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LITERATURE REVIEW

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Intraneural ganglion cysts: a systematic review and reinterpretation of the world's literature

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OBJECTIVE The etiology of intraneural ganglion cysts has been controversial. In recent years, substantial evidence has been presented to support the articular (synovial) theory for their pathogenesis. The authors sought to 1) perform a systematic review of the world's literature on intraneural cysts, and 2) reinterpret available published MR images in articles by other authors to identify unrecognized joint connections.

METHODS In Part 1, all cases were analyzed for demographic data, duration of symptoms, the presence of a history of trauma, whether electromyography or nerve conduction studies were performed, the type of imaging, surgical treatment, presence of a joint connection, intraneural cyst recurrence, and postoperative imaging. Two univariate analyses were completed: 1) to compare the proportion of intraneural ganglion cyst publications per decade and 2) to assess the number of recurrences from 1914 to 2003 compared with the years 2004–2015. Three multivariate regression models were used to identify risk factors for intraneural cyst recurrence. In Part 2, the authors analyzed all available published MR images and obtained MR images from selected cases in which joint connections were not identified by the original authors, specifically looking for unrecognized joint connections. Two univariate analyses were done: 1) to determine a possible association between the identification of a joint connection and obtaining an MRI and 2) to assess the number of joint connections reported from 1914 to 2003 compared with 2004 to 2015.

RESULTS In Part 1, 417 articles (645 patients) were selected for analysis. Joint connections were identified in 313 intraneural cysts (48%). Both intraneural ganglion cyst cases and cyst recurrences were more frequently reported since 2004 (statistically significant difference for both). There was a statistically significant association between cyst recurrence and percutaneous aspiration as well as failure to disconnect the articular branch or address the joint. In Part 2, the authors identified 43 examples of joint connections that initially went unrecognized: 27 based on their retrospective MR image reinterpretation of published cases and 16 of 16 cases from their sampling of original MR images from published cases. Overall, joint connections were more commonly found in patients who received an MRI examination and were more frequently reported during the years 2004 to 2015 (statistically significant difference for both).

CONCLUSIONS This comprehensive review of the world's literature and the MR images further supports the articular (synovial) theory and provides baseline data for future investigators.

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KEY WORDS intraneural ganglion cyst; intraneural ganglia; articular (synovial) theory; systematic review; peripheral nerve

Intraneural ganglion cysts are benign mucinous lesions that are formed within peripheral nerves and typically lead to symptoms and signs of peripheral neuropathy. Their pathogenesis has been controversial. Different treatments have been recommended. Outcomes have been disappointing and the recurrence rate high and underreported.

Over the past 15 years, our group has provided substantial evidence to support a unifying articular (synovial) theory as the etiology for all intraneural ganglion cysts. In 2003, the senior author (R.J.S.) demonstrated that the prototypical intraneural cysts of the common peroneal nerve are joint derived. Cyst formation originates in the superior tibiofibular joint (STFJ) and propagates toward

ABBREVIATIONS EMG = electromyography; NCS = nerve conduction studies; STFJ = superior tibiofibular joint.

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the parent (common peroneal) nerve through its articular branch (Fig. 1).[124,125] Since then, the articular (synovial) theory has been further substantiated by our group and others at many other nerves at several other anatomical locations.[13,19,82,102,113,114,117,118,135,143,144,147,153,170,173] Three principles for these cysts have emerged: 1) intraneural ganglion cysts are formed from a capsular defect of a neighboring joint, which allows joint fluid to egress and track along the epineurium of an innervating articular branch; 2) the fluid follows the path of least resistance; and 3) the cyst takes form due to changes in pressure and pressure fluxes.[122] These underlying principles of the articular theory explain the stereotypic patterns of formation that have best been described for peroneal and tibial intraneural cysts arising from the STFJ.

We sought to perform a systematic review of the world's literature to summarize the current state of our understanding of intraneural ganglion cysts and to provide a baseline for future investigators. A global perspective is lacking due to the relative rarity of these lesions and their publication mostly as isolated case reports. Other than a large review of intraneural cysts of the upper extremity,[170] we are unaware of an encompassing summary of cases of intraneural ganglion cysts.

As proponents of the unifying articular theory, we also wanted to reinterpret the available MR images to look for unrecognized joint connections, which we believe should exist for all cases. Ultimately, as the awareness and understanding of this theory becomes more widely circulated, joint connections should be increasingly recognized, abolishing the existing controversy regarding etiology.

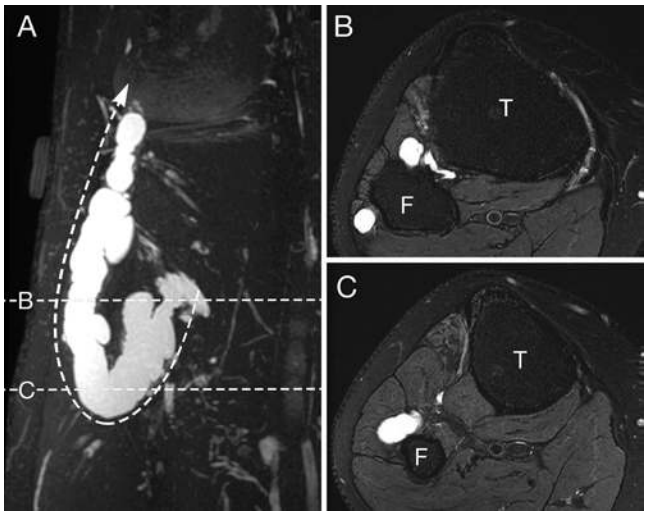

FIG. 1. Typical example of a peroneal intraneural ganglion cyst with a connection to the STFJ (unpublished case, not included in this analysis). The coronal maximum intensity projection MR image from a T2-weighted fat-saturated sequence **(A)** demonstrates the classic "U" pattern in a peroneal intraneural ganglion cyst arising from the STFJ *(dashed arrow)*. The axial T2-weighted fat-saturated MR image through the level of the fibular head **(B)** demonstrates cyst within the common peroneal nerve (signet ring sign). There is intraneural cyst near the STFJ and joint fluid in the joint itself.[146] The axial T2-weighted fat-saturated image through the level of the fibular neck **(C)** demonstrates intraneural cyst within the articular branch (transverse limb sign). F = fibula; T = tibia.

Methods

Part 1. Literature Review

Inclusion Criteria

The aim of this study was to collect and review the world's literature on intraneural ganglion cysts published over the past century. For the purposes of the study, inclusion criteria were 1) published articles or published abstracts that reported a case series or case report on appendicular intraneural ganglion cyst(s) since 1914 (inclusive); 2) review articles that included a case or cases with some patient characteristics, such as age, sex, etc., which in some instances were provided in the figure legends; 3) letters to the editor that provided new information on a reported case; and 4) articles published in any language. Exclusion criteria consisted of 1) all articles that did not specifically report on a patient with an intraneural ganglion cyst (review articles that only showed an image of an intraneural cyst and did not provide any patient information, letters to the editor that did not report new information on a case, and textbook chapters); 2) examples of extraneural ganglion cysts; 3) reports of spinal and cranial intraneural cysts, which have been controversial;[8,15,34,36,40,94,123,126,140] 4) cases of an intraneural cystic lesion that contained a pathology determined not to be an intraneural ganglion cyst or those published before 1914 as a pathological diagnosis of earlier cases could not be assured; and 5) unpublished conference abstracts. Of note, while those articles that were excluded based on the first exclusion criterion above were eliminated from the data analysis, some information from those articles was included in our overall study.

