysplasia and epibulbar dermoids raises the possibility that there might be an overlap with Goldenhar/oculo-auriculo-vertebral (OAV) spectrum and oculoauriculofrontonasal syndrome, which is associated with features of both frontonasal dysplasia and OAV spectrum.

To date, three definitions of Pai syndrome have been described[3–5]. Pai et al. postulated that three criteria, i.e., a midline cleft lip, midline facial and nasal skin polyps, and lipoma of the corpus callosum, must be present[4], whereas according to Castori et al.[5] and Lederer et al.[3], at least two criteria are sufficient: one or more hamartomatous nasal polyp(s) plus a midline facial cleft (midline cleft lip with or without cleft alveolus) and/or mid-anterior alveolar process congenital polyp (Castori et al.[5]) or the presence of a congenital nasal polyp plus one of the following three features: midline cleft lip (with or without cleft alveolus), mid-anterior alveolar process congenital polyp, or pericallosal lipoma (Lederer et al.[3]).

In all three definitions, a midline congenital skin polyp must be present. According to Pai et al.[4], the congenital skin polyp may be located not only in the nasal region but also in the midline facial regions, whereas Castori et al.[5] and Lederer et al.[3] restricted this to the nasal structure only. Contrary to Lederer et al.[3], a midline cleft lip must be present to define Pai syndrome in the two other definitions. Pericallosal lipoma is an obligatory criterion according to Pai et al.[4], a possible associated feature in the definition of Lederer et al.[3], and excluded from the diagnostic criteria of Castori et al.[5].

In the literature review, less than a third of the cases (19/60) met the criteria defined by Pai et al.[4], 34 of 60 cases met the Castori et al. criteria[5], and 50 of 60 cases corresponded to the definition of Lederer et al.[3]. In the case series of seven patients, four presented the triad as defined by Pai et al.[4] and six met the criteria described by Castori et al.[5] and Lederer et al.[3]. Patient 6 did not meet the existing definitions, as she presented with a congenital dermoid cyst of the nasal tip and not a hamartomatous polyp, in addition to a pericallosal lipoma without a midline cleft lip. Several cases diagnosed with Pai syndrome reported in the literature did not present with a hamartomatous polyp but rather with a congenital lipoma or a myolipoma[14–19] or a dermoid cyst[6]. The pathological diagnosis is not described systematically in previous reports; thus, it is possible that the number of cases without a true hamartomatous polyp may have been underestimated. In addition, these congenital skin masses diagnosed as dermoid cysts or lipoma correspond to congenital and non-progressive lesions of developmental origin that may occur in the midline facial structures. In accordance with the existing definitions, it is considered that a midline congenital skin mass should be a mandatory criterion for defining Pai syndrome, as it was present in all of the cases in the literature review, occurring in the frontal and/or nasal regions as in the definition of Pai et al.[4]. In addition, it is proposed that the possible location be broadened to the mid-anterior alveolar process and its possible pathological diagnoses to dermoid cysts and hamartomatous-like lesions, such as lipoma or myolipoma.

In fact, the initial definition of Pai et al. is relatively restrictive. However, although this congenital malformation affecting the craniofacial midline structures can be expressed in various degrees, it can

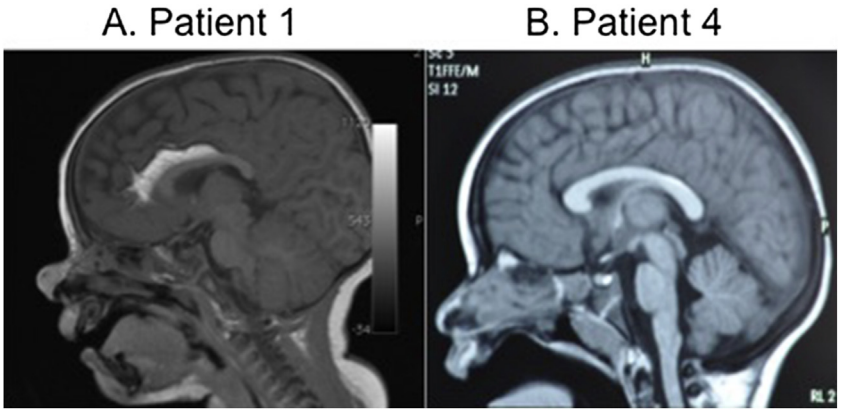

Fig. 3. Cerebral MRI depicting two types of pericallosal lipoma (sagittal plane): (A) tubulonodular-type lipoma of the corpus callosum (patient 1); (B) curvilinear-type lipoma of the corpus callosum (patient 4).

