Ganglioneuromas across age groups: Systematic review of individual patient data

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Abstract

Background: Ganglioneuromas are very rare tumours of the sympathetic nervous system. Clinical and pathological knowledge is currently based on largely incomparable registries and case series that focus on paediatric or adrenal cases. To comprehensively characterize the full clinical spectrum across ages and locations, a meta-analysis was performed where amenable and complemented by systematic literature review of individual patient data (IPD).

Design: Articles containing "ganglioneuroma" in English on humans, published from 1/1/1995-6/27/2018, were identified from PubMed. Aggregate data from 10 eligible patient series on 19 variables were considerably inhomogeneous, restricting meta-analysis to age and gender distribution. To determine basic disease characteristics across ages and locations, IPD were retrieved from case reports and small case series (PROSPERO CRD42018010247).

Results: Individual patient data representing 364 cases revealed that 65.7% (60.6%-70.4%) were diagnosed in adults, more frequently in females (62%, 56.9%-66.9%). 24.5% (20.3%-39.1%) were discovered incidentally. Most often, ganglioneuromas developed in abdomen/pelvis (66.2, 32.1% adrenal). With age, the proportion of ganglioneuroma localizations with high post-surgical complication rate (35.6% head/neck and 16.3% thorax) decreased. Contrarily, the diagnosis of adrenal ganglioneuromas (<1% post-surgical complications) increased with age. Hormone production, hypertension or coincidence with another non-neuroblastic neural-crest-derived tumour component was more common for adrenal location. Recurrence and metastatic spread have not been reported for ganglioneuromas without secondary tumour component.

Conclusions: This work summarizes characteristics of the currently largest number of international GN patients across all ages. The data confirm a benign nature of GN, independent of age. Age-related differences in predominant tumour location, associated post-surgical complications and hormone production suggest case-centred management strategies.
1 | INTRODUCTION

Ganglioneuromas (GN) are the most mature entity of neuroblastic tumours. They are benign and develop from the sympathetic nervous ganglia, including the adrenal medulla. Reliable epidemiological data including incidence and prevalence are not available. GN were estimated to account for 4% of adrenal incidentalomas (prevalence ~ 2%).1

Mature elements including ganglion cells, neurites, fibrous tissue and Schwannian stroma are the dominant histologic features. Current classification systems distinguish ‘mature’ and ‘maturing’ GN, and the latter contain maturing gangliocytes.2-4 In the currently largest study including 144 maturing and 18 mature GN, Decarolis et al showed an excellent outcome for all GN patients after resection.5 Spontaneous or treatment-induced differentiation from the most unfavourable immature neuroblastomas (NB) and the more mature ganglioneuroblastomas (GNB) may occur. Coincidence of GN with another non-neuroblastic neural-crest-derived tumour component (pheochromocytoma/paraganglioma, neurofibroma, or peripheral nerve sheath tumour (PNST)) rarely occurs and is referred to as non-neuroblastic composite GN in analogy to the well-defined classification of composite pheochromocytoma/paraganglioma,6 but not to be confused with nodular GNB.3,6,7

The age at diagnosis is generally higher for GN than NB or GNB; however, reported means range from the 1st to 5th decade of life.8,9 Clinical presentation of GN is nonspecific, and thus, diagnosis is often made incidentally (26%-78%).9-11 Catecholamine metabolism, determined by increased blood or urine levels of homovanillic acid (HVA) and/or vanillylmandelic acid (VMA), (the final metabolite of dopamine and epinephrine/norepinephrine, respectively), or tumour uptake of the norepinephrine analogue metaiodobenzylguanidin (MIBG), was reported in up to 39% and 57% of GN.12 In addition to HVA and VMA, increased urine and plasma levels of catecholamines and their metabolites (dopamine/methoxytyramine, norepinephrine/normetanephrine, and to a lesser extent epinephrine/methamphetamine) have been observed in patients with neuroblastoma12 and are almost always increased in patients with pheochromocytoma/paraganglioma.13 Thus, elevated catecholamine metabolism may also indicate presence of a paraganglioma or immature neuroblastic element, and can be most sensitively diagnosed based on elevated plasma metanephrines.12,14