Literature Search

An extensive literature search was performed using multiple scientific databases (PubMed, Scopus, Embase, Quertle, Google, Google Scholar, CiNii, J-Stage, Science Links Japan, KoreaMed, and KoMCI). Search terms included "intraneural ganglion cyst", "intraneural ganglia", "intraneural cyst", and "intraneural cystic degeneration." The reference section of each article identified was also analyzed for additional reports. The search ended April 1, 2015.

Study Selection

Selected studies were those that contained at least one of the 4 search terms. Articles that were found in the reference sections of selected studies but that did not necessarily contain one of the search terms were also included. The reports were read in detail to confirm the presence of at least one case of an intraneural ganglion cyst or new information on a previously reported patient. Duplicate case reports were identified for exclusion as well as articles that did not mention a patient with an intraneural ganglion cyst.

Data Extraction

Aspects of each publication, which consisted of the first author, year of publication, and written language were recorded. Demographic data included patient age, sex, side of the body that was affected, and nerve involved. Symp-

tom duration as well as a history of trauma was also extracted. It was noted if patients underwent electromyography (EMG) or nerve conduction studies (NCS) as well as imaging, including radiography, ultrasonography, computed tomography (CT), and MRI. The presence of an arthrogram was also determined. Additional data included: the type of surgical treatment, the identification of a joint connection, amount of follow-up, development of an intraneural cyst recurrence, and whether any postoperative imaging was performed. The number of intraneural recurrences and joint connections were analyzed twice in 2 different groups: 1) all publications identified for analysis and 2) all articles excluding those associated with the senior author (R.J.S.). A translator was used to help with data extraction for all articles published in a language other than English or French.

Statistical Analysis

To assess the proportion of published intraneural ganglion cysts over time, the study period was categorized into 2 eras: 1) cases published from 1914 to 2003 and 2) cases reported from 2004 to 2013. Using a single-sample chi-square test, the proportion of cases reported from 2004 to 2013 (inclusive) was compared with the expected proportion of 10% under the null hypothesis (since 2004 to 2013 represents 10% of the total 100-year study period). A chi-square test was used to assess the comparative absolute numbers of published intraneural ganglion cyst recurrences within 2 groups covering the entire study period: 1) 1914–2003 and 2) 2004–2015. The designated year for each cyst recurrence was given according to the year that the intraneural cyst was first reported. Three separate multivariate logistic regression models were used to identify risk factors for intraneural cyst recurrence. All 3 regression models used intraneural cyst recurrence or persistence as the dependent variable and patient age, sex, and type of surgery as the independent variables for cyst recurrence. A histogram was used to determine that age, which was the only continuous variable, had a normal distribution. The 3 analyses differed with respect to the type of surgery analyzed. The first multivariate regression analysis used 2 surgical treatment groups: 1) cases where surgical treatment did not disconnect the articular branch or address the joint and 2) cases in which the articular branch was disconnected or the joint was treated as part of surgery. The second multivariate analysis used the same treatment groups, while excluding all patients initially treated by the senior author of this systematic review to eliminate bias as much as possible. The third multivariate regression model separated the surgical treatment groups into 1) patients treated with open surgery and 2) patients treated with percutaneous aspiration. Only patients that had uniform data and reported follow-up were included in the analyses. Patients treated nonoperatively were excluded from all 3 multivariate analyses. Values were considered statistically significant with a p value < 0.05. All analyses were performed using JMP Pro 11 software (SAS Institute Inc.).

Part 2. MRI Review

All case reports that contained published MR images were reviewed. Evidence of joint connections was determined in cases in which the original authors did not report the identification of a joint connection and MR images were available within the published case report for our review. For the most common example, the peroneal nerve at the fibular neck, in particular, we used previously reported signs as being diagnostic, namely the tail sign (cyst at the STFJ) and transverse limb sign (cyst within the articular branch along the fibular neck), both of which have been shown to be highly sensitive and specific for detecting intraneural cyst joint connections.[130] The secondary finding of cyst wrapping around the fibular neck (toward the articular branch) was considered suggestive (but not diagnostic) of an example of a joint-related intraneural ganglion. Several of these examples and our reinterpretations of the published images were published previously to support the articular theory, define its underlying principles, and demonstrate the utility of these radiological signs.[113,114,128,170]

In addition, 16 full series of original MR images from published cases were obtained from authors who did not identify a joint connection in their original publication and these images were reviewed. These cases had been randomly sampled over the past 15 years. Eleven of these cases and our reinterpretations were published.[115,116,120,124,136,143,144,147,153]

The MR image reviews were all done by a fellowship-trained musculoskeletal radiologist and the senior author, a neurosurgeon, both highly experienced in evaluating intraneural ganglion cysts.

Statistical Analysis

A chi-square test was used to determine whether joint connections were more commonly identified when an MRI study was obtained as part of patient assessment. A chi-square test was also used to ascertain whether joint connections were reported more frequently since 2004 (2004– 2015) compared with the first 90 years included in this study (1914–2003). A p value < 0.05 was considered statistically significant. The analysis was performed using JMP Pro 11 software (SAS Institute Inc.).

Results

Part 1. Literature Review

A total of 640 papers were identified following the initial search across all databases and article reference sections. Eighteen duplicate case reports were identified, 17 of which were excluded.[6,26,46,60,67,71,97,111,121,131,134,135,158,163,165,168,172] The 1 duplicate case report that was included consisted of a retracted article,[2,56] which contained information on 2 new cases and therefore remained for analysis. Twenty-three articles were excluded during the screening process because they were published prior to 1914. After carefully reading each article for eligibility, 172 papers were excluded because they either did not provide a case report (n = 73), the lesion was an extraneural ganglion cyst (n = 69), they described a spinal (n = 2) or cranial intraneural cyst (n = 6), or the pathology presented differed from a ganglion cyst (n = 22). Eight case reports were considered indeterminate and were also excluded because a diagnosis

