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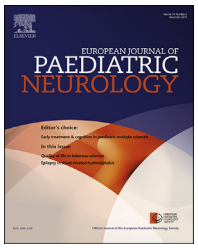

Review article

Prenatal diagnosis of pericallosal lipoma: Systematic review

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ABSTRACT

The aim is to present a systematic review of all the published cases of prenatally diagnosed pericallosal lipomas, their features and associations with other anomalies or syndromes and their post-natal evolution.

We performed a Pubmed-based systematic review, including all the published cases of prenatal diagnosis of pericallosal lipoma, written in English, Spanish or French. We analysed gestational age at diagnosis, prenatal ultrasound characteristics of the lipoma, prenatally diagnosed associated anomalies, neonatal findings, outcomes and duration of follow-up. We gathered data from 49 cases of prenatally diagnosed pericallosal lipoma. Mean gestational age at diagnosis was 29.6 weeks. The type of lipoma was: not specified in 8 cases, tubulonodular in 17 cases, curvilinear in 24 cases. Corpus callosum was hypoplastic in 19 cases of curvilinear lipomas (79.2%) and 3 cases of tubulonodular lipomas (17.6%) ($p < 0.001$). There was agenesis (partial or complete) of corpus callosum in 76.5% of the cases of tubulonodular lipoma and 8.3% of the cases of curvilinear lipoma ($p < 0.001$). There were three cases of Pai syndrome, and three cases of Goldenhar syndrome. Mean post-natal follow-up was 36.3 months. Neurological evaluation was normal in 92.1% of the cases (75% of the tubulonodular lipoma, 100% of the curvilinear lipoma, $p < 0.05$). Tubulonodular lipomas present a higher frequency of associated neurological anomalies. A thorough study of the lipoma and a search of associated anomalies is paramount. Parental counselling should take into account this classification and associated findings as the prognosis varies widely. Further studies with longer follow-up are necessary to increase our knowledge.

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Contents

1. Introduction

Advances in fetal ultrasound and fetal magnetic resonance imaging (MRI) have allowed defining most neurological tumours and other neurological anomalies that can be present during prenatal life. Intracranial lipomas are very rare congenital brain tumours representing less than 0.1% of intracranial lesions.[1] Although the lipomas may develop in all cerebral cisternae, they are more frequent in the region of the corpus callosum (CC).[2] A pericallosal lipoma is visualized on ultrasound as a hyperechogenic image situated in the CC area, which may interfere with its normal development, being frequently associated with abnormalities of the CC. Besides the callosal anomaly, lipomas can be associated with midline defects, dysraphism and genetic syndromes.[3] With the progress in prenatal diagnosis, pericallosal lipomas are more frequently diagnosed. Increasing the knowledge of this entity will impact in the prenatal counselling that we are able to deliver to parents.

We present a systematic review of the literature of the prenatally diagnosed cases of pericallosal lipomas to analyse their diagnostic features, additional imaging techniques findings and their post-natal evolution.

2. Methods

We have followed the Prisma criteria[4] to perform this systematic review.

2.1. *Literature search and inclusion criteria*

We have performed a systematic review of the literature including all the case reports or case series of prenatal diagnosis of pericallosal lipoma published during the last 30 years - between 1989 and February 2019. We included those articles describing prenatal characteristics of the lipomas, whether they were associated to other anomalies or not, and what their post-natal evolution was.

We performed a PubMed-based search using a combination of MeSH terms: "*Lipoma*", "*Corpus Callosum*", "*Prenatal diagnosis*", "*Ultrasonography, Prenatal*" and "*Magnetic Resonance Imaging*". We included all the articles written in English, French or Spanish, presenting one or more cases of prenatal diagnosis of pericallosal lipoma. References were cross-checked in order to find additional articles on the topic.

2.2. *Study selection*

Titles and abstracts were first analysed to select the articles that would be subsequently studied. Articles that did not meet our inclusion criteria were eliminated. We excluded duplicate cases (published in different articles).

2.3. *Data extraction and analysis*

The following variables were retrieved by one author from each article to create a table: author, year of publication, gestational age at diagnosis (weeks), type of lipoma, prenatal ultrasound characteristics of lipoma, associated ultrasound findings, prenatal MRI findings, neonatal findings, neonatal outcomes and follow-up, and length of postnatal follow-up. All the descriptions of the ultrasound or fetal magnetic resonance imaging have been copied with the same words as they were described in the original publications. These were afterwards reviewed by a second author.

Statistical analysis was performed using SPSS software package, version 21.0 (IBM Co., Somers, NY, USA) in its default settings. Results are presented as means, with minimum and maximum, for continuous variables, number of cases (n) and percentage for categorical variables. Chi square was used to assess statistical significance of differences between categorical variables. $P < 0.05$ was considered as statistically significant.

2.4. *Risk of bias*

There is a risk of bias of publication, as there might exist other cases of cases of prenatal diagnosis of pericallosal lipoma that have not been published. Moreover, some cases might have not been diagnosed (and therefore reported) as protocols for prenatal diagnosis have changed since the first case reported.

There is a risk of bias due to the variability in the descriptions of the imaging findings.

We have not received any funding for this review.

2.5. *Data availability statement*

All data used in the article have been gathered from published articles as previously mentioned. These articles are available in the Pubmed database.

3. Results

We found sixteen articles[1,5–19] meeting the inclusion criteria that were reduced to fourteen after excluding two of them to avoid duplicate cases[18,19] (Graphic 1). To this date, 49 cases of prenatal diagnosis of fetal pericallosal lipoma have been reported (Table 1) from 1989 to February 2019. Two thirds of the cases were published after 2011. The average gestational age at diagnosis was 29.6 weeks (22–37.5 weeks) (Table 2). All the diagnosis of pericallosal lipoma were first made by ultrasound. The type of lipoma was not described in 8 cases (six of these were published before 1997); curvilinear was the most frequent type (24 cases) and the lipoma was categorized as tubulonodular lipoma in 17 cases.

The pericallosal lipoma was visualized by ultrasound prior to referral in 8 cases (61.5%) of tubulonodular lipoma, in 6 cases (35.3%) of curvilinear lipoma and in 6 cases (75.0%) in patients without specified type of lipoma (Table 3). In the cases where the lipoma was not visualized, the reason for referral or follow-up sonography was the presence of other findings in the ultrasound.

Of all the tubulonodular lipomas, 13 (76.5%) had partial or complete agenesis of corpus callosum (ACC), 3 (17.6%) had a hypoplastic or dysplastic CC and 1 (5.9%) had a normal CC.

In the case of curvilinear lipomas, there was a partial or complete ACC in 2 cases (8.3%) a hypoplastic or dysplastic CC in 19 (79.2%), and 3 (12.5%) had a normal CC.

