Tenosynovial giant cell tumours

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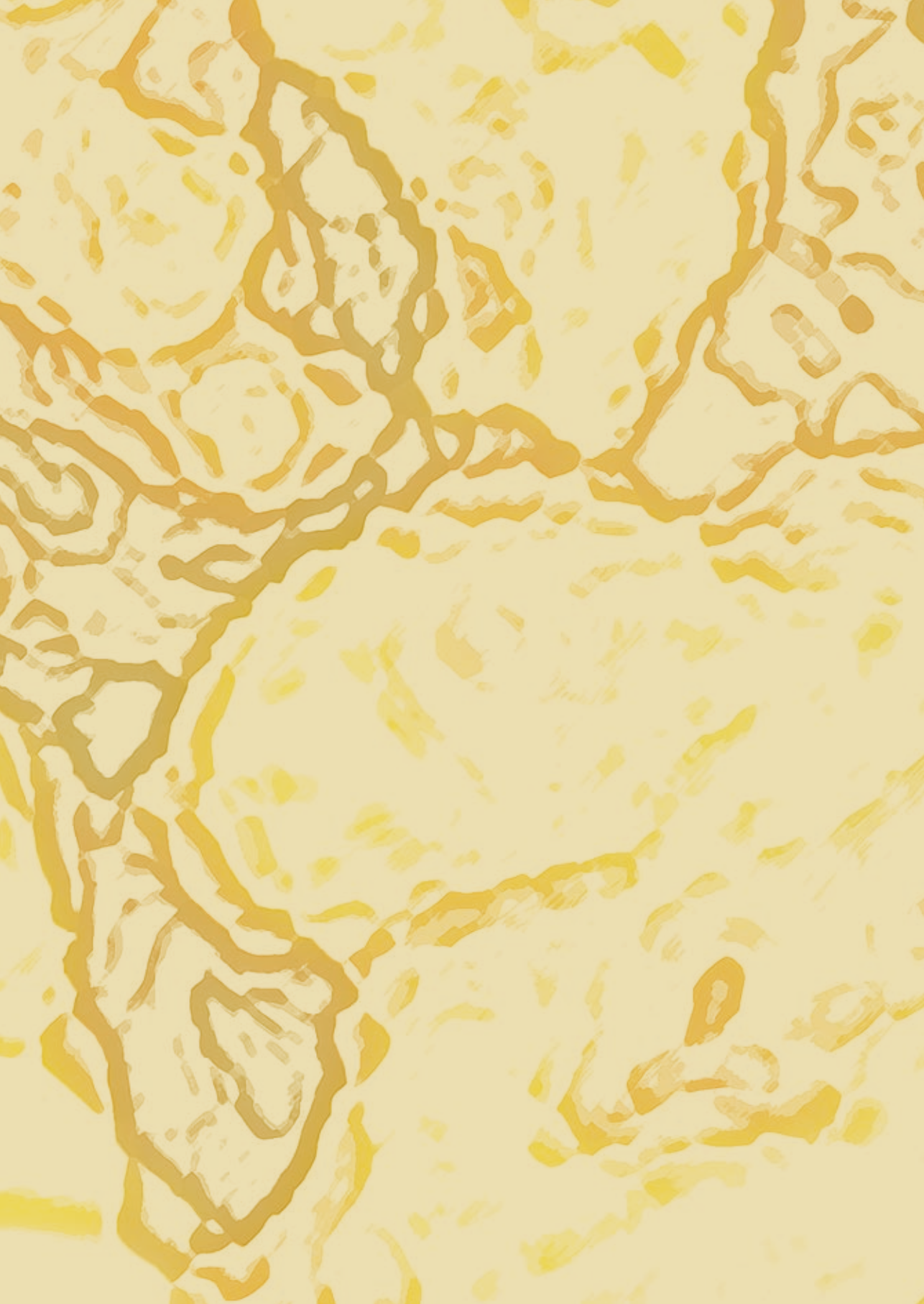

chapter six

CHILDREN

Tenosynovial Giant Cell Tumours in children

a similar entity compared with adults

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Clin Orthop Relat Res. 2018 Sept;476(9):1803-1812

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Abstract

Background

Tenosynovial Giant Cell Tumour (TGCT) is a rare, benign, monoarticular entity. Many case-series in adults are described, whereas TGCT is only incidentally reported in children. Therefore, its incidence rate and natural history in children are unknown.