Clear distinction of GN from other tumour entities based on imaging is currently not possible. In hormonally inactive GN, biopsies can be safely performed; however, overlooking poorly differentiated cells or other tumour entities due to insufficient sampling may have fatal consequences for the patient. Thus, complete resection followed by thorough histopathological confirmation is preferred. Even after incomplete resection, progression15 is rare. Individual cases of potential transformation into a more aggressive tumour have been proposed.16,17 Considering the relatively high risk for surgical complications, less radical, case-centred surgical strategies have been suggested5,8,10,11,15

Current information on GN shows discrepancies in basic characteristics like mean age of onset, most frequent localization or post-surgical complication rate between reports. Most likely, differences in patient selection between published studies are responsible. The majority of data are from juvenile patient registries, while patient series including adult patients are restricted to adrenal location. Aim of the present work was to comprehensively summarize clinical and pathological characteristics of patients with GN independent of age and GN location.

2 | MATERIALS AND METHODS

Literature selection and data collection were performed according to the PRISMA statement18 as detailed in PROSPERO protocol CRD42018010247, adhering to the PRISMA-IPD checklist 'items to include when reporting a systematic review and meta-analysis of individual participant data', where applicable. In brief, pilot searches were performed on PubMed to establish most accurate results. Final search criteria were full-text articles containing "ganglioneuroma". Filters were set to "humans", "English" and publication date between 1/1/1995 and the date of last search 6/27/2018. Article type was initially set to "Clinical Trial", "Comparative Study", "Evaluation Studies", "Meta-Analysis", and "Systematic Review" to reveal aggregate patient data. To focus on identifying individual patient data (IPD), article selection was changed to "Case Report", "Case Series", "Review", and "Clinical Trial".

All studies on GN patients were considered eligible for data extraction. Studies on other tumour entities, for example ganglioneuromatosis or ganglioneuroma, were excluded.

For meta-analysis, studies presenting 20 or more GN patients were collected. Studies reporting inseparable data from patients with other tumour entities (eg GNB or NB) were excluded. For systematic review of unselected patients, studies accommodating extraction of single-case data were included.

Abstracts and full texts were screened to dismiss irrelevant publications (PW). Further articles of interest were selected from references of included articles (PW). Variables listed in Table S1 were extracted from relevant articles and entered into separate tables for aggregate and IPD (PW). Reported evidence for elevated hormones varied widely, and 24-hours urine and plasma tests were
mentioned. However, often test and/or body fluid was not specified. Documented catecholamine-related metabolites included epinephrine, metanephrine, norepinephrine, normetanephrine, dopamine, methoxytyramine, VMA, and/or HVA and were summarized to reflect the level of differentiation of the cells of origin as adrenergic (elevated epinephrine and/or metanephrine), noradrenergic (elevated norepinephrine and/or normetanephrine without elevation of epinephrine and/or metanephrine), dopaminergic (elevated dopamine and/or methoxytyramine without elevation of epinephrine, norepinephrine, metanephrine and/or normetanephrine). In other cases, elevation of unspecified metanephrines, catecholamines, VMA and/or HVA was indicated, as reported by the authors.

Articles not specifying any data of interest were excluded. The number of excluded articles and reasons for exclusion at each stage are given in Figure 1.

The data tables were extensively checked for accuracy and consistency and coded for analysis together with a statistician (SF, RW). Any inconsistencies or ambiguities were resolved by reaching consensus among PW, SF and/or RW after discussion.

Meta-analysis (RV) was performed for homogeneous variables from aggregate data. Homogeneity was measured by $I^2$. Proportions were summarized by the inverse-variance method applied to the logit transform to estimate the random-effects confidence interval using the DerSimonian-Laird estimator of variance in R 3.4.4 (R Foundation, Vienna, Austria). Means were summarized by the inverse-variance method using the restricted maximum likelihood estimator and Hartung-Knapp adjustment.

