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Review

Nasal glial heterotopia: a systematic review of the literature and case report

Eterotopia gliale nasale: una review sistematica della letteratura e case report

Montserrat Gallego Compte[1], Thomas Menter[2], Nicolas Guertler[1,3], Simona Negoias[1]

[1] Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital of Basel, Basel, Switzerland; [2] Department of Pathology, Institute of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Switzerland; [3] Department of Otorhinolaryngology, University Children's Hospital Basel, University of Basel, Switzerland

SUMMARY

Nasal glial heterotopia (NGH) is a rare congenital, non-neoplastic displacement of cerebral tissue in extracranial sites. Together with a case report of NGH, we present the first systematic review of all published cases in order to summarise the relevant clinical findings and appropriate therapy, making the available evidence accessible to decision makers. A total of 72 original publications including 152 NGH cases were identified. The male:female ratio was 3:2. Most patients were children under 18 years (130 patients) and only 8% of cases were diagnosed in adults. The main clinical presentation forms were asymptomatic masses around the nasal root as well as nasal congestion. Magnetic resonance imaging was performed in 39% of patients, computed tomography in 22% of patients and a combination of both in 20% of patients. A diagnostic biopsy was performed in only 7 patients. All patients underwent surgical treatment and recurrence was reported in 14 patients within the first year of follow-up. In conclusion, NGH should be considered as a differential diagnosis of nasal masses in children. MRI is mandatory in order to exclude a connection to the central nervous system. Complete resection is curative treatment.

KEY WORDS: nasal glial heterotopia, nasal glioma, neuroglial heterotopia, nasal cerebral heterotopia

RIASSUNTO

L'eterotopia gliale nasale (NGH) è una rara dislocazione congenita e non neoplastica del tessuto cerebrale nei siti extracranici. Insieme a un case report di NGH, presentiamo la prima revisione sistematica di tutti i casi pubblicati al fine di riassumere i risultati clinici rilevanti e la terapia appropriata, rendendo le prove disponibili accessibili ai decisori. Sono state identificate un totale di 72 pubblicazioni originali, che hanno analizzato 152 casi di NGH. Il rapporto maschi:femmine era 3:2. La maggior parte dei pazienti erano bambini sotto i 18 anni (130 pazienti) e solo l'8% dei casi è stato diagnosticato negli adulti. Le principali forme di presentazione clinica erano masse asintomatiche intorno alla radice nasale e congestione nasale. La risonanza magnetica è stata eseguita nel 39% dei pazienti, la tomografia computerizzata nel 22% dei pazienti e una combinazione di entrambe le tecniche è stata utilizzata nel 20% dei pazienti. Una biopsia diagnostica è stata eseguita in soli 7 pazienti. Tutti i pazienti sono stati sottoposti a trattamento chirurgico ed è stata segnalata una recidiva in 14 pazienti entro il primo anno di follow-up. In conclusione, l'NGH dovrebbe essere considerato fra le diagnosi differenziali delle masse nasali nei bambini. La risonanza magnetica è indispensabile per escludere una connessione con il sistema nervoso centrale. Una resezione completa è il trattamento curativo.

PAROLE CHIAVE: *eterotopia gliale nasale, glioma nasale, eterotopia neurogliale, eterotopia cerebrale nasale*

Introduction

Neuroglial heterotopias are rare congenital, non-neoplastic displacements of cerebral tissue in extracranial sites. The incidence of congenital nasal masses

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Correspondence
Montserrat Gallego Compte
Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital of Basel, Petersgraben 4, CH-4031 Basel, Switzerland
Tel. +41 77 9916092
E-mail: montserrat.gallego@usb.ch

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is reportedly 1 in 20,000-40,000 live births [1,2], and nasal glial heterotopia (NGH) accounts for approximately 5% of them [3]. Since the nose and nasopharynx are the most commonly involved areas, NGH is also known as nasal glioma [4]. Other affected sites include ear, face, neck and orbit. Nasal glioma was probably reported for the first time by Reid in 1852 [5], but the term itself was introduced by Schmidt in 1900 [6].