Questions/purposes

(1) How many cases have been reported of this condition, and what were their characteristics?

(2) What is the standardized paediatric incidence rate for TGCT?

(3) Is there a clinical difference in TGCT between children and adults?

(4) What is the risk of recurrence after open resection in children compared with adults?

Methods

Data were derived from three sources: (1) a systematic review on TGCT in children, seeking sources published between 1990 and 2016, included 17 heterogeneous, small case-series; (2) the nationwide TGCT incidence study: the Dutch paediatric incidence rate was extracted from this nationwide study by including patients younger than 18 years of age. This registry-based study, in which eligible patients with TGCT were clinically verified, calculated Dutch incidence rates for localized and diffuse-type TGCT in a 5-year timeframe. Standardized paediatric incidence rates were obtained by using the direct method; (3) from our nationwide bone and soft tissue tumour data registry, a clinical data set was derived. Fifty-seven children with histologically proven TGCT of large joints, diagnosed and treated between 1995 and 2015, in all four tertiary sarcoma centres in The Netherlands, were included. These clinically collected data were compared with a retrospective database of 423 adults with TGCT. Chi square test and independent t-test were used to compare children and adults for TGCT type, sex, localization, symptoms before diagnosis, first treatment, recurrent disease, followup status, duration of symptoms, and time to followup. The Kaplan-Meier method was used to evaluate recurrence-free survival at 2.5 years.

Results

TGCT is seldom reported because only 76 paediatric patients (39 female), 29 localized, 38 diffuse, and nine unknown type, were identified from our systematic review. The standardized paediatric TGCT incidence rate of large joints was 2.42 and 1.09 per million person-years in localized and diffuse types, respectively. From our clinical data set, symptoms both in children and adults were swelling, pain, and limited ROM with a median time before diagnosis of 12 months (range, 1-72 months). With the numbers available, we did not observe differences in presentation between children and adults in terms of sex, symptoms before diagnosis, first treatment, recurrent disease, followup status, or median time to followup. The 2.5-year recurrence-free TGCT survival rate after open resection was not different with the numbers available between children and adults: 85% (95% confidence interval [CI], 67%-100%) versus 89% (95% CI, 83%-96%) in localized, respectively ($p = 0.527$) and 53% (95% CI, 35%-79%) versus 56% (95% CI, 49%-64%) in diffuse type, respectively ($p = 0.691$).

Conclusions

Although the incidence of paediatric TGCT is low, it should be considered in the differential diagnosis in children with chronic monoarticular joint effusions. Recurrent disease after surgical treatment of this orphan disease seems comparable between children and adults. With targeted therapies being developed, future research should define the most effective treatment strategies for this heterogeneous disease.

Introduction

Tenosynovial Giant Cell Tumour (TGCT) is a benign, monoarticular entity. Two histologically identical but clinically different types are distinguished: localized and diffuse lesions[1]. This distinction can be made either on MRI or at the time of surgery. The localized type is defined by the World Health Organization (WHO) Classification of Tumours of Soft Tissue and Bone of 2013[2] as a well-circumscribed benign small lesion (*figure 1*). By contrast, the diffuse type, previously named pigmented villonodular synovitis (PVNS), shows unclear boundaries with extensive involvement of the entire synovial membrane and infiltrative growth through adjacent structures[1] (*figure 2*). The knee is the most common large joint affected by TGCT with 46% of localized and 64% of diffuse-type TGCTs affecting that joint; the hand and wrist are the next most common joints affected by the localized form, and the ankle and hip are the next most common joints affected by diffuse TGCT[3]. Delayed diagnosis is not uncommon as a result of different nonspecific clinical signs and symptoms[4, 5], and the definitive diagnosis must be made histologically. The standard treatment remains surgical resection, but recurrence occurs in 4% to 6% patients with localized and 14% to 40% of diffuse TGCT affecting the knee[5]. Histologic or radiologic risk factors for recurrent disease are unknown.

All described case-series on TGCT concern adults, whereas TGCT is only incidentally reported in children. Owing to the rarity of the disease, the available evidence base on TGCT contains predominantly retrospective, relatively small cohort studies, including heterogeneous data[6]. Sufficient data on paediatric patients with TGCT are lacking.