For systematic review, IPD were summarized under exclusion of cases with missing data for the respective variable(s) by descriptive statistics, contingency tables and histograms using R, SPSS 22 (IBM, Armonk, NY, USA) and Stata/SE 14.2 for Macintosh (StataCorp, College Station, TX 77845) (RV, RW). Age distribution was fitted with a beta distribution (JMP 9.2, SAS Inst. Inc, Cary, NC, USA). Median and extremes or quartiles are reported where metric variables exhibited skewed distributions. Variables were grouped by sex, age group, presence or absence of symptoms, tumour location, hormone production, secretotype, or resection margin, were relevant. Exact chi-squared and Wilcoxon tests with simulated distributions were used as a rule. Logarithm

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**FIGURE 1** Article selection for (A) registries and case series summarizing information on 20 or more ganglioneuroma patients and for (B) systematic review of case reports and small case series (<20 patients)
Performance of surgery was high (88.9%-100%). Complete resection was less often achieved in juvenile patient series (56.5%-83.3% \cite{10,11,15} vs 100% \cite{21,23}). Surgical complications were particularly high in studies focusing on young patients (18.4%-30.4%) \cite{8,10,15}. De Bernardi et al described 6.2% as severe, including one death (rupture of major artery (4), brain (1) or thoracic (1) haemorrhage (the latter with cardiocirculatory arrest), paraparesis and bladder dysfunction (1)). Most commonly Horner’s syndrome was reported (9.8\%-12.5\%) \cite{8,10}, persistent in at least 2/3. Local progression was reported in 7 patients with residuals, \cite{5,15} did not occur \cite{8,22} or was not mentioned.

3.2 Systematic review

With support of the NIH library, full texts of 533 identified publications were retrieved. Screening abstracts and full text led to exclusion of 236 articles. In total, 297 included articles yielded IPD on 364 cases (Figure 1B). Numbers of eligible participants for each analysed variable, summary statistics and CI are listed in Table S2. No important issues were encountered in checking IPD.

3.2.1 Patient characteristics

On average, GN patients were 31.2 (0-93, median 28, n = 361). Age distribution was triangular with mode at zero (Figure 3A), indicating that patients below 18 were over-represented. 65.6% of patients were adults.

A significant inequality in sex distribution of 1:1.6 (male proportion 0.38, CI 0.33-0.43, P < .001) was evident, and females were 8.0 years younger at diagnosis (median 26 vs 34, CI 0-10, P = .05).

3.2.2 Symptoms

Ganglioneuromas-related symptoms were reported in 75.5% (275/364), often persisting for 4 weeks or more (79.7%). Symptomatic patients suffered from pain (47.6%, 131/275), swelling (14.5%), gastrointestinal problems (9.8%), neurological problems (9.5%), hypertension (11.3%), skin lesions (7.3%) or bleeding (5.1%). Presence of symptoms was not significantly related to tumour size (OR 1.09 per factor 10 in tumour volume, CI 0.80-1.46, P = .58). Individual symptoms were significantly related to GN location. Swelling most frequently occurred in symptomatic patients with head/neck GN (51.9%), less often for abdominal/pelvic masses (9.5%) (P < .001). Symptomatic patients with adrenal GN were hypertensive in 22.4% compared to 14.7% for abdomen/pelvis, and 0% for head/neck or thoracic manifestation (P = .0036). In the majority of hypertensive cases, evidence for excessive hormone production by other tumours or the GN has been presented (15/17 adrenal, 9/14 abdomen/pelvis). In one case, mass-related renal vessel constriction with renal of tumour volume was normally distributed, permitting performance of t tests. A one-sample binomial test for sex ratio and Fisher’s exact test for two-by-two tables were used to test for statistical significance. P values are not adjusted for multiplicity. We conducted up to 10 tests using the same variable, so that a Bonferroni-Holm procedure would have to start with a level near 0.005. Probabilities of dichotomous features were explored for the influence of metric variables by logistic regression. All confidence intervals (CI) are unadjusted 95% CI.

Patient selection criteria have been documented and were discussed with respect to risk of bias within study and across studies, for example age range and paediatricians as authors. Quality of articles was assessed by reporting on dispersion. Estimation of the risk of bias of IPD has been assessed by comparison with aggregate reports on at least 20 cases. Quality of IPD was assessed as per cent of critical variables reported (sex, age, CT or MRI reported, tumour size, surgery, resection status, follow-up period).

3 RESULTS

3.1 Meta-analysis and descriptive summary of registries and case series

Out of 140 identified articles, 10 were found eligible and aggregate data of 550 patients were extracted (Figure 1A). Information on cohort characteristics is given in Table 1. The majority of patients (76.4%) were from registries and case series focusing on children\cite{5,8,10,15,19} or young patients (<28 years).\cite{11} Reports including older adults were restricted to adrenal GN,\cite{20,21} one explicitly excluding composite pheochromocytomas.\cite{22}

Inhomogeneous reporting and differences in patient selection restricted meta-analysis to patient age and gender distribution. However, patient age seems inappropriately represented by the registries and case series: large differences between mean patient age in paediatric (7.5 years) and other studies (32.8 years) were evident, independent of age group, sex distribution was moderately heterogeneous among studies (I² = 69%). Random-effects meta-analysis did not indicate female predominance (male proportion 0.47, CI 0.39-0.55; Figure 2B).