These differences in the frequency of ACC between tubulonodular lipomas (76.5%) and curvilinear lipomas (8.3%) were statistically significant ($p < 0.001$). Likewise, the differences in the frequency of hypoplastic or dysplastic CC between tubulonodular lipomas (17.6%) and curvilinear lipomas (79.2%) were statistically significant ($p < 0.001$).

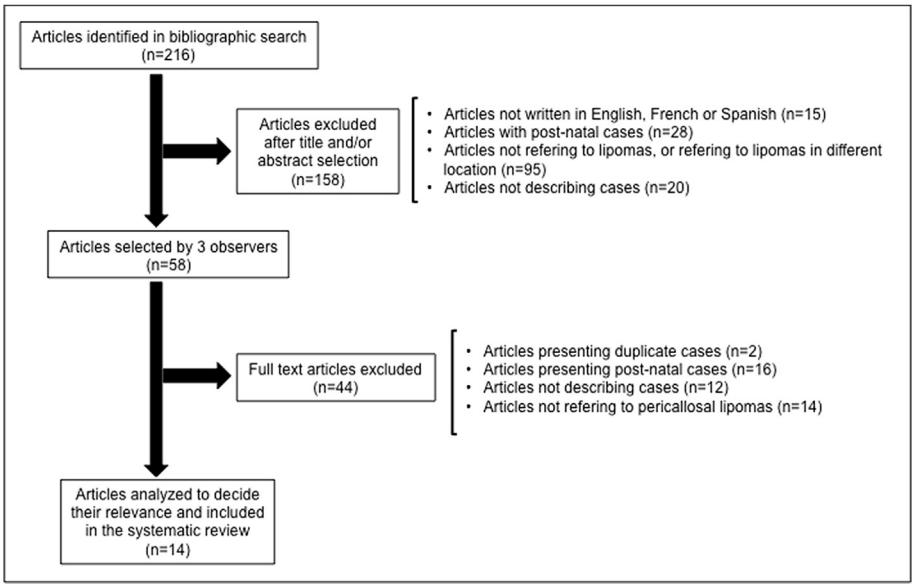
From all 24 curvilinear lipomas, anomalies of the CC were found in 21 cases (87.5%). In the two cases that had ACC, this was found to be partial. One of these had Pai syndrome, the other one had a malformation of the cortical development with the ACC being was almost complete. Nineteen cases of curvilinear lipoma presented a small or dysplastic CC (79.2%). Of these, one had Goldenhar syndrome and one had Pai syndrome, and in the rest no other anomaly was detected.

All but one of the cases of tubulonodular lipomas (94.1%) were associated with anomalies of the CC: complete ACC in 10 cases (58.8%), partial ACC in 3 cases (17.6%) and dysgenesis or hypoplasia of CC in 3 cases (17.6%).

Among the lipomas without specified type, complete ACC was described in 3 cases (37.5%), partial ACC in 1 case (12.5%), hypoplasia of the CC in one case (12.5%) and in 3 cases (37.5%) there were no CC anomalies described.

Enlargement of the lipoma in utero or after birth was described in nine cases (5 cases in a tubulonodular lipoma, 3 cases in a curvilinear lipoma and 1 case in a non-specified type of lipoma).

Two cases of curvilinear lipoma presented other intracranial anomalies (malformation of the cortical development in one case, and cerebellar hypoplasia, ventriculomegaly and



Graphic 1 – Flow-chart showing the selection of the articles included in the systematic review.

Table 1 – Characteristics of the prenatally diagnosed pericallosal lipomas and post-natal evolution.

Case	Author Year	GA at diagnosis (weeks)	Type of lipoma	Prenatal ultrasound characteristics of lipoma	Associated ultrasound findings	Prenatal MRI findings	Neonatal findings	Neonatal outcomes and follow-up	Length of postnatal follow-up
1	Mulligan et al.[5] 1989	37,5	NR	- Brightly echogenic mass - Anterior genu of CC - Pericallosal and callosal marginal arteries within the mass	- ACC - Choroid plexus lipomas - Hydrocephalus. - Possible colpocephaly. - Head circumference at 90th centile.	- NR	- Head circumference at 90th centile. - US and CT scan · Confirmed the diagnosis · Small lipoma in the left Sylvian fissure. · Extensive calcifications around the margin of the central mass.	- Caesarean section (breech presentation) at term. - NNE. - Head circumference with normal growth rate at follow-up.	Not specified.
2		35	NR	- Hyperechoic mass - In the anterior interhemispheric fissure	- CC not fully evaluated (fetal lie and body habitus). - Calculated fetal weight greater than 90th centile. - No other findings.	- NR	- US: · Lipoma of the CC · ACC	- Vaginal delivery at term. - NNE.	Not specified.
3	Jeanty et al.[6] 1991	34	NR	- Brightly echogenic area - Anteriorly located - 13 × 19mm	- Ventriculomegaly - Hypoplasia of the vermis - Limbs around 5th centile	- NR	- Left sided cleft lip - Limbal dermoid on the inner aspect of the left eye. - CT scan: · lipoma of the CC · hypoplasia of the vermis. - Goldenhar syndrome.	- Vaginal delivery (GA not specified). - Follow-up not specified.	Not specified.
4	Multz et al.[7] 1996	34	NR	- Hyperechoic structure - At the expected location of CC	- Hypoplasia of CC. - Colpocephaly, ventriculomegaly.	- NR	- CT scans: confirmed the diagnosis	- Delivery at term. - NNE.	17 months
5	Bork et al.[8] 1996	30 (visible at 26 weeks[a])	NR	- Hyperechoic mass - Anterior genu of CC - 14 mm - Follow-up (38 weeks): 17 × 25 mm	- Partial ACC. - Colpocephaly. - Mild bilateral ventriculomegaly - Follow-up (34 and 38 weeks): occipital horns of lateral ventricles 16 mm	- NR	- CT scan: · Lipoma of the CC with perilesional calcifications · Possible heterotopic grey matter. · Colpocephaly.	- Vaginal delivery at 40 weeks. - NNE.	6 months

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Table 1 – (*continued*)