We therefore combined a systematic review with analysis from a nationwide paediatric TGCT incidence study in The Netherlands[3] and clinical data on TGCT in children and adults from four tertiary sarcoma centres in The Netherlands to answer the following questions: (1) How many cases have been reported of this condition, and what were their characteristics? (2) What is the standardized paediatric incidence rate for TGCT? (3) Is there a clinical difference in TGCT between children and adults? (4) What is the risk of recurrence after open resection in children compared with adults?

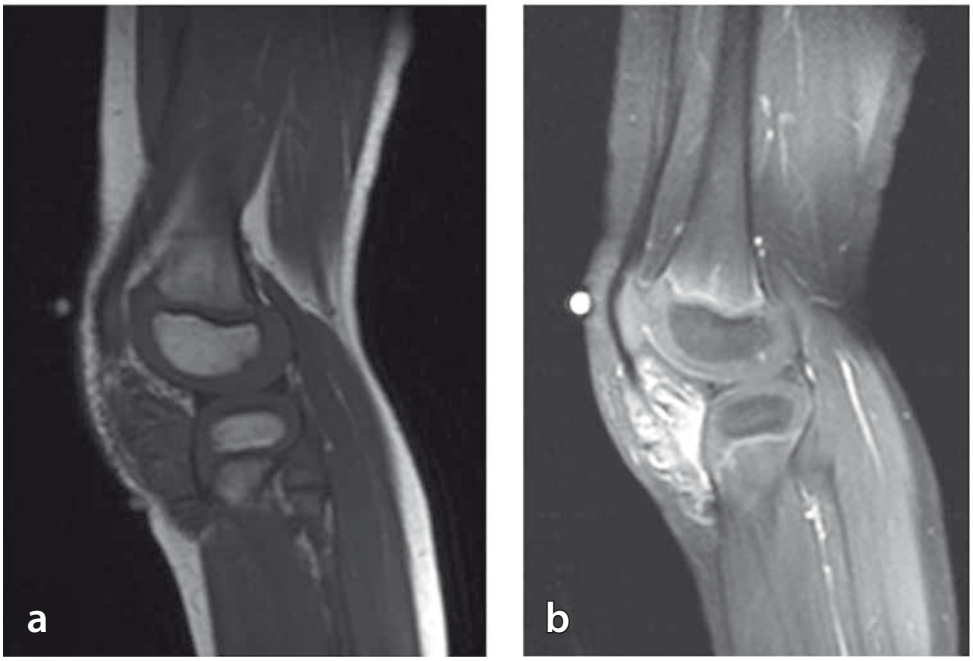

Figure 1 Localized type TGCT: MRI of a 6-year-old boy with TGCT in his left knee. **a.** Sagittal T1-weighted image showing a well-circumscribed nodular lesion at the synovial lining of the anterior knee compartment. **b.** Sagittal T1-weighted spectral presaturation with inversion recovery (SPIR) image after IV gadolinium administration shows heterogeneous enhancement.

Patients and Methods

Children were defined as patients younger than 18 years at presentation. Large joints were defined as all joints proximal to the metatarsophalangeal and metacarpophalangeal joints. Data were derived from three sources: a systematic review, the nationwide TGCT incidence study, and from our bone and soft tissue tumour data registry.

A systematic review on TGCT in children was performed, seeking sources published between 1990 and 2016. Search terms and MeSh headings were "tenosynovial giant cell", "diffuse type giant cell", "giant cell tumors", "PVNS", "pigmented villonodular synovitis", and "synovitis, pigmented villonodular" combined with "infant", "child", "neonat", "pediatric", "paediatric", "toddler", "teen", "teenager", "juvenile", "adolescent", "girl", and "boy". A total of 619 articles were identified in PubMed,