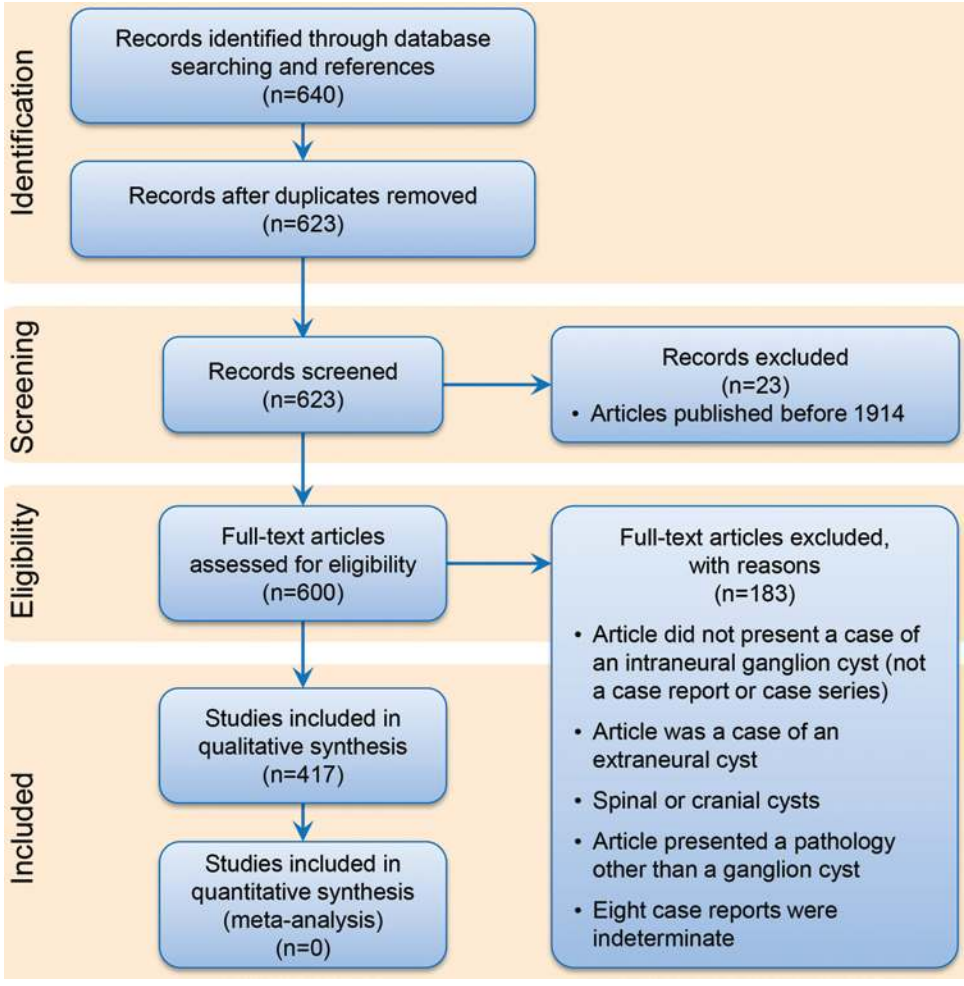

FIG. 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flow diagram demonstrating our search strategy and study selection. Based on Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009): Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med 6*:e1000097.

of an intraneural ganglion cyst could not be reached with certainty.[9,27,35,38,39,64,76,110] Three articles that reported on a series of patients with ganglion cysts were excluded because it was not possible to distinguish between individual patients that had an intraneural or extraneural cyst.[47,49,65] Finally, 417 articles remained for inclusion in the analysis (Fig. 2) (see online Appendix 1). The number of articles in each language is represented in Table 1.

Patient Demographics and Nerves Affected

The pooled demographic data from all cases are presented in Table 2 (645 patients with 648 cysts). As expected, the common peroneal nerve was the most common location affected by intraneural ganglion cysts overall (391 patients, 393 limbs), while the ulnar nerve and its branches were most frequently involved in the upper extremity, with a total of 93 cysts at all sites of the upper extremity (Fig. 3).

Patient Management and Follow-Up

A total of 368 patients underwent either EMG or NCS. A variety of imaging studies were performed as part of patient assessments. An MRI study was completed for 297 patients. Of those patients that did not receive an MRI, 21 had a CT scan, 35 had an ultrasound examination, 9 had a CT scan and ultrasonography, 42 patients had only a radiograph, and 2 patients received only a plain arthrogram. In total, an arthrogram was obtained as part of the patient workup in 15 case reports (4 plain arthrograms, 3 CT arthrograms, and 8 MRI arthrograms). In 239 cases no imaging was reported.

Several treatment modalities have been reported in the literature for intraneural ganglion cysts (Table 3). Five patients with unilateral cysts were treated nonoperatively because they were either asymptomatic or mildly symptomatic or the cyst had resolved spontaneously, and 1 limb of each of the 3 bilateral cases was also treated nonoperatively due to a lack of symptoms. In 110 cases, specifically ligating or disconnecting the articular branch was reported as part of the surgical strategy, and in 2 of these cases ligation of the articular branch was the sole treatment.[77,153] In 23 of those cases in which the articular branch was addressed, the associated joint was also treated (STFJ resec-

TABLE 1. Number of articles that were reviewed in each language for data extraction (417 articles; 645 patients with 648 cysts)

Language	No. of Articles
Afrikaans	1
Chinese	7
Czech	1
Danish	1
English	238
French	19
German	27
Hungarian	1
Italian	11
Japanese	68
Korean	19
Polish	4
Portuguese	2
Russian	1
Spanish	14
Thai	1
Turkish	2

TABLE 2. Patient demographic and clinical characteristics*

Characteristic	Pediatric	Adult	Total
No. of pts (no. of cysts)	84 (84)	535 (538)	645 (648)
Mean age (range) in yrs	12 (4–17)	44 (18–76)	40 (4–76)
Sex, no. of pts (%)†			
Male	65 (79)	361 (73)	429 (74)
Female	17 (21)	136 (27)	153 (26)
Limb side			
Right (%)	25 (30)	186 (35)	213 (33)
Left (%)	38 (45)	156 (29)	195 (30)
Bilateral (%)	0 (0)	3 (0.6)	3 (0.5)
Not reported (%)	21 (25)	190 (36)	234 (36)
History of trauma (%)	22 (26)	64 (12)	87 (13)
Mean symptom duration (range) in mos	7 (0.1–96)	13 (0.1–240)	12 (0.1–240)

pts = patients.
* The age was not reported for 26 patients. They were excluded from the pediatric and adults subgroups, but counted in the total group.
† The sex was not reported for 2 patients in the pediatric subgroup, 38 patients in the adult subgroup, and for 63 patients overall.

tion). In another 2 reports the joint was targeted primarily without necessarily treating the articular branch during surgery (STFJ resection with cyst resection and hip joint offset procedure with labral repair).

Follow-up was inconsistently reported, with 76% of cases providing a time of follow-up (average 26 months, range 0.5–420 months). Follow-up imaging was obtained in only 94 reports (15%) and consisted of MRI (in 74 cases), MRI arthrogram (in 1), ultrasonography (in 13), all 3 tests (in 1), MRI and ultrasonography (in 3), a plain arthrogram (in 1), and MRI with a plain arthrogram (in 1). In those that reported follow-up, the patients' clinical condition improved subsequent to treatment in 376 cases (76%), remained unchanged in 47 cases (10%), and worsened after surgery in 5 cases (1%); in 65 cases (13%), clinical outcomes were not reported.