The development of nasal cerebral heterotopias is embryologically similar to that of nasal encephaloceles or dermoids. During retraction of the embryonic dural diverticulum, remnants of neural glial tissue become sequestered when their connections to the subarachnoid space are pinched off and obliterated [7,8]. The lack of subarachnoid communication distinguishes NGH from anterior encephaloceles [9]. The distinction between glioma and encephalocele is not possible based on histopathologic findings because glial tissue may be the predominant or exclusive component in both types of lesions [10].

Due to the rarity of this entity, its diagnosis can be delayed and the diagnostic tools, treatment options and follow-up may be unclear. Although some reviews exist, they are neither systematic or complete [4,11]. We present a case report and the first systematic review of all reported NGH.

Case report

A 4-month-old boy was referred to our clinic due to nasal obstruction with choking when breast-feeding since birth. No further symptoms were reported. The physical examination revealed an obstructive swelling of the inferior turbinate in the right nasal cavity as well as a nasal septum deviation to the left side. Initial therapy with cortisone-containing nasal spray proved unsuccessful. The follow-up showed that the findings were persistent and the symptoms did not improve. Imaging was advised, which was refused by the parents. Due to persistent symptoms, a magnetic resonance imaging (MRI) was performed at the age of 1 year, which showed a tumour in the right nasal cavity in contact with the inferior nasal turbinate with extension to antero-cranial to the roof of the nose. An intracranial connection as well as an encephalocele were ruled out (Fig. 1). Subsequently, endoscopic examination with biopsy under general anaesthesia was performed. During procedure, it was found that the basal part of the lesion was located in the anterior part of the inferior turbinate and extended cranially to the roof of the nose (Fig. 2A). Histopathological examination confirmed a diagnosis of neuroglial heterotopia (Fig. 3). Immunohistochemical staining for glial fibrillary acidic protein (GFAP) confirmed the presence of glial tissue, S100 and synaptophysin and chromogranin A were positive in neurons. There were no signs of malignancy. An endoscopic excision was planned at the age of 1 year and 2 months. The tumour appeared as a white doughy mass with no clear margins. Owing to its extension and difficulty to identify the tumour margins, we decided to improve the exposure of the mass by a combined approach with a lateral rhinotomy (Figs. 2B-D). During the operation, there were no defects of the anterior skull base and no signs of intracranial connection. Histologically, the surgical margins on the lateral and anterior nasal wall as well as inferior turbinate were involved and revision surgery was performed one week later. These additional resections did not identify more remnants of the glioneuronal heterotopia. The postoperative recovery period was uncomplicated and the child was discharged.

Postoperative endoscopy and control MRI confirmed that the mass was completely removed. At 1 year follow-up, both MRI and nasal endoscopy including biopsy under general anaesthesia showed no signs of residual tissue or recurrence (Fig. 1B, Fig. 2E,F). The scar of the lateral rhinotomy was barely visible.

Materials and methods

A systematic literature search was done using PubMed and following a flow diagram based on the PRISMA Statement from 2015 [12] (Fig. 3). PubMed was searched up to October 27th 2021 using the keywords (nasal OR nose OR endonasal OR intranasal OR extranasal) AND (glial OR neuroglial OR glioma) AND (heterotopia OR heterotopic). No further search restrictions were made. Additional articles were identified through hand searching from reference reviews. In order to avoid duplication, there were no reviews included in the analysis, but only original case publications.

The search results were screened by titles and abstracts on the basis of the exclusion criteria. After this selection, articles were retrieved or requested in full text and assessed for eligibility. Some articles were excluded from further study for reasons of "full text not available" or insufficient clinical information. In one case of possible duplication, the author was contacted. A graphical representation of the screening process is shown in Figure 3.

The following parameters were listed for analysis: gender, age at the time of surgery, location of the tumour, laterality, symptoms, imaging, biopsy, type of surgery, bony defect, intracranial connection, length of follow-up and recurrence.

Statistics

The data of patients included in the review were analysed by descriptive statistics.