Other prespecified parameters were merely amenable for descriptive analysis. The rate of symptoms at diagnosis ranged from 17.1%\cite{20} to 73.4%.\cite{11}

The predominant localization of GN was thoracic (37.5%-58.3%)\cite{11,19} or abdominal (29.2%-50.0%).\cite{8,10} However, interpretation was impeded by differences in categorization, for example no distinction of adrenal from abdominal location or combination of abdomen with either thorax or pelvis. Adrenal location was reported in 8.3%-31.7% (100% in series including older adults).\cite{20-22} Head/neck GN were only specified in two studies with 4.2%-5.5%.\cite{10,15}

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| First Author | Geoerger | De Bernardi | Okamatsu | Retrosi | Sanchez-Galan | Li | Shawa | Decarolis | Lee | Xie |
|--------------|----------|-------------|----------|---------|-------------|----|-------|-----------|-----|-----|
| Year         | 2001     | 2008        | 2009     | 2010    | 2014        | 2013| 2014  | 2016      | 2016| 2018|
| Age group    | <27 y    | Juvenile patients | Juvenile patients | Juvenile patients | Not specified | Juvenile and adult patients | Juvenile patients | Juvenile and adult patients | Juvenile and adult patients |
| Restriction to specific tumour location | None | None | None | None | Adrenal | Adrenal, no composite GN | None | Adrenal | Adrenal |
| Country      | Germany\(^a\) | Italy | USA | UK | Spain | China | USA | Germany\(^a\) | Korea | China |
| Number of patients | 49 | a) 70 b) 45 total: 115\(^c\) | 43 | 24\(^b\) | 24 | 29 | 27 | 162 | 35 | 42 |
| Time frame   | 1981-1999 | a) 1979-2005, b) 1982-2005 | 1991-2006 | 1989-2009 | 1992-2012 | 1988-2011 | 1993 - 2012 | 2000-2009 | 2002-2015 | 2005-2016 |
| Relative sex distribution (m:f) | 1.04:1 | 1:2.03 | Not specified | 1.18:1 | 1.18:1 | 1.64:1 | 1:2.38 | Not specified | 1:1.50 | 2:2.3:1 |
| Symptoms at first diagnosis [%] | 73.4 | Not specified | Not specified | 62.5 | 25 | 41.4 | 34.6 | 56.5 | 17.1 | 33.3 |
| Surgery [%]  | 93.8 | a) 93.3 b) 95.7 | 93.0 | 95.8 | 100 | 100 | 88.9 | 92.5 | 100 | 100 |
| R0 [%]       | 57.1 | a) 64.3 b) 70.2 (incl. microscopic margin) | Not specified | 56.5 | 83.3 | 100 | Not specified | 71.1 | 100 | 100 |
| R1 [%]       | 12.2 | a) 19.0 b) 17.2 (includes small macroscopic margin) | Not specified | 17.4 | 0 | 0 | Not specified | Not specified | Not specified | 0 |
| R2 [%]       | 24.5 | a) 16.7 b) 11.9 | Not specified | 26.1 | 16.7 | 0 | Not specified | 28.9 | Not specified | 0 |
| Complications | Not specified | a) 21.4 b) 16.4 | Not specified | 30.4 | 25.0 | Not specified | Not specified | Not specified | 0 | 0 |
| Follow-up years, interval | 0.8-8.2 | Not specified | Not specified | 0.08-11.42 | 0.08-16.17 | Not specified | 0.17-11.25 | Not specified | 0.08-10.0 | 0.31-13.69 |
| Follow-up years, median | 2.1 | 7 | Not specified | 2.8 | 7 | Not specified | 4.17 | Not specified | 1.58 | 5.88 |
| Recurrence/progression | Not specified | Not specified | Not specified | 0 | Not specified | Not specified | 0 | Not specified | Not specified | 0 |

\(^a\)No overlap between Geoerger and Decarolis.