Joint Connections

All 648 intraneural cysts were para-articular. Overall, 313 joint connections (48%) were identified in the literature (Table 4) (see online Appendix 2). Two hundred eighty-four of those connections were found during the initial management, and 29 were discovered subsequent to cyst recurrence on follow-up MRI or at revision surgery. The joints with reported intraneural cyst connections include: glenohumeral joint (4 cases), ulnohumeral joint (18), distal radioulnar joint (2), radiocarpal joint (1), carpal joints (8), carpometacarpal joint (3), thumb metacarpophalangeal joint (1), thumb interphalangeal joint (2), acetabulofemoral joint (10), tibiofemoral joint (12), STFJ (221), inferior tibiofibular joint (2), tibiotalar joint (5), subtalar joint (16), calcaneocuboid joint (1), and metatarsophalangeal joint (1). Six reports did not specify the joint that had a connected intraneural cyst. When the publications of the senior author were excluded, 238 joint connections (40%) were reported. In 27 of the 74 recurrences a joint connection was not identified at the time of the initial evaluation and treatment, retrospectively (by the original authors), or at revision surgery.

Recurrences

At least 1 cyst recurrence or cyst persistence occurred in 74 patients (11%) overall (Table 5) (see online Appendix 3), with 8 of those patients having 2 or more recurrences. Three recurrences were reported following ligation of the articular branch as part of the initial surgery.[12,84,85] There were 5 recurrences that occurred from cysts in the upper extremity and 69 following the treatment of cysts in the lower extremity. When the patients initially treated by the senior author were excluded, a recurrence rate of 12% was determined.

Statistical Analysis

The single-sample chi-square test determined that intraneural ganglion cysts were reported statistically significantly more frequently within the years 2004–2013 compared with the expected 10% number of cases under the null hypothesis ($p < 0.0001$). The chi-square test identified that recurrences were more commonly reported in the years 2004–2015 (20%) as compared with the years 1914–2003 (10%) ($p = 0.0039$). Based on the multivariate logistic regression analyses, failure to disconnect the articular branch (cystic joint connection) or failure to address the joint is a statistically significant risk factor for cyst recurrence (OR 5.3, 95% CI 1.9–22.2, $p = 0.0006$) (Table 6). Failure to treat the articular branch or joint remained as a statistically significant risk factor for cyst recurrence when those cases treated by the senior author were excluded (OR 4.1, 95% CI 1.4–17.3, $p = 0.0059$). Percutaneous aspiration is also statistically significant for cyst recurrence (OR 12.6, 95% CI 2.4–93.8, $p = 0.0035$) compared with open surgical procedures (Table 7). Age is

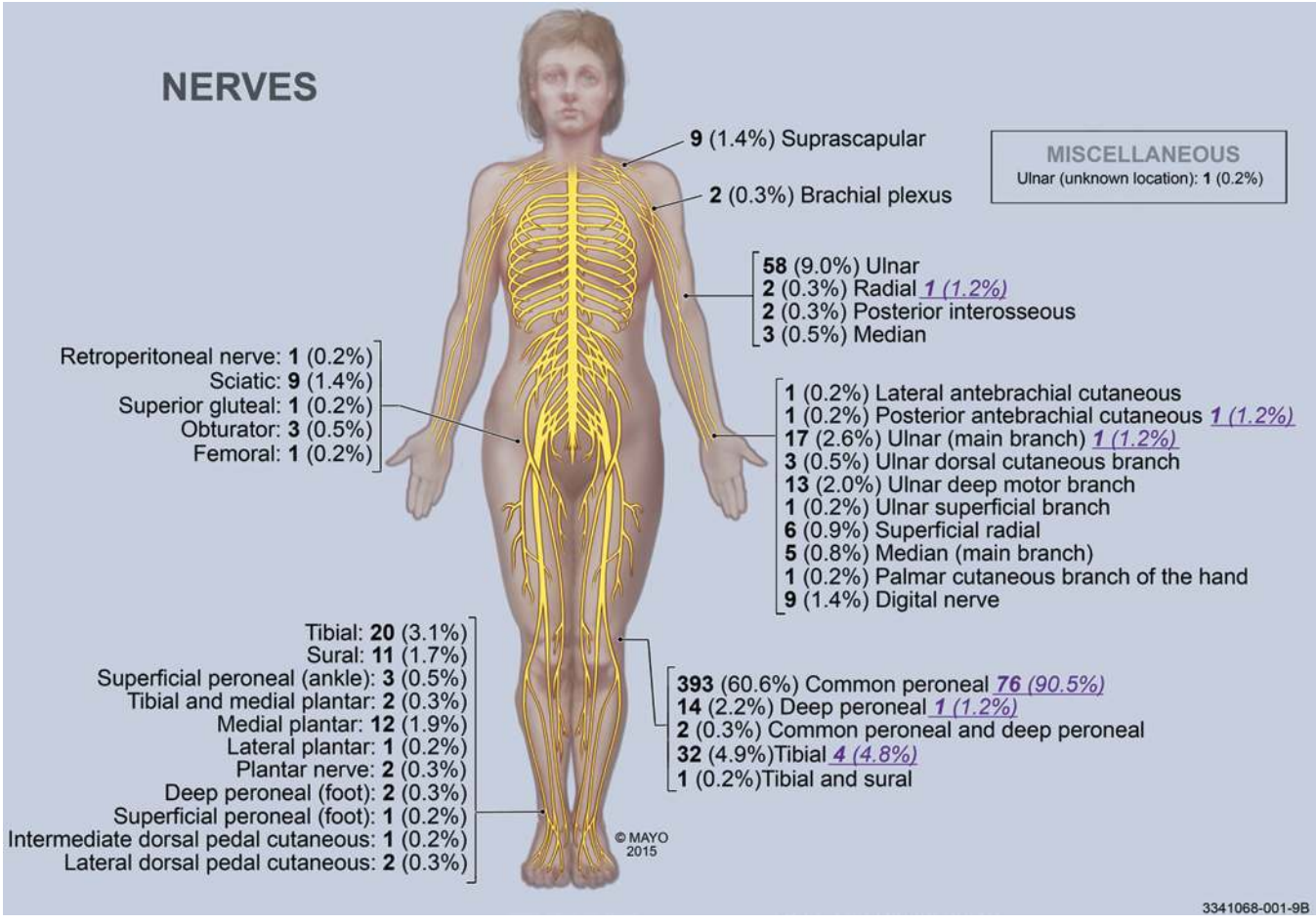

FIG. 3. Artistic illustration depicting the various neural sites of intraneural ganglion cysts reported in the world's literature. Numbers in *black* represent the total amount of cases, the *underlined purple* numbers correspond to pediatric cases. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.

statistically significant when adjusting for sex and failure to ligate the articular branch or address the joint but did not reach significance when using percutaneous aspiration as the treatment method. Sex was not a statistically significant risk factor for cyst recurrence in all analyses (Tables 6 and 7).