Case	Author Year	GA at diagnosis (weeks)	Type of lipoma	Prenatal ultrasound characteristics of lipoma	Associated ultrasound findings	Prenatal MRI findings	Neonatal findings	Neonatal outcomes and follow-up	Length of postnatal follow-up
							· Suspicion of agenesis or dysgenesis of CC. - MRI: confirmed CT scan findings.		
6		37	NR	- Hyperechoic mass - Partially replacing CC (from genu to thalamus) - 41 × 14 mm	No associated anomalies.	- NR	- CT scan: · Lipoma of the CC with some calcifications	- Vaginal delivery at 37 weeks. - NNE.	6 months
7	Kieslich et al.[9] 2000	25	Tubulonodular	- Hyperchogenic lesion - In the CC area	- Ventriculomegaly	- NR	- MRI: · lipoma in the anterior CC poorly demarcated, with abnormal vessels. - Lipomatous lesions in the choroid plexi of the lateral ventricles. - Dysplastic CC. - Ventriculomegaly.	- First 3 years, normal neurological development - Afterwards: mild spastic distal disparesis.	3 years
8	Ickowitz et al.[10] 2001	32	Tubulonodular	- Mass with echogenicity similar to PB - 33 × 13mm	- Partial ACC - Cleft lip and palate - Ocular cyst	- NR	- US and MRI: · Pericallosal lipoma · ACC · Vermian dysgenesis. - Goldenhar Syndrome-Pierre Robin anomaly	- Delivery at term. - Death at day 27 of respiratory distress	–
9		32	Tubulonodular	- Echogenicity inferior to PB - Anterior, with extension to frontal lobes - 22 × 12mm	- ACC	- NR	- US and MRI: · Lipoma extending into frontal lobes · ACC	- Delivery at term. - NNE. - Last follow-up reported (9 years old): increasing size of lipoma at control MRI	9 years
10		35	Tubulonodular	- Echogenicity similar to PB - Anterior, with extension to frontal lobes - 35 × 15mm	- ACC	- Extension of the lipoma toward frontal lobes - ACC	- US and MRI: · Lipoma extending towards frontal lobes	- Delivery at term. - NNE. - Last follow-up reported: 3 years old: increasing size of lipoma at control MRI	3 years

11		33.5	Tubulonodular	- Echogenicity similar to PB - Anterior with extension to choroid plexuses - 16 × 8mm	- CC not visible on ultrasound	- Small CC	- US and MRI: · Pericallosal lipoma · Partial ACC	- Delivery at term. - NNE.	10 months
12		35	Tubulonodular	- Echogenicity inferior to PB - Anterior - 3 × 10mm	- ACC	- ACC	- US and MRI: · Lipoma · ACC	- Delivery at term. - NNE.	10 months
13		33	Tubulonodular	- Echogenicity similar to PB - Anterior - 14 × 16mm	- ACC	- ACC	- Termination of pregnancy	–	–
14		23.5	Curvilinear	- Echogenicity similar to PB - 21 × 4mm	- No associated anomalies.	- No associated anomalies	- US and MRI: · Lipoma of CC - Nasal appendages.	- Delivery at term. - NNE.	1 month
15	Kim et al.[1] 2002	26	Tubulonodular	- Hyperechogenic mass - Anterior - 13 mm	- Mild colpocephaly at 20th weeks, increased in weeks 30 and 35. - CSP not visualized.	- Lipoma (28 mm) - ACC - Colpocephaly	- US and MRI: · Lipoma · ACC · Scattered echogenic spots in cingulate sulcus	- Delivery at term. - NNE.	4 days
16	Chousta et al.[11] 2008	26	Tubulonodular	- Hyperechogenic lipoma - Anterior	- Possible mild hypoplasia of splenium - Lip cleft (suspicion of Pai syndrome)	- No associated cerebral anomalies	- US and MRI: · Pericallosal lipoma · Partial ACC - Median cleft of the upper lip; - Four pediculated skin appendages. - Suspicion of Pai syndrome.	- Delivery at term. - NNE.	2 years
17	Nanni et al.[12] 2011	33	NR	- Hyperechoic round-shaped mass - Below the insertion of the falx, replacing CSP - 21 × 12 mm	- ACC - Mild bilateral ventriculomegaly - Dilated 3rd ventricle - Two other round-shaped hyperechoic masses, within the frontal horns of the lateral ventricles in direct continuity with the choroid plexus.	- Performed at 34 weeks - Confirmed ultrasound findings. - T2 or FLAIR sequences: appearance of the masses compatible with lipomas	- MRI: · Confirmed prenatal findings. · Severe hypoplasia of the corpus callosum	- Delivery at 38 weeks (elective caesarean section on maternal request). - Thriving normally, no specific syndrome suspected.	6 months

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Table 1 – (*continued*)

Case	Author Year	GA at diagnosis (weeks)	Type of lipoma	Prenatal ultrasound characteristics of lipoma	Associated ultrasound findings	Prenatal MRI findings	Neonatal findings	Neonatal outcomes and follow-up	Length of postnatal follow-up
18	Ocak et al.[13] 2013	28	NR	- Hyperechogenic structure	- Abnormally shaped nose - Polyp-like structure on the forehead	- NR	- MRI: Pericallosal lipoma of 30 mm. - Multiple dysmorphic features.	- Delivery at term (caesarean section) - Pai syndrome - Follow-up not specified	Not specified.
19	Blouet et al.[14] 2014	24	Tubulonodular	- Anterior	- Partial ACC - Midline cleft lip	- ACC - Pericallosal lipoma. - Bifid nose and two facial polyps. - Suspicion of Pai syndrome	- Termination of pregnancy - Confirmation of Pai syndrome (Postmortem examination, gross pathology and histology)	–	–
20	Atallah et al.[15] 2018	25,5	Curvilinear	- Slight band of echogenicity surrounding CC - Follow-up (30,4 weeks): stable	- Short CC (<5th centile). Rostrum not identified. - Slight CSP distortion. - Normal karyotype.	- Performed at 30,4 weeks - T2-W: Pericallosal hypointensity. - T1-W: non informative.	- MRI: · Isolated curvilinear lipoma of the CC.	- Pregnancy continued. - GA at delivery not specified. - NNE.	Not specified.
21		24,5	Curvilinear	- Slight band of echogenicity surrounding CC - Follow-up (29–34 weeks): increasing in size	- Short CC (<5th centile). Rostrum and splenium not identified. - Normal karyotype.	- Performed at 29 and 34 weeks - T2-W: Pericallosal hypointensity surrounding the posterior part of the CC - T1-W (34 weeks): Hypointensity on "in and out of phase" (suggestive of fat)	- MRI: · Isolated curvilinear lipoma of the CC.	- Pregnancy continued. - GA at delivery not specified. - NNE.	Not specified.
22		30	Curvilinear	- Nodular echogenicities surrounding CC - Follow-up (29–34 weeks): more marked	- Short CC (<5th centile). - Normal karyotype.	- Performed at 30 and 36 weeks - T2-W: Pericallosal hypointensity 5- T1-W: non informativ6.	- MRI: · Isolated curvilinear lipoma of the CC.	- Pregnancy continued. - GA at delivery not specified. - NNE.	Not specified.