\(^b\)A total of 20 cases were confirmed upon re-evaluation of the histology specimens according to the International Neuroblastoma Pathology Classification, while intermixed ganglioneuroblastoma was diagnosed in 4 patients.

\(^c\)A total of 70 cases were included based on diagnosis of GN in pathology report without re-evaluation. A total of 45 GN were histologically re-evaluated, and diagnosis was confirmed.
parenchymal insult was held responsible for triggering the renin-angiotensin-aldosterone system. Details are given in Appendix S1.

In symptomatic patients, neurological symptoms were more often reported in thoracic (18.2%) and head/neck (15.3%) than abdominal/pelvic (8.4%) or adrenal GN (3.9%) (P = .043).

### 3.2.3 | Tumour characteristics

Ganglioneuromas localization was described in 346 cases. 66.2% were detected in abdomen/pelvis (32.1% adrenal), 17.6% in head/neck and 13.3% in the thorax. Rarely, skin or bone GN in arms or legs (1.5%) or presence of GN at multiple sites (1.5%) was described. Interestingly, proportions of tumour location shifted significantly with age, showing an increasing rate of adrenal location towards middle age (Figure 2B).

Contrary to previous reports with higher numbers of right adrenal GN, IPD revealed no side preference (49 left, 47 right).

Tumour size was reported in 259 cases with maximal tumour diameters between 0.2 and 33.0 cm, median 6.0 cm. The median tumour volume was 62.8 cm³ (0.004-4354.2 cm³).

### 3.2.4 | Hormone production

Hormone release was described in 16.5% of cases (60/364, increased catecholamines or their metabolites in 52, vasoactive intestinal peptide [VIP] in 7, androgens and cortisol in two each, ADH, ACTH and aldosterone in one patient each, including 1 patient with increased VMA and cortisol, 4 patients with increased release of both catecholamines and VIP and one patient with raised catecholamines, VIP and gastrin).

In 28/52 catecholamine-producing GN, presence of pheochromocytoma/paraganglioma or GNB/NB was presented: 24 composite GN (see below), 2 separate pheochromocytomas (HVA, metanephrines), and 2 had a separate neuroblastoma/ganglioneuroblastoma (elevated HVA, VMA and unspecified catecholamine). In one case, the GN developed from a malignant PNST with GN component (dopamine).

In 23 cases, no evidence for an alternative source of catecholamines and their metabolites to GN was reported. In the latter, secretotype was noradrenergic in 6 and adrenergic or dopaminergic in 5 cases each. Elevated metanephrines (1), VMA (2), VMA and HVA (2), or HVA alone (2) were also mentioned. In one patient
without pre-op detection of increased catecholamines, hypertensive crises occurred during and post-surgery. Post-op elevated epinephrine and norepinephrine were noted, which normalized after 12 month, and the patient did not need blood pressure medication any more.70

Adrenal GN released hormones in 32.4%, compared to 13.6% for abdomen/pelvis, 8.7% for thorax and 4.9% for head/neck GN (details on secretotype are given in Appendix S1).

The rate of symptoms was slightly higher for hormone-producing GN (88.3% vs 73%, P = .013); however, this difference was not significant for catecholamine production (86.5 vs 73.7, P = .055). Hypertension was significantly more frequent in patients with hormone-producing tumours (45.3% vs 3.15%, difference 42.1%, CI 29.2%-55.6%, P < .0001), also when focusing on catecholamines and their metabolites (48.9% vs 3.91%, difference 45%, CI 30.7%-59.3%, P < .0001).

Patients with hormone-producing GN were significantly older (median (quartiles) 40.5 (21-56) vs 25 (11-46), difference 15.5 years (CI 3-17), P = .0047), also when focusing on catecholamines and its metabolites (40.5 (25-56) vs 25 (11-46), difference 15.5 years, CI 4-18, P = .0021).

3.2.5 | Functional imaging

Metaiodobenzylguanidin imaging was performed in 15.7% of cases (57/364), with uptake in 59.6% (34/57), including 50% with non-neuroblastic composite pheochromocytoma/paraganglioma component (17/34). Catecholamine-producing or non-neuroblastic composite GN were significantly more often MIBG positive (80% and 94.4%) than noncatecholaminergic (37%, CI for difference 17.7%-63.2%, P = .0013) or noncomposite GN (43.6%, CI for difference 26.5%-67.1%, P < .001).