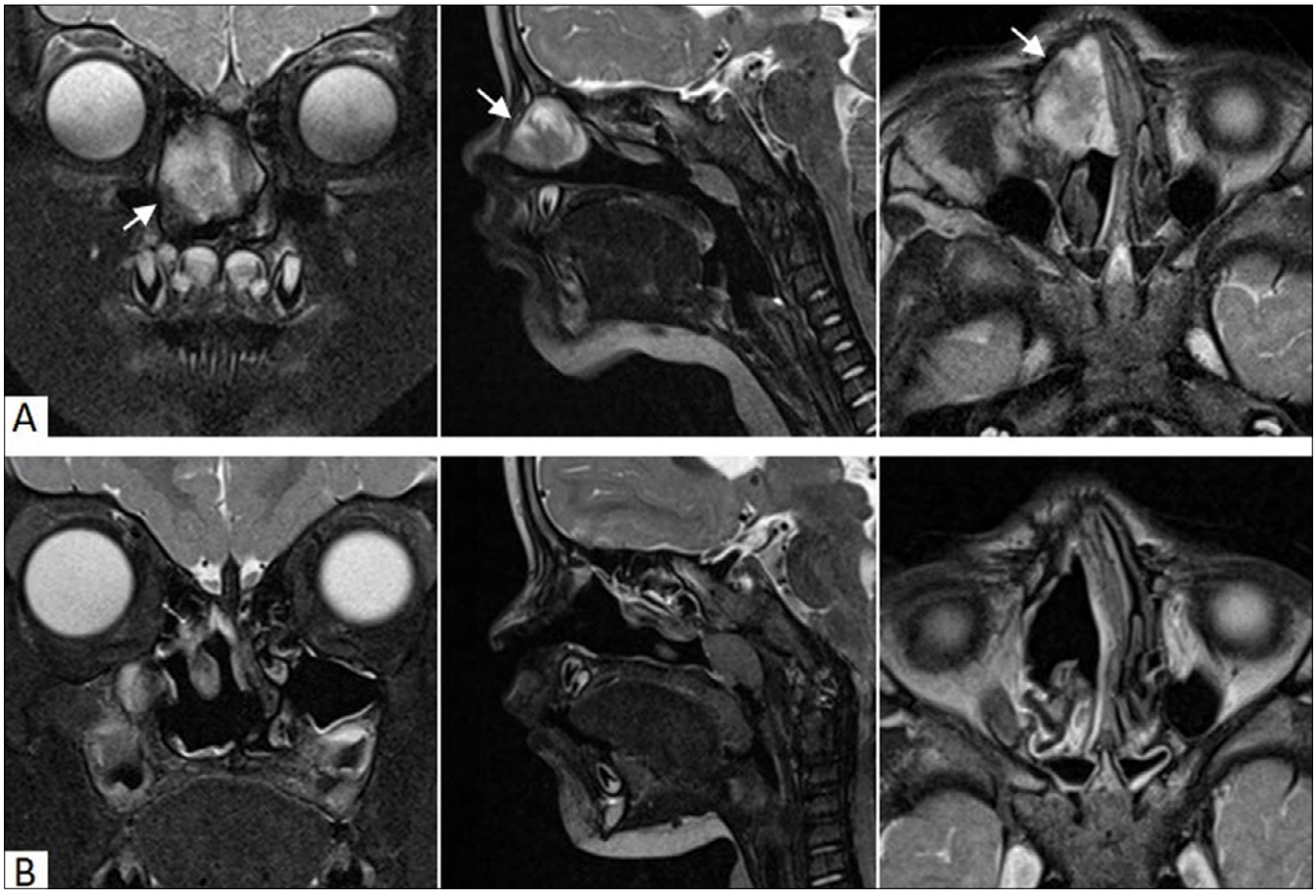

Figure 1. (**A**) MRI T2-weighted image showing the mass (arrows) in the right nasal cavity, in contact with the inferior nasal turbinate, with a dimension of 1.7 x 2.6 x 2.1 cm and no connection between the mass and the dura or brain. (**B**) MRI T2-weighted image 1 year after surgery showing no recurrence of the NGH.

Results

Our search yielded 152 case reports resulting from 72 publications and our case (Fig. 3).

An extensive review of literature undertaken by Lamesch [11] included 166 cases between 1900 and 1986 extracted from reviews as well as original case reports. Through hand searching, 24 of these 166 cases could be retrieved and included in our publication. This means, that in addition to our reviewed 152 cases, 142 additional non-retrievable cases of nasal glioma were documented in the review from Lamesch, making a total of at least 294 reported cases of this entity. These 142 cases were excluded for lack of traceable documentation.