Part 2. MRI Review

Of the 297 patients that underwent an MRI as part of their evaluation, 175 had joint connections reported by the original authors. The remaining 79 cases with published images were all reviewed for possible joint connections. By reviewing these images, we were able to identify joint connections in 27 case reports of intraneural ganglia that were previously unrecognized prospectively by others: glenohumeral joint (1), ulnohumeral joint (2), thumb interphalangeal joint (1), STFJ (20), inferior tibiofibular joint (1), and subtalar joint (2) (Fig. 4).[4,7,11,51,66,70,74,75,79,81,93,98,101,103,109,113,114,128,154,156,157,170,174,176] Most of these joint connections were found in publications that provided several MR images and some were seen based on 1 or 2 published images. In another 4 cases, the findings were suggestive of joint connections to the STFJ, but no connection could be definitively confirmed given the limitations and number and quality of the available images. Based on our reinterpretation of these cases we found examples where intraneural cases were in fact extraneural;[5,87,101] cysts described as extraneural were thought to be intraneural;[41,42,53,59,92] 2 cases that were unspecified appeared intraneural,[27,49] as did 1 case of an inflammatory pseudotumor;[31,32] and a tibial intraneural ganglion was actually a peroneal intraneural ganglion.[63]

Furthermore, of the 16 cases in which we were able to obtain the original full MRI series of select cases,[18,22,99,100,109,115,116,120,124,136,143,144,147,153] all had previously unrecognized joint connections: ulnohumeral joint (1), carpal joint (1), acetabulofemoral joint (3), tibiofemoral joint (4), STFJ (6), and tibiotalar joint (1) (Fig. 5). In 3 cases, MRI studies performed several years after surgical treatment demonstrated cyst recurrence with identifiable joint connections to the STFJ (in all 3 patients).[68,115,122,141] In an additional case, our review of the original images led us to specify the joint connection (tibiofemoral), which was not included in the original text.[62]

Statistical Analysis

The chi-square test determined that joint connections

TABLE 3. Treatment distribution*

Type of Treatment	Pediatric (%)	Adult (%)	Total (%)
Nonoperative	0 (0)	8 (1.5)	8 (1.2)
Percutaneous aspiration	1 (1.2)	3 (0.6)	4 (0.6)
Percutaneous aspiration & steroid injection	1 (1.2)	1 (0.2)	2 (0.3)
Decompression	1 (1.2)	6 (1.1)	8 (1.2)
Cyst incision & evacuation	14 (16.7)	87 (16.2)	102 (15.7)
Partial cyst resection	2 (2.4)	21 (3.9)	23 (3.5)
Partial cyst resection & nerve graft	0 (0)	1 (0.2)	1 (0.2)
Complete cyst resection	40 (47.6)	284 (52.8)	329 (50.8)
Complete cyst resection & nerve graft	1 (1.2)	5 (0.9)	6 (0.9)
Nerve transfer	0 (0)	1 (0.2)	1 (0.2)
Ligation of articular branch	0 (0)	2 (0.4)	2 (0.3)
Ligation of articular branch & STFJ resection	0 (0)	2 (0.4)	2 (0.3)
Cyst incision & evacuation & ligation of articular branch	8 (9.5)	33 (6.1)	46 (7.1)
Cyst incision & evacuation, ligation of articular branch, & STFJ resection	1 (1.2)	14 (2.6)	17 (2.6)
Cyst resection & ligation of articular branch	7 (8.3)	31 (5.8)	39 (6.0)
Cyst resection, ligation of articular branch, & STFJ resection	2 (2.4)	2 (0.4)	4 (0.6)
Cyst resection & STFJ resection	0 (0)	1 (0.2)	1 (0.2)
Hip offset procedure & labral repair	0 (0)	1 (0.2)	1 (0.2)
Type of surgery not specified	5 (6.0)	19 (3.5)	25 (3.9)
Treatment not reported	1 (1.2)	16 (3.0)	27 (4.2)

* The age was not reported for 26 patients. They were excluded from the pediatric and adults subgroups but counted in the total group.

were more commonly identified when MRI was part of patient assessment (65%) compared with joint connections that were found when an MRI was not obtained (33%) (statistically significant difference, $p < 0.0001$). It also found that joint connections were more frequently reported in the years 2004–2015 (69%) compared with the first 90 years included in this study (33%) ($p < 0.0001$). These numbers increased even more when the reinterpreted cases were included (75% compared with 34% respectively, $p < 0.0001$).

Discussion

This comprehensive retrospective review and reinterpretation provides statistically significant data in 4 areas that we believe shed important information on intraneural ganglia.

1. Intraneural cysts are not rare. They are becoming diagnosed increasingly[167] and reported more frequently now that imaging of nerves is being performed at a higher rate (Fig. 6).
2. Joint connections are becoming increasingly identified, especially in cases in which MRI is used (Fig. 6). Since the end of 2003, of the total amount of reported joint connections, a greater percentage of joint connections have been described, with 61% (191 joint connections, 73 from 2004–2008 and 118 from 2009–2015) being reported since this date.
3. Intraneural recurrences are becoming increasingly recognized. We believe that this is due to the increasing awareness of joint connections, the increasing use of MRI and the better follow-up of these patients. We wish to emphasize that joint connections have been consistently identified when initial or postoperative images from these cases have been scrutinized. We predict that the percentage of intraneural recurrences will decrease as treatment paradigms change and target the articular branch connection (see number 4 below).
4. Failure to disconnect the articular branch or treat the joint pathology has been found to be a statistically significant risk factor for cyst recurrence.

Etiology

The etiology of intraneural ganglion cysts has been controversial. From the first case to more contemporary reports, we have proven that this theory applies, even when the original authors did not find a joint connection. The first known report and specimen of an ulnar intraneural ganglion cyst (1809) described by Beauchêne[10] was recently rediscovered, reanalyzed, and shown to have evidence of an elbow joint connection (not included in the data analysis).[150] A recent case by Choi and Kwon (2013) describing a tibial intraneural cyst in the popliteal fossa could be shown to have a joint connection to the knee on our reinterpretation (Fig. 5), though these authors did not find a joint connection.[22] For the intervening years, we have supplied ample evidence to support this theory: we found a joint connection on preoperative MR images in 27 cases where it was not previously identified; in some cases we found unrecognized cyst recurrence/persistence,[116,122,141] contrary to the original published descriptions. The fact that we still could find many examples of unrecognized joint connections in other publications which only supplied a single

TABLE 4. Number of joint connections per nerve affected*

Extremity & Nerve Affected (joint connection)†	Pediatric (%)	Adult (%)	Total (%)
Upper extremity			
Suprascapular (glenohumeral)	0 (0)	4 (44)	4 (44)
Posterior interosseous (ulnohumeral)	0 (0)	1 (50)	1 (50)
Ulnar (ulnohumeral)	0 (0)	16 (28)	17 (29)
Median (radiocarpal or CMC)	0 (0)	2 (40)	2 (40)
Ulnar (DRUJ or carpal)	0 (0)	6 (38)	6 (35)
Ulnar deep motor branch (carpal or CMC)	0 (0)	5 (38)	5 (38)
Digital (IP)	0 (0)	4 (44)	4 (44)
Total	0 (0)	38 (29)	39 (29)
Lower extremity			
Sciatic (acetabulofemoral)	0 (0)	7 (78)	7 (78)
Superior gluteal (acetabulofemoral)	0 (0)	1 (100)	1 (100)
Obturator (acetabulofemoral)	0 (0)	2 (67)	2 (67)
Common peroneal (tibiofemoral or STFJ)	39 (51)	151 (51)	209 (53)
Deep peroneal (STFJ)	1 (100)	4 (36)	7 (50)
Tibial (tibiofemoral or STFJ)	4 (100)	18 (64)	22 (69)
Tibial (tibiotalar or subtalar)	0 (0)	7 (35)	7 (35)
Superficial peroneal (ITFJ or tibiotalar)	0 (0)	2 (67)	2 (67)
Tibial and medial plantar (subtalar)	0 (0)	1 (50)	1 (50)
Sural (subtalar or calcaneocuboid)	0 (0)	6 (55)	6 (55)
Medial plantar (subtalar)	0 (0)	6 (50)	6 (50)
Lateral plantar (subtalar)	0 (0)	1 (100)	1 (100)
Deep peroneal (MTP)	0 (0)	1 (50)	1 (50)
Superficial peroneal (region of ankle or foot not specified)	0 (0)	1 (100)	1 (100)
Intermediate dorsal pedal cutaneous (tibiotalar)	0 (0)	1 (100)	1 (100)
Total	44 (54)	209 (51)	274 (53)
Grand total	44 (52)	247 (46)	313 (48)