FDG-PET scan was performed for 19 patients, and tumour uptake was positive in 14, negative in two and not specified in three. This small subset of patients suggests a majority of FDG-PET-positive GN (73.7%, CI 51%-88%).

3.2.6 | Surgical resection

Surgery was performed in almost all cases (93.7%, 341/364). Complete resection (R0) was achieved in 89%, while microscopic or macroscopic margins remained in 2.1 and 8.9%, respectively. In cases where no surgery was performed, diagnosis was based on biopsy (19), exploratory resection (1) or autopsy (3).

Complications were reported for 9.7%, with significant differences between locations (P < .001): head/neck 35.6% (21), thorax 16.3% (7), abdomen/pelvis 2.7% (3) and adrenal 0.95% (1). Tumour size did not predict surgical complications (tumour volume P = .932, maximum diameter P = .568, and log10 tumour volume P = .932); also, under consideration of the different localizations, however the rate of missing values regarding exact tumour size was high (9/33), in several cases due to extensive, sometimes lobulated mass.

Post-op complications occurred more often in children (17/116 vs 16/222, P = .034), 13 of them 8 years or younger. Post-op complications were specified as transient (15) and persistent (18) in similar proportions. The most frequently reported complication was partial or complete Horner's syndrome (3 and 13, respectively), all related to GN resected from the head and neck (14) or thorax (2). In 2 cases, Horner's syndrome was accompanied by cranial nerve palsy, in 1 with difficulties swallowing and in 1 with pain.
Problems regarding the lung were encountered in 6 cases, including pulmonary atelectasis, pneumothorax, pleural injury and pleural effusion in association with CSF leak in 3. Pulmonary atelectasis occurred in an adult with complete resection of adrenal GNB, while all other lung problems occurred in patients 18 years or younger with resection of thoracic GN, 3 of them with macroscopic margin remaining.

In 3 cases, hypesthesia was reported, once in association with vision impairment. Another patient suffered from cortical blindness post-op. Cranial nerve palsy alone occurred in 2 patients, excessive bleeding in 1 and paresis of lower extremities in 4 (in 1 together with CSF leak and pulmonary effusion, in 1 together with neuralgia and neuropraxic urinary retention).

No article reported recurrence or metastases of GN without other component.

3.2.7 Non-neuroblastic composite GN and separate neural-crest-derived second neoplasia

A total of 43 GN with additional non-neuroblastic neural-crest-derived tumour element, that is non-neuroblastic composite GN, were reported, with component of pheochromocytoma/paraganglioma (38), malignant PNST (3), and neurofibroma (2). Most composite GN with pheochromocytoma/paraganglioma component were localized in the adrenals (60.5%), with composite rates of 21.6% for adrenal, 11% for abdomen/pelvis, 6.5% for thorax and 4.92% for head/neck location (P = .016).

A non-neuroblastic composite pheochromocytoma/paraganglioma component was found in 46.1% of catecholamine-producing GN (24/52). Evidence for adrenergic character was reported in 16 (66%). Noradrenergic character was seen in 2 patients. Elevation of VMA alone or VMA with HVA was reported in one patient each. In 3 patients with composite pheochromocytoma/GN, there was no specification which catecholamine or metabolite was elevated.

Catecholamines were significantly more likely increased in patients with non-neuroblastic composite component (57.1% vs 8.3% without; CI for difference 32%-61%, P < .0001).

While overall symptom rates were similar for non-neuroblastic composite and noncomposite GN, hypertension was more prevalent in the former (27.9% vs 5.92%, CI of difference 10.4%-37%, P < .0001). All hypertensive patients with composite GN (12) had a pheochromocytoma/paraganglioma component, 9 with adrenergic, 1 noradrenergic and 2 unclear secretotypes (elevated ‘metanephrines’ and not specified). Also for adrenal cases, a difference (23%, CI 5.7%-43.9%, P = .01) in hypertension rate was evident (composite 8/24, 33.3%; noncomposite 9/87, 10.3%). Tumour length was shorter for non-neuroblastic composite GN (median (quartiles) 4.8 (3.0-6.1) vs 6.0 (4.0-9.05) cm, difference 1.3 (CI 0.5-3) cm, P = .0066). Patients with non-neuroblastic composite GN were 24.5 years older at diagnosis, namely 49 years (CI 34-62, P < .0001), and that was independent of hormone production. The odds of a non-neuroblastic composite GN increased with age: OR 1.42 (CI 1.23-1.66, P < .0001 per 10 years). Interestingly, the five patients without pheochromocytoma/paraganglioma component were young (neurofibroma: 0.02 and 21 years, malignant PNST: 0.5, 1.6, and 35 years) compared to most with pheochromocytoma/paragangliomas (21-74, average 51.8).