Data regarding the analysed NGH cases is summarised in Table I. A male:female ratio of 3:2 was identified. Most patients (84%) were diagnosed and treated before the age of 3. Only 11 patients were diagnosed during adulthood, the remaining were children (92%). The location of the lesion was intra-nasal (located in the nasal cavity or sinuses) in 69 cases, extra-nasal (protruding from the nasal root) in 54 patients and mixed in 29 patients. All adult patients who were included in this study had an intra-nasal form of NGH. There was no difference in the laterality of the lesion with 42% left-sided lesions and 45% right sided lesions. In only 12 patients (12% of the reported cases) did the tumour appear in a purely midline location.

The most common clinical presentation of a NGH is an asymptomatic tumour (49%) or with nasal congestion (41%). The majority of patients underwent MRI (39%) prior to surgery. Computed tomography (CT) scan was the preferred imaging method in 22% of cases, and a combination of CT and MRI was performed in 25 patients (20%). An additional ultrasonography was used as a complementary diagnostic method only for extra-nasal tumours in 9 cases. In isolated cases between 1950 and 1998, X-ray was used. A diagnostic biopsy was performed in only 7 cases (5%).

Surgery was the only therapy applied. An external approach was used in 70 cases, while 49 patients underwent

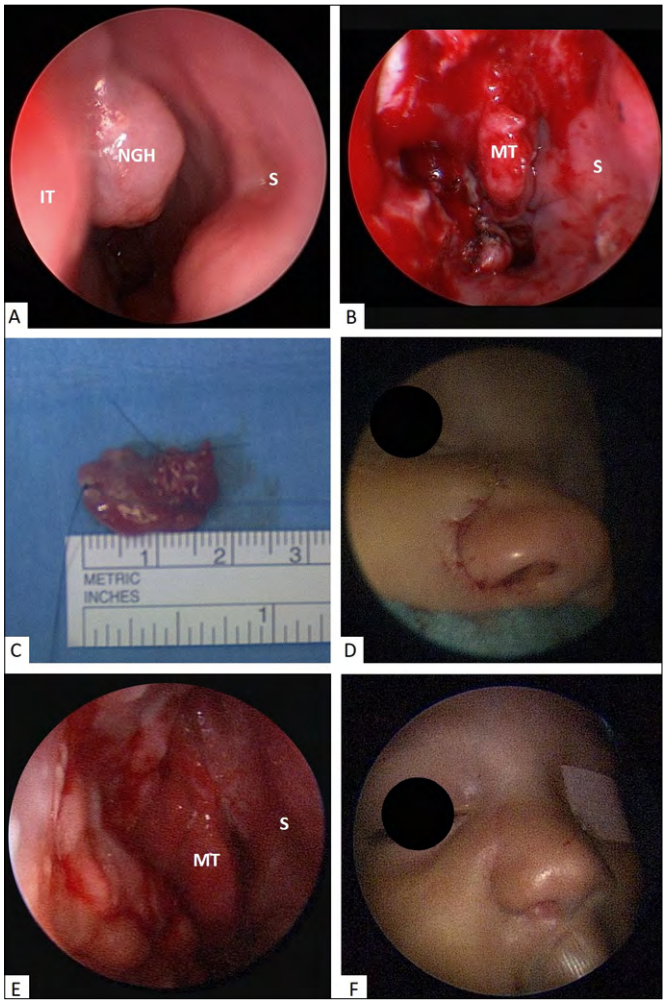

Figure 2. (**A**) nasal endoscopy before tumour resection (IT: right nasal inferior turbinate, NGH: nasal glial heterotopia, S: septum); (**B**) intraoperative nasal endoscopy (MT: right nasal middle turbinate, S: Septum); (**C**) resected mass; (**D**) result after endoscopic resection and lateral rhinotomy; (**E**) postoperative nasal endoscopy shows an unobstructed right nasal cavity (MT: right nasal middle turbinate, S: septum); (**F**) scar of the lateral rhinotomy during postoperative nasal endoscopy.

endoscopic or intranasal microscopic surgery. In 16% of cases the type of surgery was not specified. Other surgical approaches included explorative craniotomies in cases in which diagnostic imaging showed a possible intracranial connection and an intra-oral approach in a case of simultaneous cleft palate and NGH.