23		26	Curvilinear	- Slight band of echogenicity surrounding the CC - Follow-up (30 weeks): increasing in size	- Short CC (10th centile). Complete CC. - Normal karyotype.	- Performed at 30 weeks - T2-W: Pericallosal hypointensity onT2-W - T1-W: non informative.	- MRI: · Isolated curvilinear lipoma of the CC.	- Pregnancy continued. - GA at delivery not specified. - NNE.	Not specified.
24		34,5	Curvilinear	- Abnormal pericallosal hyperechogenicity	- Short CC (<5th centile). Rostrum and posterior part of CC not identified. - Normal karyotype.	- Performed at 34,5 weeks - T2-W: Pericallosal hypointensity - T1-W: non informative.	- MRI: · Isolated curvilinear lipoma of the CC.	- Pregnancy continued. - GA at delivery not specified. - NNE.	Not specified.
25	Chougar et al.[16] 2018	36	Tubulonodular	- At 36 weeks: Lipoma of 27 × 30 × 11 mm	- ACC	- Performed at 36 weeks: Hyperintense in T1, 34 × 26 × 8 mm. ACC	- Termination of pregnancy - Post-mortem data: Adipose tissue within the interhemispheric fissure, absent CC, frontal hypoplasia and polymicrogyria without any other abnormalities	–	–
26		24	Tubulonodular	- At 34 weeks: Lipoma of 25 × 12 × 11 mm	- ACC	- Performed at 34 weeks: Hyperintense in T1, 11 × 7 × 8mm. ACC	- MRI at 5 months: 27 × 15 × 15 mm	- GA at delivery not specified. - NNE at birth - NNE at follow-up (age not specified)	Not specified.
27		22	Tubulonodular	- At 34 weeks: Lipoma of 17 × 20 × 19 mm	- CC length <3rd centile	- Performed at 34 weeks: T1 hyperintense peripheral portion, isointense central portion. 18 × 12 × 17mm. CC < 3rd centile	- MRI at 1 month: 25 × 19 × 21 mm - MRI at 12 months: 36 × 40 × 25 mm - Subcutaneous lipoma increasing in size (20 × 4 mm 1st MRI, 35 × 10 mm 2nd MRI)	- GA at delivery not specified. - NNE at birth - NNE at follow-up (age not specified)	Not specified.
28		31	Tubulonodular	- At 31 weeks: Lipoma of 21 × 11 × 13 mm	- ACC	- Performed at 31 weeks: Hyperintense in T1, 22 × 11 × 9 mm. ACC	- MRI at 5 days: 31 × 15 × 13 mm - MRI at 2 months: 41 × 24 × 18 mm - Subcutaneous lipoma increasing in size (25 × 8 mm 1st MRI, 50 × 13 mm 2nd MRI)	- GA at delivery not specified. - NNE at birth - Tonicoclonic form of epilepsy associated with mild psychomotor retardation	Not specified.

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Table 1 – (*continued*)

Case	Author Year	GA at diagnosis (weeks)	Type of lipoma	Prenatal ultrasound characteristics of lipoma	Associated ultrasound findings	Prenatal MRI findings	Neonatal findings	Neonatal outcomes and follow-up	Length of postnatal follow-up
29		33	Curvilinear	- At 34weeks: Hyperechogenicity poorly delineated	- CC < 3rd centile, rostrum not seen	- Performed at 34 weeks: T1 hyperintense	- MRI at 4 months: lipoma 47 × 11 mm, CC < 3rd centile, rostrum not seen	- GA at delivery not specified. - NNE at birth - NNE at follow-up (age not specified)	Not specified.
30		33	Curvilinear	- At 34 weeks: Hyperechogenicity poorly delineated	- CC < 3rd centile	- Performed at 34 weeks: Lipoma: no prenatal T1 hyperintensity	- MRI at 11 months: lipoma 48 × 9 mm, CC 3rd centile, rostrum not seen	- GA at delivery not specified. - NNE at birth - NNE at follow-up (age not specified)	Not specified.
31		22	Curvilinear	- At 31 weeks: Hyperechogenicity poorly delineated	- CC < 3rd centile	- Performed at 31 and 34 weeks: Lipoma: no prenatal hyperintensity, Rostrum not seen	- MRI at 3.5 months: lipoma: 33 × 4 mm, CC < 3rd centile	- GA at delivery not specified. - NNE at birth - NNE at follow-up (age not specified)	Not specified.
32		24	Curvilinear	- At 29 weeks: Hyperechogenicity poorly delineated	- CC < 3rd centile	- Performed at 29 and 33 weeks: Lipoma: no prenatal hyperintensity, CC < 3rd centile	- MRI at 3.5 months: lipoma: 39 × 3 mm, CC < 3rd centile	- GA at delivery not specified. - NNE at birth - NNE at follow-up (age not specified)	Not specified.
33		23	Curvilinear	- At 29 weeks: Hyperechogenicity poorly delineated	- CC < 3rd centile	- Performed at 29 weeks: Lipoma: no prenatal hyperintensity, CC < 3rd centile	- MRI at 5 months: lipoma: 26 × 11mm, CC < 3rd centile, Genu not well seen	- GA at delivery not specified. - NNE at birth - NNE at follow-up (age not specified)	Not specified.
34		28	Curvilinear	- At 33 weeks: Hyperechogenicity poorly delineated	- CC < 3rd centile	- Performed at 33 weeks: Lipoma: no prenatal hyperintensity, CC < 3rd centile. Splenium not well seen	- MRI at 1 month: lipoma: 5 × 6mm, CC < 3rd centile, Splenium not well seen	- GA at delivery not specified. - NNE at birth - NNE at follow-up (age not specified)	Not specified.
35		28	Curvilinear	- At 32 weeks: Hyperechogenicity poorly delineated	- CC < 3rd centile	- Performed at 32 weeks: Lipoma: no prenatal hyperintensity, CC < 3rd centile. Genu, splenium not seen	- MRI at 2.5 months: lipoma: 25 × 7.5 mm, CC < 3rd centile, Genu, splenium not well seen	- GA at delivery not specified. - NNE at birth - NNE at follow-up (age not specified)	Not specified.