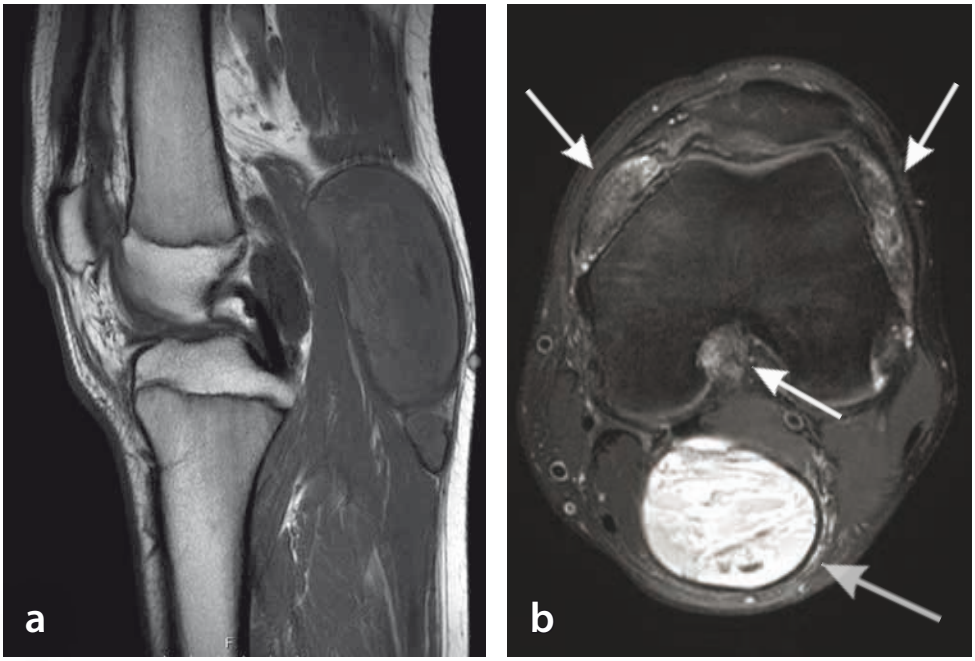

Figure 2 Diffuse type TGCT: MRI of a 16-year-old boy with TGCT in his left knee. **a.** Sagittal T1-weighted turbo spin echo (TSE) image shows extensive intra- and extra-articular villous proliferation of synovium. Posterior is a large Baker's cyst. **b.** Transversal T2-weighted TSE image with heterogeneous low to intermediate signal of the TGCT anterior and posterior (white arrows). Baker's cyst is shown posteriorly (bigger grey arrow).

EMBASE, and Cochrane library. All titles and abstracts were screened by two independent reviewers (MJLM, DU) including case-series with at least two TGCT paediatric patients and published in English. Case-series without detailed data on children were excluded, resulting in a data set of 17 heterogeneous, mostly small case-series of two to six patients (*Table 1*). The largest study included 11 patients with localized TGCT of large joints[7].

The Dutch paediatric incidence rate was extracted from the nationwide TGCT incidence study by including patients < 18 years of age[3]. Standardized incidence rates were obtained by using the direct method, applying age-specific incidence rates in each 1-year age group to the WHO standard population (http://seer.cancer.gov). This study by Mastboom et al.[3] was a registry-based study and eligible patients with TGCT were clinically verified. Patients without histologically proven TGCT were not included.

From our national bone and soft tissue tumour data registry (PALGA), a clinical data set was derived, including 57 patients < 18 years with (histologically proven) TGCT in large joints, treated between 1995 and 2015, in one of the four tertiary sarcoma centres in The Netherlands. Clinical, biologic, and imaging data on TGCT type, sex, localization, age at diagnosis, symptoms before diagnosis, treatment(s), recurrence(s), and followup were collected.

A combined retrospective database of two tertiary oncology centres (Leiden University Medical Centre and Radboud University Medical Centre) in The Netherlands has recorded all patients with TGCT since 1990 (455 patients). TGCT data on children were compared with TGCT data on 423 adults (32 children within this database were excluded from the adult group).

Statistical analyses, for our clinical data set, were predominantly descriptive. Chi square test was used to compare children and adults on TGCT type, sex (male versus female), localization (knee versus other large joints), symptoms before diagnosis (pain, swelling, and loss of function: yes versus no), first treatment (arthroscopic resection versus open resection), recurrent disease (no recurrence versus recurrence), and followup status. Independent t-test was used to compare median duration of symptoms and median time to followup. All reported p values were two-tailed. Statistical significance level was defined at $p < 0.05$. The recurrence-free survival curve was assessed with Kaplan-Meier methods.

This study was approved by the institutional review board from the Leiden University Medical Centre (medical ethical approved protocol P13.029). Data capturing and analyses were performed at Leiden University Medical Centre. SPSS Version 23 (Chicago, IL, USA) was used for analyses.