Histological evaluation of surgical margins was reported in only 11 cases.

An intracranial connection appeared in 15 cases, all described as a fibrous stalk. Out of these 15 cases with intracranial connection, 3 were located extra-nasal and the rest were intra-nasal or mixed. Bony defects were described in 13% of cases and were most frequently found in the nasal

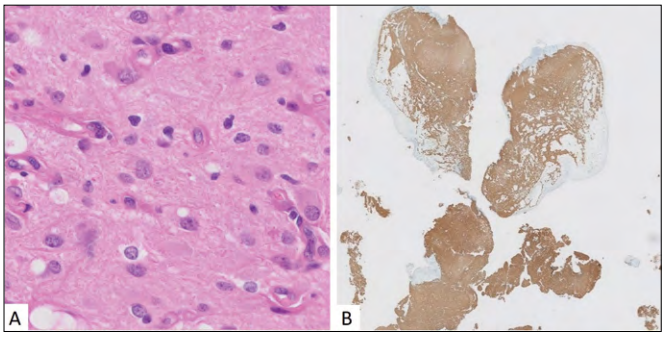

Figure 3. (**A**) high magnification of the glioneuronal heterotopia showing both neurons and glial cells (H&E, 400x); (**B**) staining for GFAP (glial fibrillary acidic protein) shows the extent of the glioneuronal heterotopia in the first resection.

bone, followed by the cribriform plate, ethmoid and sphenoid.

Recurrence after surgery was reported in 14 cases. They appeared between 5 weeks to 11 months after surgery. All patients with recurrence underwent revision surgery. Postoperative follow-up investigations to rule out recurrence were reported in only 5% of cases and included endoscopy and MRI.

Discussion

Nasal glial heterotopia is a rare nonhereditary, benign congenital anomaly. Since first described by Reid in 1852, approximately 300 cases have been reported. In this study, the first systematic review of cases of nasal glial heterotopia or the so-called "nasal glioma" in children and adults published so far is presented, including a total of 152 retrievable cases described in original publications. The available reviews lack a systematic approach. For example, the latest review of the literature, performed in 2020 by Yan [4], describes only 60 paediatric cases.

NGH occurred with a male to female ratio of 3:2, as described in previous reports [4,13]. The majority of patients were diagnosed and treated before the age of 1 year (66%). Nevertheless, this entity can also be found in adulthood (8%), always involving an intra-nasal lesion (inside the nasal cavity). The intra-nasal location of NGH is the most frequent (45%) and was generally diagnosed much later than the extra-nasal type. The incidence rate of the mixed type of NGH is 19%. The leading symptom was nasal congestion (41% of all NGH cases) although it can also appear in form of rhinorrhoea, epistaxis, meningitis, chronic rhinosinusitis and strabismus (8%). The extra-nasal type of NGH (36%) is normally detected after birth in form of a firm, non-compressible mass often with a red or bluish appearance on the dorsum of the nose. The most common locations for NGH

Table I. Results of the systematic review on nasal glial heterotopia.