36	Shinar et al.[17] 2018	23	Tubulonodular	- At 23 weeks: Suspected partial ACC - At 27 and 32 weeks: Normal CC	- Performed at 34 weeks: Normal CC, confirmed presence of pericallosal lipoma		- Term delivery - Lipoma confirmed - Normal development	5.5 years
37		22	Curvilinear	- At 19 weeks: Short CC - At 22, 26 and 29 weeks: Normal CC, curvilinear lipoma and lipoma in choroid plexus	- Performed at 31 weeks: Short CC, lipoma not visualized		- Term delivery - Lipoma confirmed - Normal development	3 years
38		34	Curvilinear	- At 21 weeks: Short CC - At 34 weeks: Normal CC, curvilinear lipoma	- Performed at 28 weeks: Short CC, lipoma not visualized		- Term delivery - Lipoma confirmed - Normal development	3 years
39		26	Curvilinear	- At 20 weeks: Short CC - At 26 and 35 weeks: Normal CC, curvilinear lipoma	- Performed at 35 weeks: Short CC, confirmed presence of lipoma		- Term delivery - Lipoma confirmed - Normal development	4 years
40		25.6	Curvilinear	- At 25.6 weeks: Suspected complete ACC, curvilinear lipoma, lipomatosis	- Performed at 25 weeks: Almost complete ACC, Malformation of cortical development	- Termination of pregnancy at 26 weeks - Prenatal diagnoses confirmed by autopsy	–	–
41		37	Tubulonodular	- At 37 weeks: Short CC, Tubulonodular lipoma and lipoma in choroid plexus	- Not performed		- Term delivery - Lipoma confirmed - ADHD	10 years
42		31	Curvilinear	- At 31 and 35 weeks: Short CC, curvilinear lipoma, asymmetrical ventricles	- Performed at 36 weeks: Short CC, confirmed presence of lipoma		- Term delivery - Lipoma confirmed - Normal development	11 years
43		31.3	Tubulonodular	- At 21 weeks: mild ventriculomegaly, CC not studied - At 31.3 weeks: complete ACC, tubulonodular lipoma, colpocephaly	- Not performed	- Termination of pregnancy at 32 weeks - Prenatal diagnoses confirmed by autopsy	–	–

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Table 1 – (*continued*)

Case	Author Year	GA at diagnosis (weeks)	Type of lipoma	Prenatal ultrasound characteristics of lipoma	Associated ultrasound findings	Prenatal MRI findings	Neonatal findings	Neonatal outcomes and follow-up	Length of postnatal follow-up
44		27	Curvilinear		- At 23.4 weeks: Short and thick CC - At 27 and 32 weeks: Short CC, curvilinear lipoma	- Performed at 32 weeks: complete ACC, lipoma not visualized		- Term delivery - Lipoma confirmed - Normal development	4 years
45		33	Curvilinear		- At 26 weeks: Short CC - At 33 weeks: normal CC, curvilinear lipoma	- Performed at 36 weeks: short and thick CC, confirmed presence of lipoma		- Term delivery - Lipoma confirmed - Normal development	6 years
46		29	Curvilinear		- At 29 weeks: Short CC, curvilinear lipoma, slight facial asymmetry	- Not performed		- Term delivery - Goldenhar syndrome - Lipoma confirmed	0.2 years
47		29	Curvilinear		- At 29 and 34 weeks: normal CC, curvilinear lipoma, facial dysmorphism, periventricular nodular heterotopia, cerebellar hypoplasia	- Performed at 34 weeks: normal CC, confirmed presence of lipoma. Cerebellar hypoplasia, ventriculomegaly, suspected heterotopia	- Termination of pregnancy at 34 weeks - Prenatal diagnoses confirmed by autopsy - Megalencephaly	–	–
48		27	Tubulonodular		- At 23 weeks: suspected complete ACC - At 27 and 31.6 weeks: complete ACC and tubulonodular lipoma	- Performed at 31.6 weeks: complete ACC, suspected lipoma		- Term delivery - ACC, lipoma confirmed - Normal development	1 year
49		36.5	Curvilinear		- At 23 weeks: Nasal polyp - At 36.5 weeks: Short CC, curvilinear lipoma, nasal polyp	- Performed at 36 weeks: Short CC, confirmed presence of lipoma. Nasal polyp		- Term delivery - PAI syndrome - Lipoma confirmed - Normal development	0.3 years

ACC: Agenesis of corpus callosum; ADHD: Attention deficit hyperactivity disorder; CC: Corpus callosum; CSP: Cavum septum pellucidum; CT: Computed tomography; GA: Gestational age; MRI: Magnetic resonance imaging; NNE: Normal neurological evaluation; NR: Not reported; PB: parietal bone; US: Ultrasound.

[a] Diagnosis was performed at 30 weeks, but reviewing the previous explorations, the authors realised that it was visible at an ultrasound performed at 26 weeks of gestation.

Table 2 – Summary of main results depending of the type of pericallosal lipoma.

	Type of lipoma			p (between Tubulonodular and Curvilinear)
	Tubulonodular (n = 17, 34.7%)	Curvilinear (n = 24; 49.0%)	Not reported (n = 8, 16.3%)	
Gestational age at diagnosis in weeks Mean (min and max)	29.8 (22–37)	28.1 (22–36.5)	33.5 (28–37.5)	–
Pericallosal lipoma visualized before the referral	8 (61.5%)[a]	6 (35.3%)[b]	6 (75.0%)	0.153
Association with partial or complete ACC N (%)	13 (76.5%)	2 (8.3%)	4 (50.0%)	<0.001
Association with hypoplastic or dysplastic CC N (%)	3 (17.6%)	19 (79.2%)	1 (12.5%)	<0.001
Other intracranial anomalies associated N (%)	4 (23.5%)	2 (8.3%)	5 (41.7%)	0.175
Association with syndromes (Pai or Goldenhar syndromes) N (%)	2 (11.8%)	2 (8.3%)	2 (25.0%)	0.715
Normal neurological evolution N (%)	9 (75.0%)[c]	21 (100%)[d]	5 (100%)[e]	<0.05
Duration of follow-up in months Mean (min and max)	44.3 (0.7–120)[f]	40 (1–132)[g]	8.7 (6–17)[h]	–

Min: Minimum; Max: Maximum.

[a] Findings of the ultrasound before referring or indicating follow-up not reported in 4 patients.

[b] Findings of the ultrasound before referring or indicating follow-up not reported in 7 patients.

[c] After excluding four terminations of pregnancies, follow-up not reported in one case.

[d] After excluding two terminations of pregnancy; follow-up not reported in one case.

[e] Follow-up not reported in three cases.

[f] After excluding one neonatal death at 27 days and 4 terminations of pregnancy, lengths of follow-up not specified in 3 cases.

[g] After excluding two terminations of pregnancy, length of follow-up not reported in 14 cases.

[h] Length of follow-up not reported in 4 cases.

Table 3 – Reason for referral or follow-up of patients with pericallosal lipoma.