Results

Our systematic review identified 17 case-series involving 76 children (39 female) with TGCT, 29 localized, 38 diffuse, and nine unknown type (*Table 1*). The paediatric group ranged from 3 to 18 years of age. The knee was most frequently affected (44 [58%]). Swelling, pain, and limited ROM were described symptoms before diagnosis (mean duration, 15 months). The majority of patients were primarily treated with synovectomy, either arthroscopic or open. Recurrent disease was described in 10 patients (13%). Only five paediatric studies described function or quality of life after treatment. Patients with (multiple) recurrences experienced impaired function and quality of life, according to van der Heijden et al.[22]. Five children with diffuse TGCT, described by de Visser et al.[13], had fair to

excellent results on the Musculoskeletal Tumour Society (MSTS) score after surgical treatment (MSTS by Enneking). Gholve et al.[7] described 11 children with surgically treated localized TGCT without disabling joint function according to a telephone questionnaire survey. Seven surgically treated children, described by Baroni et al.[4], recovered full ROM and two patients showed impaired joint movement with occasional mild to moderate pain in four children with localized and five children with diffuse type. Nakahara et al.[21] showed three children with diffuse disease of the knee with almost maximum Knee Society Scores and improved postoperative ROM of at least 0° to 145°.

The standardized paediatric TGCT incidence rate of large joints was 2.42 and 1.09 per million person-years in localized and diffuse types, respectively[3]. Between 2009 and 2013, 53 children with localized TGCT (excluding digits) and 24 children with diffuse TGCT were diagnosed in The Netherlands. This resulted in a Dutch incidence rate of 2.86 per million person-years for localized TGCT (excluding digits) and 1.30 per million person-years for diffuse TGCT; this was converted to standardized incidence rates (*Supplemental Table 1 [Supplemental materials are available with the online version of CORR®.]*). In both localized and diffuse types, the knee was most commonly affected (*Figure 3*).

Clinical data of TGCT in children from the four Dutch tertiary sarcoma centres seemed similar to those observed in the combined two Dutch retrospective adult databases (*Table 2*). Fifty-seven children (median age at diagnosis, 16 years; range, 4-18 years) with TGCT of large joints were identified (*Table 2*). Symptoms before diagnosis were swelling, pain, and limited ROM with a median duration of 12 months (range, 1-72 months). These symptoms and the diagnostic delay seemed similar to those observed in adults (*Table 2*). Children showed a localized diffuse ratio of one to one; the knee was predominantly affected (13 of 28 [46%] localized, 19 of 29 [66%] diffuse) and there was a predilection for females (15 of 28 [54%] localized, 18 of 29 [62%] diffuse). In 423 adults, the localized:diffuse ratio was 1:1.6; the knee was predominantly affected (121 of 172 [70%] localized, 189 of 251 [75%] diffuse) with a predilection for females (107 of 172 [62%] localized, 142 of 251 [57%] diffuse).

Recurrence-free survival curves were not different with the numbers available between children and adults at the four involved tumour centres (*Figure 4*). The 2.5-year recurrence-free survival, after surgical treatment, in paediatric patients compared with adults was 85% (95% confidence interval [CI], 67%-100%) versus 89% (95% CI, 83%-96%; p = 0.527) in localized and 53% (95%

Table 1 Literature overview on TGCT affecting all joints in children, including at least two TGCT cases (1990-2016, English language)*