Variable	N = 152	Ignoring not reported cases for each variable
Gender		**N = 123**
Female	49 (32%)	49 (40%)
Male	74 (49%)	74 (60%)
Not reported	29 (19%)	
Age at time of surgery		**N = 141**
≤ 1 year	93 (61%)	93 (66%)
1-3 years	26 (17%)	26 (18%)
4-6 years	6 (4%)	6 (4%)
6-18 years	5 (3%)	5 (4%)
Total children	130 (86%)	130 (92%)
> 18 years	11 (7%)	11 (8%)
Not reported	11 (7%)	
Location		
Extra-nasal	54 (36%)	
Intra-nasal	69 (45%)	
Mixed	29 (19%)	
Laterality		**N = 99**
Left	42 (28%)	42 (42%)
Right	45 (30%)	45 (45%)
Midline	12 (8%)	12 (12%)
Not reported	53 (35%)	
Symptoms		**N = 139**
Asymptomatic	68 (45%)	68 (49%)
Nasal congestion	57 (38%)	57 (41%)
Cough, choking when feeding	3 (2%)	3 (2%)
Other: rhinorrhoea, epistaxis, meningitis, strabismus, chronic rhinosinusitis	11 (7%)	11 (8%)
Not reported		
Imaging		**N = 124**
CT	27 (18%)	27 (22%)
MRI	49 (32%)	49 (39%)
CT + MRI	25 (16%)	25 (20%)
Additional ultrasonography	9 (6%)	9 (7%)
No imaging	7 (5%)	7 (6%)
Other: X-Ray, PET-CT	17 (11%)	17 (14%)
Not reported	27 (18%)	
Diagnostic biopsy	7 (5%)	
Surgical approach		**N = 148**
External / rhinotomy	70 (46%)	70 (47%)
Intranasal /endoscopic	49 (32%)	49 (33%)
Combined	2 (1%)	2 (1%)
Not defined	23 (15%)	23 (16%)
Other (craniotomy, enoral)	4 (3%)	4 (3%)
Not reported	4 (3%)	
Bony defect	19 (13%)	
Intracranial connection		**N = 134**
Fibrous stalk	15 (10%)	15 (11%)
No connection	119 (78%)	119 (89%)
Not reported	18 (12%)	
Follow-up (2 months to 26 years)		**N = 101**
Recurrence	14 (9%)	14 (14%)
No recurrence	90 (57%)	90 (86%)
Not reported	51 (34%)	
Postoperative imaging/endoscopy	8 (5%)	