Case	Author Year	Type of lipoma	Indications for referral or follow-up	Pericallosal lipoma visualized by US before referral
1	Mulligan et al.[5]; 1989	NR	Hydrocephalus	No
2		NR	Hyperechoic mass	Yes
3	Jeanty et al.[6]; 1991	NR	Hyperechoic structure (suspicion of recent bleeding)	Yes
4	Multz et al.[7]; 1996	NR	Hyperechoic structure and associated cerebral lesions	Yes
5	Bork et al.[8]; 1996	NR	Mild bilateral dilatation of occipital horns	No
6		NR	Hyperechoic mass	Yes
7	Kieslich et al.[9]; 2000	Tubulonodular	Widening of intracranial ventricles and hyperechogenic lesion	Yes
8	Ickowitz et al.[10]; 2001	Tubulonodular	Labial cleft	No
9		Tubulonodular	Complete ACC, lipoma visualized	Yes
10		Tubulonodular	Complete ACC, lipoma visualized	Yes
11		Tubulonodular	CC not visible, lipoma visualized	Yes
12		Tubulonodular	Suspicion of intracranial haemorrhage or tumour	Yes
13		Tubulonodular	Complete ACC, lipoma visualized	Yes
14		Curvilinear	Lipoma visualized	Yes
15	Kim et al.[1]; 2002	Tubulonodular	Mild colpocephaly	No
16	Chousta et al.[11]; 2008	Tubulonodular	Cleft palate and cutaneous nasal and frontal appendages	No
17	Nanni et al.[12]; 2011	NR	Suspicion of intracranial haemorrhage	Yes
18	Ocak et al.[13]; 2013	NR	Hyperechogenic structure	Yes
19	Blouet et al.[14]; 2014	Tubulonodular	Midline cleft lip and abnormality of the corpus callosum	No
20	Atallah et al.[15]; 2018	Curvilinear	Short CC	No
21		Curvilinear	Short CC	No
22		Curvilinear	Short CC	No
23		Curvilinear	Short CC	No
24		Curvilinear	Short CC and abnormal pericallosal echogenicity	Yes
25	Chougar et al.[16]; 2018	Tubulonodular	NR	NR
26		Tubulonodular	NR	NR
27		Tubulonodular	NR	NR
28		Tubulonodular	NR	NR
29		Curvilinear	NR	NR
30		Curvilinear	NR	NR
31		Curvilinear	NR	NR
32		Curvilinear	NR	NR
33		Curvilinear	NR	NR
34		Curvilinear	NR	NR
35		Curvilinear	NR	NR
36	Shinar et al.[17]; 2018	Tubulonodular	Suspected pACC, lipoma visualised	Yes
37		Curvilinear	Short CC	No
38		Curvilinear	Short CC	No
39		Curvilinear	Short CC	No
40		Curvilinear	Suspected complete ACC, lipoma visualised	Yes
41		Tubulonodular	Short CC, lipoma visualized	Yes
42		Curvilinear	Short CC, lipoma visualized	Yes
43		Tubulonodular	Mild Ventriculomegaly	No
44		Curvilinear	Short and thick CC	No
45		Curvilinear	Short CC	No
46		Curvilinear	Short CC, lipoma visualised, slight facial asymmetry	Yes
47		Curvilinear	Curvilinear lipoma, facial dysmorphism, other cerebral anomalies	Yes
48		Tubulonodular	Suspected complete ACC	No
49		Curvilinear	Nasal polyp	No

ACC: Agenesis of corpus callosum; CC: Corpus callosum; GA: Gestational age; MRI: Magnetic Resonance Imaging; NR: Not reported; pACC: Partial Agenesis of Corpus Callosum; US: Ultrasound.

suspected heterotopia in the other case). There were four cases with other neurological anomalies among the tubulonodular lipomas (vermian dysgenesis, scattered echogenic spots in cingulate sulcus, frontal hypoplasia with polymicrogyria and colpocephaly with mild ventriculomegaly). Overall, the most frequent additional findings were ventriculomegaly (8 cases), lipomas in the choroid plexus (5 cases) and hypoplasia of the cerebellar vermis or the cerebellum (3 cases).

Pai syndrome and Goldenhar syndrome were diagnosed in three cases equally distributed in the three groups of types of lipomas.

Prenatal MRI was performed in 37 cases. Post-natal imaging techniques (ultrasound, computed tomography and MRI) confirmed the prenatal findings in all the cases.

There were six terminations of pregnancies (4 cases of tubulonodular lipomas and 2 cases of curvilinear lipomas), all of them after 24 weeks of gestation. Excluding these six cases,

the gestational age at delivery was not specified in 17 cases and delivery was at term in all the cases where this variable was specified (26 cases).

Mean postnatal follow-up length was 36.3 months (4 days–11 years). Duration of follow-up was not specified in 26 cases. Postnatal neurological evolution was informed as normal in 92.1% cases (35 cases), after excluding the six terminations of pregnancies, and five cases with no reported postnatal neurological follow-up. The frequency of normal neurological evolution was statistically significant different: 75% of the cases in the group of tubulonodular lipomas compared to 100% of the cases of curvilinear lipomas ($p < 0.05$). One patient passed out at day 27 due to respiratory distress (Goldenhar syndrome with Pierre Robin anomaly). Of the three patients who did not have a normal neurological examination, one had mild spastic distal disparesis diagnosed at 3 years, another one presented a tonicoclonic form of epilepsy associated with mild psychomotor retardation and the third one had attention deficit hyperactivity disorder. Finally, Table 4 presents all the cases that had anomalies associated to the pericallosal lipoma and their neonatal evolution.

An asymptomatic increase in the size of the lipoma was described in 4 cases at 2 months, 1, 3 and 9 years old, all of them classified as tubulonodular lipomas.

4. Discussion

We present, to our knowledge, the first literature review on the reported cases of prenatally diagnosed pericallosal lipomas. We gathered information of 49 cases of prenatally diagnosed lipomas, divided into tubulonodular and curvilinear lipomas, allowing us to obtain the specific characteristics of each type. More than two thirds of the cases of pericallosal lipomas reported have been published after 2011 reflecting the evolution of prenatal diagnosis and the increasing interest in this type of malformations and its prognosis.

Pericallosal lipomas are more frequently diagnosed during the third trimester when they usually present an echogenicity similar to the parietal bone.[20] However, some cases have been described as soon as the 22 nd week of gestation (Table 1).[16,17] In 64.7% of the cases of curvilinear lipoma, the diagnosis of pericallosal lipoma was made after a referral or in a follow-up sonography indicated for other reasons, whereas the tubulonodular lipoma was visualized before the referral in 61.5% of the cases. This highlights the difficulty that the diagnosis of these lesions can convey, notably in the case of curvilinear lipomas.

The pathogenesis of intracranial lipomas is considered to be an abnormal reabsorption of the primitive meninx[21] between weeks eight and ten of development. When the reabsorption is not complete, the remaining tissue may become lipomatous and when located in the interhemispheric fissure it may provoke an abnormal growth of the CC, leading to complete or partial agenesis or hypoplasia. Indeed, formation of the CC begins at its genu during the 11th week of gestation, coinciding with the reabsorption of the primitive meninx.

Pericallosal lipomas are considered to be congenital lesions, and thanks to the advances in prenatal diagnosis, their detection is sometimes possible at early stages of pregnancy, even when the lipomas are small. However, some cases are diagnosed late in pregnancy, during childhood or adulthood. Unfortunately, in the postnatally diagnosed cases that have been reported in the literature, it has not been possible to prove that the lesion was present at the moment of birth[22,23] and we can't ascertain that these lesions are the same entities as the ones found prenatally.