CMC = carpometacarpal; DRUJ = distal radioulnar joint; IP = interphalangeal; ITFJ = inferior tibiofibular joint; MTP = metatarsophalangeal.
* The age was not reported for 26 patients, which included 22 joint connections. They were excluded from the pediatric and adult subgroups but counted in the total group.
† The following nerves affected by intraneural cysts have not had joint connections reported to date (0 joint connections/number of cases): brachial plexus (0/2), radial at the elbow (0/2), median at the elbow (0/3), median palmar cutaneous branch (0/1), ulnar dorsal cutaneous branch (0/3), ulnar superficial branch (0/1), lateral antebrachial cutaneous nerve (0/1), superficial radial (0/6), posterior antebrachial cutaneous nerve (0/1), retroperitoneal nerve (0/1), femoral (0/1), lateral dorsal pedal cutaneous nerve (0/2), plantar nerve (0/2).

TABLE 5. Summary of cyst recurrence or persistence per type of surgical treatment and associated recurrence rate*

Type of Surgery	Pediatric (%)	Adult (%)	Total (%)
Percutaneous aspiration	1 (100)	2 (67)	3 (75)
Percutaneous aspiration & steroid injection	1 (100)	0 (0)	1 (50)
Decompression	0 (0)	3 (50)	3 (38)
Cyst incision & evacuation	3 (21)	18 (21)	21 (21)
Partial cyst resection	0 (0)	1 (5)	1 (4)
Complete cyst resection	8 (20)	27 (10)	35 (11)
Cyst incision & evacuation & ligation of articular branch	1 (13)	1 (3)	2 (4)
Cyst resection & ligation of articular branch	0 (0)	1 (3)	1 (3)
Type of surgery not specified	0 (0)	6 (32)	7 (28)
Total	14 (17)	59 (11)	74 (11)

* The age was not reported for 26 patients, which included 1 cyst recurrence. This patient was excluded from the pediatric and adult subgroups but counted in the total group.

TABLE 6. Multivariate logistic regression analysis to identify risk factors for cyst recurrence*

Parameter	OR	p Value	95% CI
Age	0.98	0.0277	0.96–0.99
Female sex	1.3	0.4735	0.7–2.3
Failure to disconnect the articular branch or address the joint	5.3	0.0006	1.9–22.2

* The surgical treatment groups included: 1) failure to disconnect the articular branch or address the joint and 2) surgical treatment included disconnecting the articular branch or addressed the joint.

image or two is quite remarkable, in some cases even obtained using first-generation MRI units. Ironically, in some figures in the reports, the arrow depicting the cyst was actually pointing to the joint connection. In addition, we found unrecognized joint connections in all 16 cases where full MRI series were randomly sampled from papers previously published at other locations reported by other groups in which a joint connection was not identified by the original authors. Many of these cases were purposefully gathered by us to challenge the applicability of the theory in cases of apparent outliers, which in turn advanced our understanding. Such outliers included examples with several interconnected intraneural cysts,[122,141] or "extreme" cysts (i.e., those with unusual extensions far from a joint, such as ones extending from the STFJ to buttock, shoulder to neck, or elbow to chest).[21,52,112,118,141,169] We acknowledge several outliers that remain in the literature which have limited[99,159] or no imaging[1] in which we still believe that a joint connection is present.

Our own extensive clinical experience with this entity has demonstrated a joint connection in all cases at different sites—not only the many cases we have reported but an additional cohort of 40 other unreported cases treated by our group or seen in consultation that were not included in this paper. Based on our literature review and clinical experience, we strongly believe that with meticulous scrutiny, the articular (synovial) theory can explain all cases of intraneural ganglia.

Not finding joint connections is understandable. Consistent with inattentional blindness,[106] we miss things if we are not looking for them. Even if these connections are looked for, they are often small. Several imaging and surgical pitfalls have been described to highlight avoidable scenarios that can help clinicians increase diagnostic accuracy and joint connection recognition for cysts.[133] Not fully imaging the associated joint or full extent of the lesion can easily lead to missing these small joint connections; high-resolution MRI with a limited field of view, small skip and slice thickness, and 3D fat-saturated fluid sequences can help. Modern MRI at high resolution is typically acquired with 3 planes, and the examination is comprised of hundreds of images and is adequate to diagnose a cyst and joint connection. The use of arthrography also demonstrated the direct communication between neighboring joint and intraneural cyst in all patients who received this study.[28,30,44,72,80,96,119,139,141,142,144,145,148,151,152] However, despite

TABLE 7. Multivariate logistic model to identify risk factors for cyst recurrence using the surgical treatment groups 1) open surgery and 2) percutaneous aspiration

Parameter	OR	p Value	95% CI
Age	1.0	0.0608	1.00–1.02
Female sex	1.2	0.4940	0.7–2.2
Percutaneous aspiration	12.6	0.0035	2.4–93.8

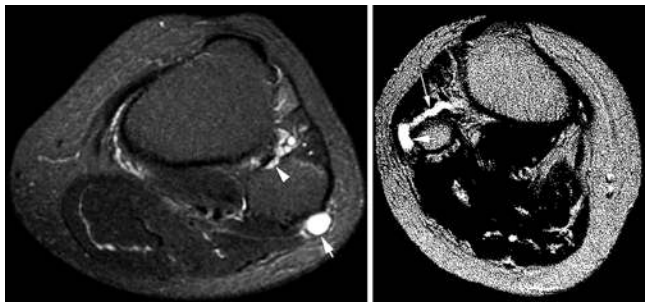

FIG. 4. Previously reported cases with new joint connection. **Left:** Axial T2-weighted fat-saturated MR image of the leg at the level of the mid–fibular head demonstrates cyst in the common peroneal nerve *(arrow)*. A previously unrecognized classic "tail sign" is seen on this image *(arrowhead)*. Modified from Hahn SB, Choi CJ, Kang HJ: [Intraneural ganglion of the peroneal nerve—a report of 3 cases.] *J Korean Orthop Assoc 41:*163–166, 2006 (Korean). Published with permission. **Right:** Axial non–fat-saturated T2-weighted MR image demonstrating a "transverse limb" sign[146] *(thin arrow)* in this example of a peroneal intraneural ganglion *(arrow)*. The finding of cyst within the articular branch is classic and diagnostic of the joint-related nature of the intraneural ganglion despite the low-quality reproduction of the original image in its published form. Modified from Park GY, Bae JH, Lee SY, Lee SM, Kong KS: [Common peroneal nerve palsy caused by an intraneural ganglion—a case report.] *J Korean Acad Rehab Med 30:*289–293, 2006 (Korean). Published with permission.