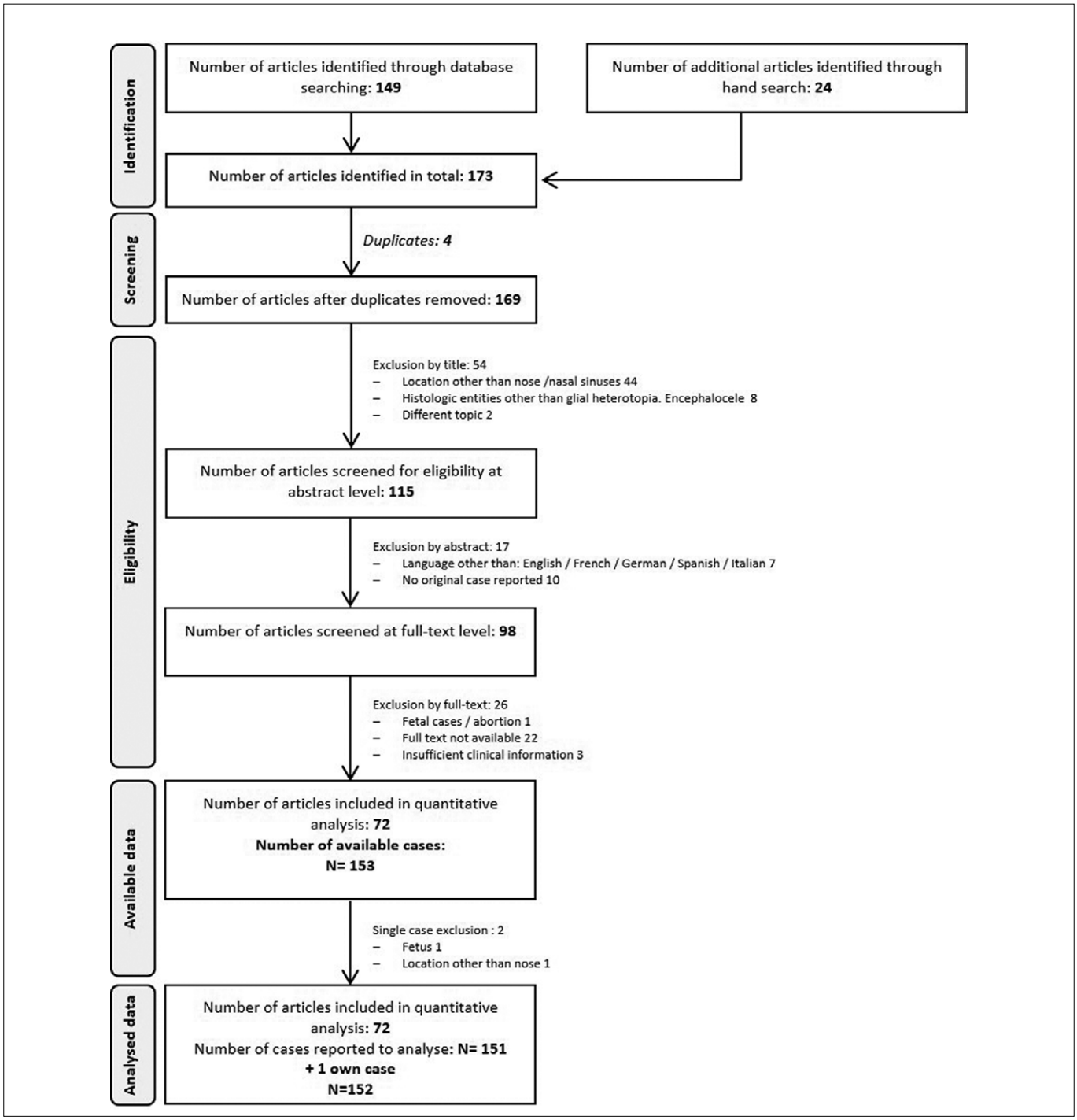

Figure 4. Flow diagram of the publication search, based on the PRISMA Statement 2015 [12].

include the glabella and nasomaxillary suture and they tend to grow in proportion to the child [14].

The evaluation of a congenital midline mass includes nasal endoscopy as well as an imaging technique to evaluate the extension of the tumour and exclude intracranial involvement or association with bone defect prior to surgery. The most common diagnostic imaging was MRI alone (39%) or with additional CT (20%), while CT alone was used in 22% of cases. In MRI, the lesion has signal intensity similar to the brain on T1-weighted images (T1-WI) and high signal intensity on T2-weighted images (T2-WI), with many cystic regions and does not enhance. No diffusion restriction

appears in diffusion-weighted imaging (DWI). MRI is essential to rule out intracranial communication. Computed tomography demonstrated adjacent osseous structures and bone defects preoperatively. In CT images, it appears as a large, well-defined, hypodense soft-tissue mass [15]. X-ray alone (14%) and no imaging diagnosis (6%) was reported in a few cases. A timeline bias must be considered for imaging diagnosis, with more recent case reports increasingly using MRI with or without CT. B-mode ultrasonography was used in 7% of cases to evaluate extension and bony defects of ex-nasal NGH. In summary, an MRI would be mandatory, while CT is highly recommended if bony defects are suspected or as navigation support for endoscopic surgery.

A diagnostic biopsy was performed in only 7 cases (5%). According to the previous reviews, biopsies are not advised in congenital midline masses because of CSF leak risk in case of intracranial connection [16]. In our opinion, a biopsy may be advisable especially in adults to exclude malignity, always after an appropriate diagnostic imaging (MRI) to rule out an intracranial connection. MRI and biopsy could be combined to avoid a second anaesthesia in paediatric patients. Neurosurgical consultation may still be necessary in cases of reasonable doubts or intraoperatively discovered tract coursing to the skull base.

Tetzlaff et al. published the only case of sinonasal undifferentiated carcinoma (SNUC) arising in a background of NGH in a 37-year-old patient [17]. Numerous syndromes have been described in association with encephaloceles, but NGH are typically isolated lesions, with syndromic association being exceedingly rare and only 1 case reported of NGH in association with metopia craniosynostosis [18]. There is no association described between the presence of heterotopic neuroglial tissue with an epithelial-derived malignancy [17]. This could be explained due to the young age of most patients diagnosed and treated for NGH. Although there is no data to suggest a causal connection between SNUC and NGH, it would be interesting to follow cases of both entities in order to report any potential causal or syndromic association between these two conditions.