In several cases, a separate neural-crest-derived tumour has been reported: 3 pheochromocytoma/paraganglioma, 1 schwannoma and 2 malignant PNST (see below).

3.2.8 Second other second neoplasia and development into GN

Secondary neoplasias without neuroectodermal origin were reported in 28 cases. The second component was intermixed with the GN in ten. A total of 15 patients had separate neoplasias together with GN (including two mixed GN). In four cases, secondary neoplasia and GN were diagnosed at different times. Most frequently, an association with rhabdomyosarcoma was reported (7/23, overall 1.9% (7/364)). Details are listed in Table S2.

For 8 cases (2.3%), evidence of maturation into GN from NB/GNB (6), an embryonal rhabdomyosarcoma and a malignant PNST with GN component were proposed. In all cases, chemotherapy had been previously applied. Overall, 6.9% (25/361) received chemotherapy. Particularly in the latter case, successful treatment of the malignant PNST and persistence of the GN component may explain the finding.

Separate NB and GNB were reported in 7 young patients (5-23 years), in 3 cases they occurred previous to the diagnosis of GN, and in 3 cases GN and NB/GNB were present at the same time. Dedifferentiation of GN into metastatic NB was claimed in one report.16

3.2.9 Genetic background

Syndromic presentation was reported in 7.4% (27/364). Of those, 20 were diagnosed with neurofibromatosis 1 (NF1), 1 with NF2, 2 with multiple endocrine neoplasia (MEN) 2A and four with MEN2B.

As expected, patients with NF1 or MEN had an increased likelihood of non-neuroblastic composite GN (10/27, 37%), compared to 9.79% (33/337, difference 27.2%, CI 11.3%-46.3%, P = .00035). Of 8 patients with non-neuroblastic composite GN related to NF1, 2 had a composite orbital plexiform neurofibroma with choroid GN and in 6 the composite component was pheochromocytoma/paraganglioma. In 1 of those, bilateral composite adrenal pheochromocytoma/GN occurred together with gastrointestinal stromal tumour.43

In another case, the composite pheochromocytoma/GN was mixed with adrenocortical adenoma and the patient had a history of breast cancer.44 The rate of NF1 (18.6% 8/43) was significantly higher for non-neuroblastic composite cases (3.74%, difference 14.9%, CI 5.6%-29%, P < .001). Two patients with NF1 presented with multiple GN.43,45
This systematic review of IPD revealed an increasing proportion of adrenal GN with age, while thoracic and head/neck frequency decreased, as previously observed for paragangliomas. In agreement, adrenal localization was less frequently observed in a juvenile cohort than abdominal/thoracic GN. This difference in local distribution highly likely contributes to the higher rate of surgical complications (18.4%-30.4%) reported for juvenile cohorts, because of the predominance of localizations associated with increased surgical risk (37.5%-58.3% thoracic). Head/neck location was infrequently reported in registries and case series; IPD revealed 17.8% with the highest rate of surgical complications (35.6%), followed by thoracic GN (16.3%). Catecholamine production and composite component were comparably low for these locations (<6.5%). Across different localizations, outcome was excellent, even after incomplete resection. Thus, a cautious surgical approach has been suggested in difficult to operate cases. Nonsurgical management or a watch-and-wait approach may also be considered in certain cases, similar to non-secretory head/neck paragangliomas.

In agreement with adrenal single-centre experiences, this systematic review on IPD found almost no post-operative complications for adrenal GN. As adrenal GN showed the highest rate of catecholamine production (31%), hypertension (22.1%) or presence of non-neuroblastic composite component (21.6%), tumour removal clearly appears advisable. However, proper biochemical analysis, preferentially with highly sensitive mass spectrometric analysis of urinary or free plasma metanephrines, including methoxytyramine (sensitivity 97.9% for PGL and 92%-95% for NB), and corresponding pre-op adrenoceptor blockade need to be considered. MIBG avidity may also indicate immature or non-neuroblastic composite GN component, however with lower sensitivity. Thorough histopathological examination remains necessary, because other secondary components cannot be ruled out by metanephrine assay.