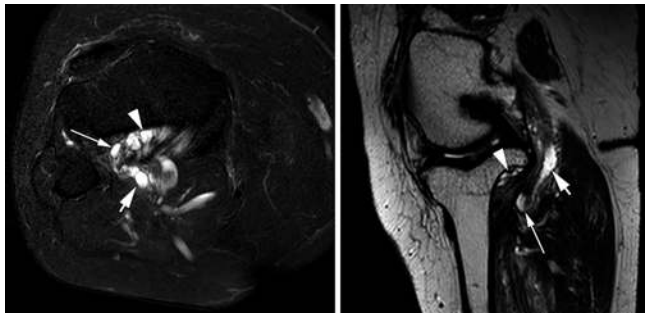

FIG. 5. Previously reported case, which on reinterpretation by our group, demonstrates a joint connection. Axial fat-saturated **(left)** and sagittal non–fat-saturated **(right)** T2-weighted MR images of the knee demonstrate a tibial intraneural ganglion cyst *(arrows)*. A "tail sign" is demonstrated arising from the posterior aspect of the tibiofemoral joint *(arrowhead)* from a lobulated ganglion cyst. The tubular cyst extends from the joint connection to the tibial nerve in a U-shaped configuration typical of an articular nerve branch *(thin arrow)*. The cyst appearance and its joint connection are quite similar to that of a case published by our group.[151] The bony deformities from the patient's dwarfism are apparent (see also the case report by Choi and Kwon[22]). Images courtesy of T. W. Choi and H. K. Kwon.

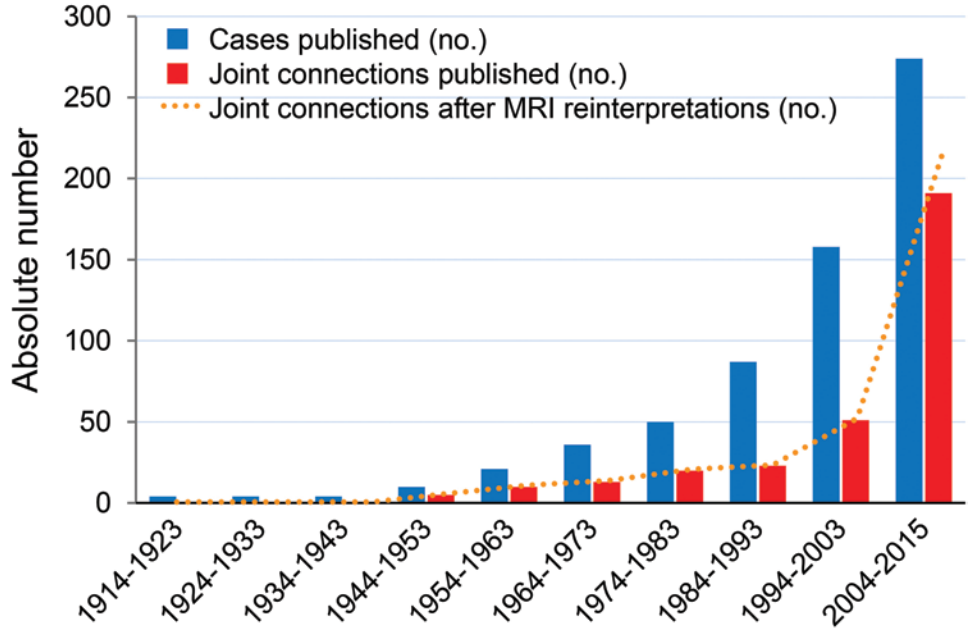

FIG. 6. Graph showing the number of published cases of intraneural ganglion cysts and reported joint connections per decade studied. An increasing trend is seen with the number of published cases of intraneural ganglion cysts *(blue columns)* and joint connections *(red columns)* per each successive decade before the articular theory (1914–2003) and time since (2004–2015). More joint connections were identified in the years 2004–2015 compared with the previous 90 years of this study (1914–2003) (statistically significant difference). The *yellow dotted line* represents the total number of joint connections found after MRI reinterpretations in Part 2 of our study.

the fact that our group has utilized advanced imaging techniques to help visualize joint connections, we have come full circle to show that even routine modern imaging can be used: understanding the existence of these joint connections is the first, and in our opinion the most important, step to avoid pitfalls in identifying them. Furthermore, an incomplete surgical dissection—not adequately displaying the entire anatomy, including the articular branch as it penetrates into the joint capsule—can also understandably lead to unappreciated joint connections.

Based on the articular (synovial) theory, while the articular branch serves as a conduit for cyst fluid propagation toward the parent nerve, the neighboring joint is the inciting factor for intraneural cyst formation. As shown in our cases and others, many joints associated with intraneural cysts are degenerative.[69,83,86,88–90,107,124,141,147,149,160,161,175] Trauma, which was identified in 13% of patients, has also been found to play a role in intraneural ganglion cyst formation. Either direct articular trauma[17] or an indirect mechanism of injury, such as a torsional load applied away from the joint can cause a capsular defect that permits cyst fluid extravasation.[16,127,145]

We believe that the articular (synovial) theory fits with the principle of Occam's razor and provides a single logical explanation for the formation of not only intraneural ganglion cysts but all para-articular cysts. It seems intuitive to us to invoke one theory to explain all cases rather than several different theories. Knowledge of detailed articular branch innervation is tantamount to the theory,[55] and we appreciate that additional studies are needed at many joints. Application of this information not only can explain unusual cases but also predict nonexistence of intraneural cysts. For example, a case from the inferior tibiofibular joint that would not be immediately obvious can be explained.[114] Conversely, the absence of cases affecting the superficial peroneal nerve alone at the STFJ (despite the large number of peroneal nerve cysts at the fibular neck) can be understood by its lack of an articular branch to the STFJ. We have shown that separate synchronous or metachronous intraneural cysts affecting different nerves at the same anatomical location are derived from the same joint,[131] which would explain a previous case of ipsilateral intraneural cysts affecting both the digital radial and dorsal collateral nerves of the thumb.[43] It seems likely that joint-connected intraneural ganglion cysts also exist in the spine[140] and cranium but have been confused with extraneural ganglion cysts.[8,34,40,94,123,126] The more common extraneural/extra-adventitial ganglion cysts also arise from neighboring joints and can sometimes be mistakenly identified as intraneural or adventitial. Recently, our group has also demonstrated robust evidence to support the articular (synovial) theory as the etiology of cystic adventitial disease in arteries and veins,[29,129] an entity analogous to intraneural ganglion cysts. Finally, several cysts can form at the same time from the same joint, as demonstrated with a complex cyst from the STFJ or ulnohumeral joint leading to an intraneural, extraneural, and intraosseous cyst,[135,137] or combinations of intraneural and adventitial cysts from the STFJ.[54,142,149]