Intracranial lipomas are most frequently located in the interhemispheric fissure, followed by the quadrigeminal plate and the hypothalamic region. Other less frequent locations as posterior fossa or lateral ventricles have also been reported.[24]

There are two morphological types of pericallosal lipomas[25] (Graphic 2) distinguishable by ultrasound (Table 2). The tubulonodular type is more frequent, usually anteriorly located, close to the genu, measuring more than 2 cm, round or oval shaped. It is commonly associated with frontofacial anomalies and callosal agenesis (partial or complete), probably related to an earlier insult in the callosal area.[26] The curvilinear type is thin (thickness less than 1 cm), elongated and usually located posteriorly, around the splenium. The CC is usually hypoplastic or dysplastic. The associated anomalies are less frequent in the curvilinear type.[26] Indeed, we found that whereas tubulonodular lipomas associated CC anomalies in all but one cases, curvilinear lipomas were associated to small CC or partial ACC in 87.5% of the cases. We found the differences in the association with CC anomalies between these groups to be statistically significant. The type of lipoma was not specified in 16.3% of the cases, not allowing us to include these cases in the previously mentioned categories and the statistical analysis. Six of these cases were published before 1997, proving that the evolution of prenatal diagnosis has been accompanied by an interest of being as precise as possible.

Fetal MRI adds valuable information about extension, type and characteristics of the lesion[18] and detects additional cerebral alterations such as late sulcation and migration disorders. However, the hyperintensity of the lipoma expected in T1-sequences can be absent on prenatal MRI in some cases of curvilinear lipomas.[15–17]

Pericallosal lipomas can be associated with ventriculomegaly, choroid plexus lipomas, midline defects, frontonasal dysgenesis[27,28] or dysraphism. They have been described in trisomy 13,[29] Pai and Goldenhar syndromes. Pai syndrome[30] comprises midline orofacial cleft, cutaneous polyps and central nervous system lipomas, and usually has favourable neurological prognosis. Goldenhar syndrome[6] presents facial, ear and oral anomalies accompanied by vertebral abnormalities and epibulbar dermoid.

Differential diagnosis must be made with teratomas, glioblastomas, craniopharyngioma[2] and intracranial haemorrhage. Teratomas can be differentiated from pericallosal lipomas in that they frequently present as an irregular, rapidly growing, solid mass, distorting cerebral anatomy that may contain cystic or calcified components. Therefore they usually appear on ultrasound as heterogeneous masses with hypo and hyperechogenic features. Glioblastomas present as hyperechogenic homogeneous masses usually involving the supratentorial cerebral parenchyma.[31] Craniopharyngioma are most frequently found in the suprasellar region. They may present as a large echogenic mass, similar to teratomas.[32]

Table 4 – Neonatal outcome and follow-up of cases presenting other anomalies associated to the pericallosal lipoma.

Case	Type of anomaly of the CC, apart from the lipoma	Other anomalies associated	Neonatal outcomes and follow-up
Tubulonodular pericallosal lipoma			
9	ACC	- Lipoma extending into frontal lobes - Lipoma increasing in size	NNE
10		- Lipoma extending into frontal lobes - Lipoma increasing in size	NNE
15		- Scattered echogenic spots in cingulate sulcus	NNE
19		- Pai syndrome - Midline cleft lip - Bifid nose and two facial polyps.	TOP Pai syndrome
25		- Frontal hypoplasia - Polymicrogyria	TOP
28		- Subcutaneous lipoma increasing in size - Pericallosal lipoma increasing in size at 2 months	Tonicoclonic form of epilepsy associated with mild psychomotor retardation
43		- Mild ventriculomegaly	TOP
12		No associated anomalies	NNE
13		No associated anomalies	TOP
26		No associated anomalies.	NNE
48		No associated anomalies	Normal development
16	pACC	- Cleft of the upper lip - Four pediculated skin appendages. - Suspicion of Pai syndrome	NNE Pai syndrome
8		- Cleft lip and palate - Ocular cyst - Vermian dysgenesis - Goldenhar Syndrome-Pierre Robin anomaly	Death at day 27 of respiratory distress Goldenhar Syndrome
11		No associated anomalies	NNE
7	Dysplastic CC	- Ventriculomegaly - Lipomatous lesions in the choroid plexi of the lateral ventricles	Mild spastic distal disparesis
27	Short CC	- Subcutaneous lipoma increasing in size - Pericallosal lipoma increasing in size at 12 months	NNE
41		- Lipoma in choroid plexus	ADHD
Curvilinear pericallosal lipoma			
40	ACC	- Lipomatosis - Malformation of cortical development	TOP
44		No associated anomalies.	Normal development
37	Short CC	- Lipoma in choroid plexus	Normal development
42		- Asymmetrical ventricles	Normal development
46		- Goldenhar Syndrome	Goldenhar syndrome
49		- Pai syndrome - Nasal polyp	Pai syndrome. Normal development.
20		No associated anomalies.	NNE
21		No associated anomalies.	NNE
22		No associated anomalies.	NNE
23		No associated anomalies.	NNE
24		No associated anomalies.	NNE
29		No associated anomalies.	NNE
30		No associated anomalies.	NNE
31		No associated anomalies.	NNE
32		No associated anomalies.	NNE
33		No associated anomalies.	NNE
34		No associated anomalies.	NNE
35		No associated anomalies.	NNE
38		No associated anomalies.	Normal development
39		No associated anomalies.	Normal development
45	Short and Thick CC	No associated anomalies.	Normal development
47	None	- Facial dysmorphism, - Periventricular nodular heterotopia - Cerebellar hypoplasia - Megalencephaly	TOP

Table 4 – (continued)