The treatment of choice is complete surgical excision, which is curative and allows pathohistological confirmation of the diagnosis. The surgical approach will depend on the extension and localisation of the NGH: external rhinotomy, endoscopic resection or combined approach are the most common techniques. Since accurate intraoperative histologic diagnosis may be difficult, the surgeon must decide either to proceed with radical, potentially deforming surgery or to operate less radically with the possibility of local recurrence. In our case, due to the location and extension of the mass towards the lateral and anterior nasal wall and insufficient exposure through endoscopic approach, we decided to perform a combined technique by lateral rhinotomy. While in the last years an endoscopic approach has been proven to be the favourite for intra-nasal lesions, we consider that each case should be individually evaluated when planning surgery. Early resection is advised to avoid the development of craniofacial deformities, particularly involving the nasal architecture. Before any surgical intervention, imaging is mandatory. A connection to the brain was found in 11% of cases, always in the form of a fibrous stalk, which does not contain a direct fluid-filled tract that communicates with the subarachnoid spaces. This incidence rate is similar to the previously described by Moron et al. [9]. Bone defect appeared in 13% of cases and were most frequently found in the nasal bone.

A complete surgical excision showing no remains of NGH in the margins should guarantee no recurrence in the future. In our case, a revision had to be performed one week after primary surgery due to histologically positive surgical margins. Although most authors describe to have performed a complete surgical resection, histological margins were reported in only 11 cases: 10 showed negative margins and never developed recurrence, while in our case margins were involved in the primary excision. Only 14% of cases presented recurrences after surgery and all appeared in a short period of time (from 5 weeks to 11 months). These incidence rates differ from those reported by Yan et al. who described a 5% recurrence during a follow-up from 0.5 to 3 years [4]. This difference may be attributable to the relatively small sample size (60 patients) of the study by Yan et al. Previous reviews reported the lack of recurrence or tumour-invasion into adjacent tissues during long-term follow-up [19]. Schroth et al. [20] described a regrowth of an intra-nasal NGH mass just 5 weeks after primary excision, which was more infiltrating than the initial tumour which required a much more mutilating excision including nasal cartilages, upper nasal septum and parts of the nasal bone, as well as a posterior reconstruction of the nose with autologous skin and ear cartilage transplants to correct the defects. Although differentiation between recurrence and persistence is always difficult, we postulate that given the benign character of the entity, a persistence due to incomplete resection is more probable than a true recurrence. Based on this data and our experience, we would recommend performing a complete excision with histologically free margins and a follow-up period of at least 12 months after surgical excision including clinical examination. In uncertain cases, MRI should be evaluated during the follow-up. In our case, we performed both MRI and nasal endoscopy with biopsy simultaneously to increase safety and avoid a possible future anaesthesia for the patient.

In terms of strengths and limitations of our study, we present the first systematic review of NGH in both paediatric and adult patients comprising the most comprehensive analysis of published cases. The systematic method ensures transparency and reproducibility. On the other hand, it misses data from incomplete or not properly documented cases, which were excluded, as well as data on older non-retrievable cases, which could have an impact on the results.

Conclusions

The greatest difficulty in yielding a diagnosis of nasal glial heterotopia is not thinking of the diagnosis, especially in case of older patients. Despite its rare occurrence, NGH should be considered as a differential diagnosis of nasal masses in neonates and young children. An MRI is mandatory to exclude communication with the central nervous system and to plan a surgical approach. An additional CT should be performed if bony involvement is suspected or necessary for endoscopic surgery. A complete resection is the curative treatment. Histological evaluation of the surgical margins can reduce the risk of recurrence. A follow-up period of 1 year seems to be sufficient, as all recurrences appeared in the first 12 months and which might be related to incomplete resection in the cases reported.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

MGC: investigation, methodology, writing – original draft and editing. TM: resources. NG: supervision, writing-review. SN: conceptualisation, methodology, supervision, writing – reviewing and editing.

Ethical consideration

We consulted the Ethikkomission Nordwest - und Zentralschweiz (EKNZ). According HFG Art. 3 our Case Report does not require an ethical aproval as the patient's personal details were kept anonymous. The authors certify. that they have obtained all appropriate patient consent forms.
The systematic review of this article does not contain unpublished human or animal trials.

Data availability

The references of all included cases as well as datasets generated and analysed during the present study are available from the corresponding author on reasonable request.

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