The other 2 major theories that have been put forth we believe can be dismissed. The tumoral theory suggests that intraneural cysts are formed from the transformation of

pre-existing tumors into cystic lesions.[25,45,50,61,78] This theory has been largely rejected based on the lack of pathological and histological proof. The de novo degenerative theory, which is based on the premise that intraneural ganglion cysts are formed spontaneously from a degenerative process affecting nerves, has been applied to cases with unidentified joint connections.[3,20,23,33,37,43,73,169] In effect, the degenerative theory is a theory of exclusion—one invoked when authors fail to find an articular connection. This degenerative theory in our opinion fails to provide a logical explanation for all cases: if it were true, then intraneural cysts could occur away from joints, such as in the midportion of limbs; in fact, we have shown that these extreme cysts also have joint connections (see previous discussion). As even more clinicians become aware of the existence of joint connections with intraneural ganglion cysts, we believe that all will be recognized, subsequently ending the controversy regarding their etiology.

Surgical Management

The surgical treatment of intraneural ganglion cysts has also been controversial, likely a consequence from the contention surrounding their pathogenesis. Understanding the etiology of these lesions has allowed for the refinement of surgical techniques.[77,132,138] Contrary to the most popular form of treatment (cyst resection) or even a more radical approach (nerve resection with or without nerve grafting or nerve transfer),[14,17,18,23,24,48,57,78,91,95,104,105,108,155,162,164,171] we recommend treating the articular branch connection and/or the joint. Even with isolated nerve transfer,[91] the articular branch remains connected to the neighboring joint, which would conceivably allow for cyst recurrence. We have shown that addressing the articular branch by ligating or disconnecting it near the joint or treating the articular pathology prevents intraneural cyst recurrence. Failure to disconnect the articular branch or treat the joint pathology has been found to be a statistically significant risk factor for cyst recurrence. In fact, we identified only 3 cases of intraneural cyst recurrence or persistence (3%) following articular branch disconnection among 112 patients that were treated with either articular branch disconnection, surgery to the joint, or both.[12,84,85] In 1 case, cyst recurrence was explained by failure of disconnecting the articular branch near the joint. An attempt was made at ligating and transecting the articular branch, but it was not done in close proximity to the joint. This allowed the articular branch joint connection to remain, which permitted intraneural cyst recurrence that propagated along the persistent articular branch, but in a different direction.[12] Furthermore, percutaneous aspiration should be avoided as a method of definitive care, given its high recurrence rate (4 [67%] of 6 cases). Percutaneous aspiration was found to be a statistically significant risk factor for cyst recurrence in comparison with open surgery. Analogously, as with intraneural ganglion cysts, a high recurrence rate (9%) was found in patients with cystic adventitial disease when the articular (vascular) branch was not identified and in patients treated with percutaneous surgery rather than open surgery ($p < 0.0001$).[29]

It is important to recognize that by not addressing the associated joint itself, the origin of cyst formation remains, permitting the continued development of other para-articular cysts. Our experience and the literature review identified several cases of extraneural cyst formation following intraneural cyst treatment, even though they were not specifically researched in this study.[58,69,72,95,124,133,149,166] Treatment of the joint (cyst origin) can effectively remove the possibility for all para-articular cyst development. It is for this reason that STFJ resection has become a critical part of surgery for STFJ-associated intraneural cysts. Some have even advocated a proximal fibulectomy to treat initial complex ganglion cysts of the STFJ with intraneural involvement or for recurrent disease.[49] While we recognize that not all joints are as expendable as the STFJ, it is important to anticipate the possible formation of extraneural cysts following intraneural cyst treatment despite articular branch disconnection around nonexpendable joints.

Moreover, we believe that addressing the joint connection and/or the joint pathology may obviate the need for cyst/nerve decompression. It is unknown whether concomitant cyst decompression, however, facilitates nerve recovery by expediting the nerve decompression or cyst resolution. If cyst decompression is part of the surgical plan, iatrogenic nerve injury can be avoided by concomitant simple cyst incision and evacuation of the mucinous fluid to decompress the cyst instead of more radical procedures, such as full cyst excision.

Limitations

There are several limitations to this study. Despite our aggressive attempt to summarize the world's literature, we acknowledge the reality that we have missed some cases of intraneural ganglia in our search or had some data mistranslated. We understand that all intraneural cysts are not necessarily intraneural ganglion cysts, thus we limited our study to the past 102 years and more modern pathological descriptions. We also purposefully excluded examples of intraneural ganglia when they were admixed with and not distinguished from extraneural ganglia in series of ganglia affecting nerve. All of the articles provided Level IV evidence in the form of either case series or case reports, and complete uniform data were inconsistently reported. Therefore, many patients were excluded from the regression analyses. We recognize the limitations of performing univariate and multivariate statistical analyses based on a review of case reports that contain a large amount of heterogeneity. Publication bias likely exists, given that case reports typically favor rare occurrences while ignoring more common aspects, which may under-represent the norm. All of the data do not currently fully support the articular theory for universal application. Despite the fact that these cysts are all para-articular, joint connections were not reported uniformly. Most cases that had published MR images only showed 1 or several images. The quality of many of the published figures reviewed was marginal or suboptimal because of the technique of the MRI or of the article reproduction from libraries either as hard copy or a pdf file. The lack of regimented long-term clinical and radiological follow-up likely underestimates the true recurrence rate. The reporting of postoperative functional outcomes was highly diversified and frequently incomplete, which, combined with an incomplete follow-

up rate, makes comparing operative techniques for postoperative results difficult. Finally, and most importantly, a lack of experience of surgeons and radiologists with this entity leads to missed joint connections. While the aim of this interpretation was to establish the applicability of the articular theory, we fully acknowledge our inherent bias given our strong belief in this theory. In fairness, in the majority of cases, we could not confirm that a stated joint connection was present and connected to the specified joint, as the supportive images or operative findings were typically not published. Only through international collaboration can we work together to remedy these limitations and definitively answer some of the remaining unanswered questions.

Conclusions

This systematic review provides a comprehensive summary of the data and a modern perspective on intraneural ganglion cysts. This study can serve as a baseline for future investigations. With further refinement of surgical techniques, improved neurological outcomes can be assessed in the literature retrospectively and of course prospectively. We believe that the articular (synovial) theory explains the formation of these lesions. Surgical management should be directed toward either the joint or joint connection (articular branch). By following these principles, both the risk of iatrogenic nerve injury and cyst recurrence can be avoided with improved patient outcomes.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Spinner. Acquisition of data: all authors. Analysis and interpretation of data: Spinner, Desy, Howe. Drafting the article: Desy. Critically revising the article: Spinner. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Spinner. Statistical analysis: Desy. Administrative/technical/material support: Wang. Study supervision: Spinner.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Appendices 1–3. http://thejns.org/doi/suppl/10.3171/2015.9.JNS141368.

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