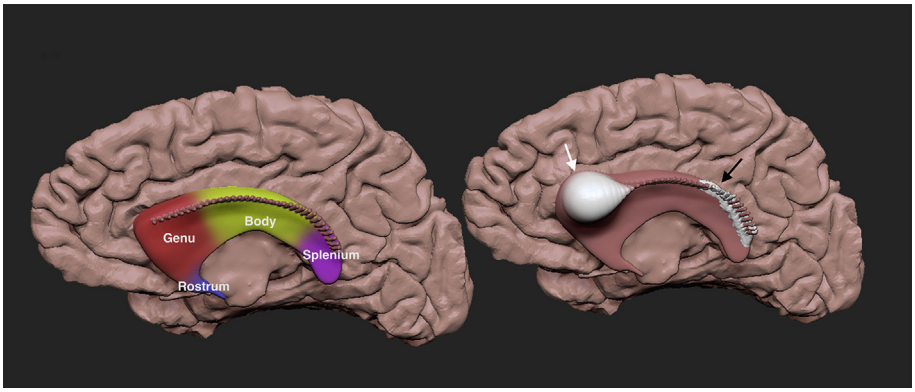
Case	Type of anomaly of the CC, apart from the lipoma	Other anomalies associated	Neonatal outcomes and follow-up
Type of lipoma not reported			
1	ACC	- Choroid plexus lipomas - Hydrocephalus. - Head circumference at 90th centile.	NNE
2		- Calculated fetal weight greater than 90th centile.	NNE
17		- Mild bilateral ventriculomegaly - Dilated 3rd ventricle - Two other round-shaped hyperechoic masses, within the frontal horns of the lateral ventricles in direct continuity with the choroid plexus.	Thriving normally, no specific syndrome suspected.
5	Suspicion of ACC or Dysgenesis of CC	- Mild bilateral ventriculomegaly - Possible heterotopic grey matter	NNE
4	Hypoplasia of CC	- Ventriculomegaly	NNE
18	None	- Pai syndrome - Abnormally shaped nose - Polyp-like structure on the forehead	NR Pai syndrome
3		- Ventriculomegaly - Hypoplasia of the vermis - Limbs around 5th centile - Goldenhar syndrome - Left sided cleft lip - Limbal dermoid on the inner aspect of the left eye.	NR

ACC: Agenesis of corpus callosum; ADHD: Attention deficit hyperactivity disorder; CC: Corpus callosum; NNE: Normal neurological evaluation; NR: Not reported; pACC: Partial Agenesis of corpus callosum; TOP: Termination of Pregnancy; US: Ultrasound.

Finally, intracranial haemorrhage may mimic some brain tumors, however it usually presents changing echographic features in follow-up sonographic exams.

The anomalies that are most frequently associated with pericallosal lipomas are CC alterations, making antenatal counselling difficult even in cases without associated cerebral malformations. Neurodevelopmental evolution in isolated ACC was assessed in a systematic review suggesting abnormal outcomes in 25–35% of the cases.[33] Parental counselling is challenging since clinical manifestations of ACC vary widely. Perinatal and postnatal outcomes of pericallosal lipomas with or without ACC have usually been reported as normal.[1,5–19] We could think that the presence of other anomalies in the central nervous system would probably indicate a wider damage and therefore be associated with a worse perinatal outcome (Table 4). Unfortunately, the literature review does not allow us to draw any conclusions on this matter, and further studies would be needed to assess this.

However, the longest follow-up reported was 11 years,[17] which seems short considering that problems associated with ACC could appear later. Neurological examination was normal in all cases diagnosed with curvilinear lipoma, whereas up to 25% of the cases with tubulonodular lipomas in which evolution was specified had some anomaly in the follow-up. All the authors agree that even with normal neurological examination, long-term prognosis is unknown and clinicians should be cautious when counselling. Pericallosal lipomas have been associated to seizures in paediatric



Graphic 2 – Morphology of normal corpus callosum and typical localisations of corpus callosum lipoma. Left: Morphology of normal corpus callosum. Right: Typical localisations of corpus callosum lipoma depending on the type of lipoma: tubulonodular lipoma (white arrow) typically anteriorly located and curvilinear lipoma (black arrow) typically posteriorly located.

or adult life,[34] mental retardation, headache[22] and motor, sensory and neuropsychological disorders.[35] Most of the data we currently have regarding the symptoms associated with pericallosal lipomas come from cases diagnosed in the childhood[22] or adulthood.[23] This is a limitation that needs to be taken into account as we cannot ascertain whether these lipomas were already present in the prenatal life or appeared in the post-natal period. The relationship between these symptoms and the presence of the pericallosal lipomas has been described as being incidental.[36] It is therefore advisable to follow-up patients until late childhood.

The increasing number of pericallosal lipomas prenatally diagnosed and the improvement in the description of the prenatal findings as shown in our review go hand in hand with the efforts that are being performed to improve knowledge about ACC's prognosis. Diffusion Tensor Imaging (DTI) and tractography have allowed studying fetal axonal organization from 20 weeks of gestation.[37] ACC is one of the most frequent anomalies related to failure in the development of white matter, also known as axonal guidance. Axonal guidance is primarily based on processes that depend on multiple genes, axon guidance molecules, growth factors, cell adhesion molecules and neurotransmitters.[38] Failure in axonal guidance may be due to lack or anomalies of these factors, but the presence of a mechanical factor such as an interhemispheric cyst or lipoma can act as a barrier preventing these tracts from decussating.[39,40]

In isolated ACC, DTI has proven that heterotopic interhemispheric connectivity is present and has depicted the accessory Sigmoid[39] and Probst bundles, considered functional compensations, with a structural integrity similar to normally configured CC.[41,42] Tractography has revealed a prenatally differently organized connectome in acallosal brains[43,44] with greater interindividual variability than that of normal patients.[45] These abnormal pathways, already present at early stages of fetal brain development,[44] are not exclusively due to postnatal neuronal plasticity. This variability could be one of the reasons why neurological prognosis of ACC can vary so widely. Future studies with these imaging techniques in the presence of an interhemispheric lipoma might be useful in optimizing prenatal counselling.

Finally, management does not include surgical excision of the lipoma.[46] Not only is this lesion benign, but also its excision would not solve the symptoms as there is usually a much wider lesion of the brain underlying, as we previously mentioned.

There were 6 terminations of pregnancy among the published cases, all of them after 24 weeks (4 of them after 32 weeks). This is not always an option, depending on the law of the countries.

The main limitations of this review are the heterogeneity in the description of the cases, the lack of report of the type of pericallosal lipoma in these articles and the short follow-up of the infants. The heterogeneity in the description could be explained by the fact that most of the articles are single case reports, some published almost thirty years ago. The type of pericallosal lipoma was not reported in 16.3% of the cases included, not allowing us to include those cases in the two groups of lipomas to further describe their characteristics (Table 2). And finally, short follow-ups are frequently an issue given patient mobility and their shift into paediatric care. Despite these limitations, we have extracted valuable information on pericallosal lipomas in a way that has not been presented before.

5. Conclusions

In summary, prenatal diagnosis of pericallosal lipomas should prompt an exhaustive examination. It is of utmost importance to classify the type of lipoma and assess intracranial and extracranial structures with ultrasound and fetal MRI. According to our review curvilinear lipomas are mostly associated to CC hypoplasia and present favourable neurological prognosis whereas tubulonodular lipomas present a higher frequency of associated neurological anomalies including complete or partial ACC. Parental counselling should be based on this classification and the associated findings as the prognosis varies widely. However, clinicians should be cautious, as further studies with longer follow-up are necessary to increase our knowledge of this entity.

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Conflict of interest

The authors report no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.09.009.

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