Conflicting information on sex distribution, ranging between 0.30 and 0.69 male proportion, led to assumption of close to equal distribution from the meta-analysis of registries and case series. IPD however clearly indicate a female predisposition with younger age at diagnosis.

The range of symptomatic patients for the registries and case series ranged from 17.1%-73.4%. Our systematic review of IPD indicated symptoms in the majority of patients (75.5%). Size-related symptoms such as pain and swelling were most frequently reported in both data sets. IPD allowed further stratification by tumour locations and revealed that swelling was overrepresented in patients with head/neck GN. Hypertension was most frequently evident in patients with adrenal GN (22.1%), a level similar to previously reported data (4/18). We cannot exclude bias towards late diagnosis of large GN contributing to a high rate of symptoms, because of possible differences in international standards for diagnosis between centres. However, tumour length and volume summarized from IPD is comparable or smaller to size measures reported in single-centre cohorts (Table S3). Over-representation of patients with curious symptoms or increased reporting of unspecific symptoms due to the retrospective character

### 3.2.10 Quality of articles

Stringent quality criteria, reporting at least six out of seven critical variables, were met by 80.8% of included articles (Table 2). Reanalysis restricted to these 294 led to minor changes in numeric distributions. All P values < .02 yielded identical decisions to the data presented. Only 2.7% of articles reported four or less of the critical variables.

Of note, for some variables no mention was interpreted as not present, because absence of symptoms, hormone production, or second neoplasia was more likely than lack of reporting.

### DISCUSSION

With the aim to provide evidence based characteristics of clinical and pathological features of GN, meta-analysis of reported registries and case series was attempted. However, discrepancies in patient selection and inhomogeneous reporting prevented conclusive analysis. To avoid restriction to a specific age group or GN, locus IPD on the currently largest number of 364 GN patients were systematically reviewed.

Age information from this large group indicates that GN are not uncommon in older children and among adults. Because the majority of registries and case series focused on young patients, not even the random-effects estimate of mean age was near the mean of IPD. A similar selection bias within and across studies, including tumour location, or presence of mixed tumour components highly likely also influenced other results. Consequently, summarization of IPD appears representative across ages and locations, even though rare or unusual cases may be overrepresented.
of case reports may have contributed to the overall high rate of symptomatic patients. Nevertheless, the rate of incidentally discovered GN remains high and may further increase with more frequent use of imaging modalities. Surprisingly, FDG uptake was positive in 14/19 GN patients and may further contribute to incidental findings in the future. Larger patient series will be necessary to evaluate the FDG avidity of GN.

The collected IPD confirm a benign nature of GN. Recurrence or metastases were only reported for cases with non-neuroblastic composite GN or other neoplasias. To the contrary, development of more aggressive tumour entities into GN has been observed in 8 cases with chemotherapy. Recurrence of GN as a more aggressive tumour has been suggested\(^\text{17,49,55}\); however, true evidence for the origin of the recurrence has not been reported.

Based on this analysis, syndromic presentation (7.4%) appears slightly higher than previously reported (3.6%; 4/111).\(^\text{38}\) Molecular data on GN tumorigenesis are sparse; however, increased RET activation, hedgehog- and erbB3 signalling have been implied.\(^\text{57-59}\) Pseudohypoxia may also play a role.\(^\text{60-64}\) Increased utilization of diagnostic gene panel analysis will likely increase recognition of underlying genetic causes.

In conclusion, systematic review of 364 cases of GN showed that GN most often occurred in children and young adults, more frequently in females. The most common localization was the abdomen (66.2%), with approximately equal proportion at intra- and extraadrenal sites. Non-neuroblastic composite component or hormone production was not uncommon (11.8%, 16.5%), and most prevalent for adenral GN (21.6%, 32.4%). MIBG avidity was increased for non-neuroblastic composite and catecholamine-producing GN. A high rate of surgical complications (35.5%) combined with a low rate of potentially aggressive non-neuroblastic composite component (4.9%) or hormone production (4.9%), may justify consideration of incomplete resection or nonsurgical management for head/neck GN, or other difficult to operate cases. For none of the GN summarized here, convincing evidence for recurrence or metastases from the GN has been presented.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.