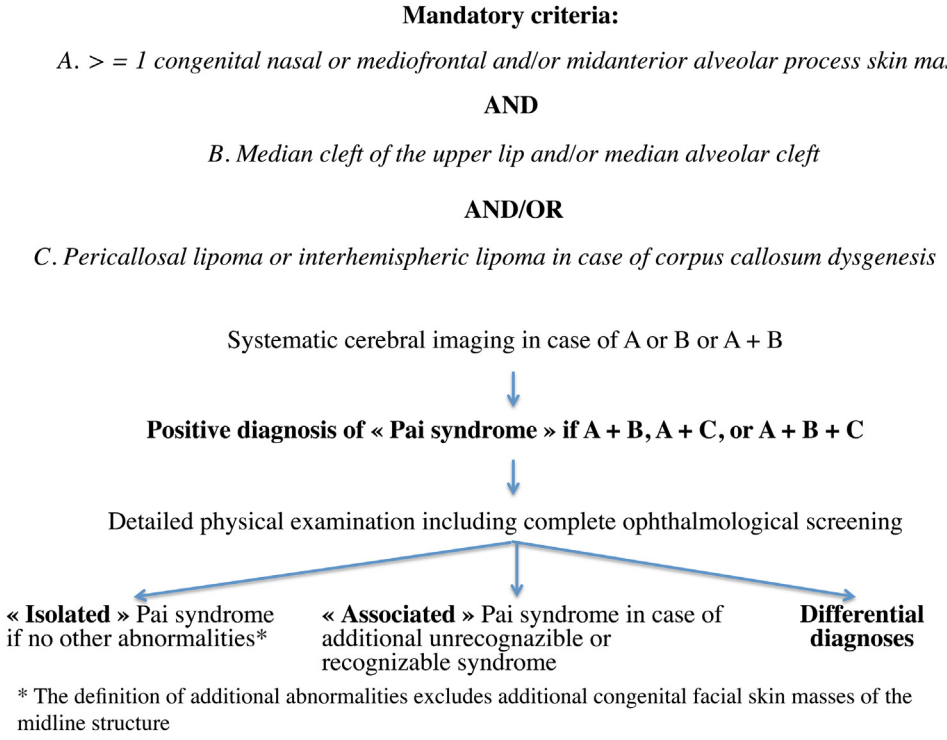

Fig. 4. Flowchart of new diagnostic criteria for Pai syndrome and suggested investigations.

nevertheless be explained by similar pathophysiological processes. From a pathophysiological point of view, two theories may explain the occurrence of a median cleft of the upper lip: the 'fusion theory' and Veau's theory of mesodermal penetration. According to the fusion theory, the cleft of the upper lip is due to a lack of fusion of the maxillary processes with the frontonasal process during foetal face development[31]. In Veau's theory, the median cleft of the upper lip results from abnormal mesenchymal penetration in the epithelial wall of the primary palate during the sixth week of gestation[32]. This second mesodermal theory may also explain the presence of congenital skin masses associated with a median cleft of the upper lip, as a result of compensatory proliferation of mesodermal tissues, where the fusion of the facial processes occurs at the same embryonic stage[33], as well as the occurrence of pericallosal lipoma, as a result of mesodermal inclusion within the closing neural tube[34]. Several additional pathophysiological processes seem to be responsible for the development of pericallosal lipoma, including the persistence and abnormal differentiation of primitive meninx, which is a mesenchymal derivative of neural crests, into mature adipose tissue[35].

Thus, based on the literature review, a new definition for Pai syndrome spectrum is proposed: (1) a congenital nasal or mediofrontal skin mass and/or a mid-anterior alveolar process polyp (regardless of the pathological diagnosis, i.e., 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 (Fig. 4). Of the 60 cases described in the literature, 55 meet these proposed diagnostic criteria. The remaining five patients presented with only one criterion; however, an MRI was not performed in two of these patients.

The molecular basis of Pai syndrome remains unknown. To date, only one de novo reciprocal translocation, 46,X,t(X;16)(q28;q11.2), has been reported in a case of Pai syndrome including a midline cleft of the upper lip, pedunculated skin masses of the nasal septum, frontal bossing, hypertelorism, short and down-slanting palpebral fissures, short stature, and mental retardation[25]. This phenotype overlaps with frontonasal dysplasia, as observed in 32% of the cases of Pai syndrome described in the literature review and in one patient in the case series. In patients presenting with Pai syndrome and additional features, chromosomal abnormalities may be detected more frequently, especially when the phenotype overlaps with those observed in frontonasal dysplasia spectrum[36] or in Goldenhar/OAV spectrum and oculoauriculofrontonasal syndrome, which is associated with features of both frontonasal dysplasia and OAV spectrum. Establishing consensus diagnostic criteria for Pai syndrome and performing systematic genetic investigations, including clinical evaluation by a geneticist and comparative genomic hybridization array, are necessary to better delineate Pai syndrome spectrum and thus shed light on its molecular basis.

Conclusions

Through the analysis of the case series patients and a literature review, this study was able to further analyse the phenotype of Pai syndrome, leading to the proposed new diagnostic criteria, i.e., (1) a congenital nasal or mediofrontal skin mass or a mid-anterior alveolar process polyp (regardless of the pathological diagnosis, i.e., hamartoma, dermoid cyst, 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 C. Pericallosal lipoma or interhemispheric lipoma in the case of corpus callosum dysgenesis.

Systematic cerebral imaging is recommended in the event that midline facial skin masses and/or a midline cleft lip is

encountered, as well as ophthalmological assessment and evaluation by a geneticist to detect additional abnormalities and to establish the differential diagnosis of Pai syndrome or overlapping syndromes. This may help to better delineate the spectrum of Pai syndrome and elucidate its aetiology.

Funding

No funding was secured for this study.

Competing interests

All authors have no conflict of interest to declare.

Ethical approval

As a retrospective case series study, ethics committee approval was not required by the study institution.

Patient consent

Informed consent was collected from the patients' parents for the publication of the photographs prior to submission.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijom.2018.08.010.

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