Study	Year	Number	Sex	Mean age (years; range)	Symptoms before diagnosis	Mean duration of symptoms (months; range)
Givon[8]	1991	2	1 M, 1 F	7 (7-7)	S, W, LROM	60 (both patients)
Rosenberg†[9]	2001	2	2 M	12 (10-14)	S	NA
Neubauer‖[10]	2007	5	3 M, 2 F	12 (8-15)	S,P	10 (2-24)
Gholve et al.‖[7]	2007	11	6 M, 5 F	12 (7-16)	S, P	10 (1-24)
Pannier†[11]	2008	6	2 M, 4 F	12‡	NA	NA
Baroni et al.[4]	2010	9	4 M, 5 F	11 (7-15)¶	S, P, LROM	18 (2-48)
Current	2017	57	24 M, 33 F	14 (4-18)	S, P, LROM	16 (1-72)
Also adult cases included						
Abdul-Karim[12]	1992	2	2 M	10 (10-10)	S, P	NA
de Visser et al.[13]	1999	5	4 M, 1 F	16 (12-18)	NA	NA
Perka[14]	2000	2	2 F	12 (8-16)	S, P, LROM	12‡
Somerhausen[15]	2000	4	3 M, 1 F	14 (3-18)	S	7 (6-8)
Gibbons[16]	2002	3	1 M, 2 F	11 (8-15)	S	28 (6-96)§
Bisbinas[17]	2004	5	5 F	14 (12-15)	S	2‡
Brien[18]	2004	3	1 M, 2 F	13 (12-15)	S, P	7 (1-24)§
Sharma[19]	2006	4	2 M, 2 F	14 (8-17)	S, P	2‡
Sharma[20]	2007	3	2 M, 1 F	17 (16-18)	S, P	5 (2-9)
Nakahara et al.[21]	2012	3	2 M, 1 F	11 (8-13)	NA	NA
van der Heijden[22]	2014	7	2 M, 5 F	14 (6-18)	NA	NA
Total		**133**				

TGCT type	Joint	Primary surgeries	Recurrent disease	Mean followup (months; range)
1 L, 1 D	2 knee	1 AS, 1 US	0	24 (12-36)
1 L, 1 D	2 knee	1 OS, 1 US	NA	NA
5 unknown	4 knee, 1 ankle	5 AS	1	36 (12-84)
11 L	2 knee, 3 ankle, 4 foot, 1 hand, 1 wrist	11 OS	0	54 (15-130)
2 L, 4 D	5 knee, 1 ankle	5 US, 1 MT	2	58[‡]
4 L, 5 D	9 knee	4 AS, 5 OS	0	82 (46-143)
28 L, 29 D	32 knee, 11 ankle, 5 foot, 4 hip, 2 hand, 2 other, 1 wrist	9 AS, 47 OS, 1 WS	23	55 (0-260)
2 D	1 foot, 1 ankle	1 US, 1 AP	0	132 (108-156)
5 D	4 knee, 1 ankle	4 US, 1 RS	5 residual disease	30 (21-75)
2 L	2 knee	2 US	0	NA
4 D	1 knee, 1 foot, 1 buttock, 1 thigh	4 US	0/1 NA	44.5 (0-114)
3 L	3 foot	3 US	0	NA
5 L	5 ankle	5 OS	0	46 (12-150)
3 D	2 foot, 1 ankle	3 US	2	NA
4 unknown	4 ankle	4 US	0	37.5 (19-65)
3 D	3 knee	3 OS	1	96 (54-138)
3 D	3 knee	3 OS	0	29 (20-36)
7 D	7 knee	4 AS, 3 OS	4	95 (24-212)
	57 L, 67 D, 9 unknown			

[*]Large joints were defined as all joints proximal to and excluding metatarsophalangeal and metacarpophalangeal joints; large case-series not describing children in detail were not included; [†]language of article was French; included information is based on an English abstract; [‡]range unavailable; [§]including adult cases; [‖]TGCT cases in digits were excluded; [¶]case number 6, a 2-year-old girl, was excluded according to a delayed time to diagnosis of 38 months; TGCT = tenosynovial giant cell tumour; M = male; F = female; NA = information not available; S = swelling; W = warmth; LROM = limited ROM; P = pain; L = localized TGCT; D = diffuse TGCT; AS = arthroscopic synovectomy; OS = open synovectomy; US = unspecified

CI, 35%-79%) versus 56% (95% CI, 49%-64%; p = 0.691) in diffuse type, respectively. In the four involved sarcoma centres, most children and adults alike were primarily surgically treated by open resection: localized TGCT in 25 of 28 children (89%) were thus treated compared with 142 of 172 adults (85%; p = 0.486); for diffuse TGCT in children, the proportion was 22 of 29 (76%) compared with 188 of 251 in adults (75%; p = 0.289). Recurrence risk in children and adults was likewise not different with the numbers available: two of 28 (7%) compared with 22 of 172 (13%; p = 0.365) in localized type and 11 of 29 (38%) compared with 119 of 251 (47%; p = 0.921) in diffuse type, respectively.

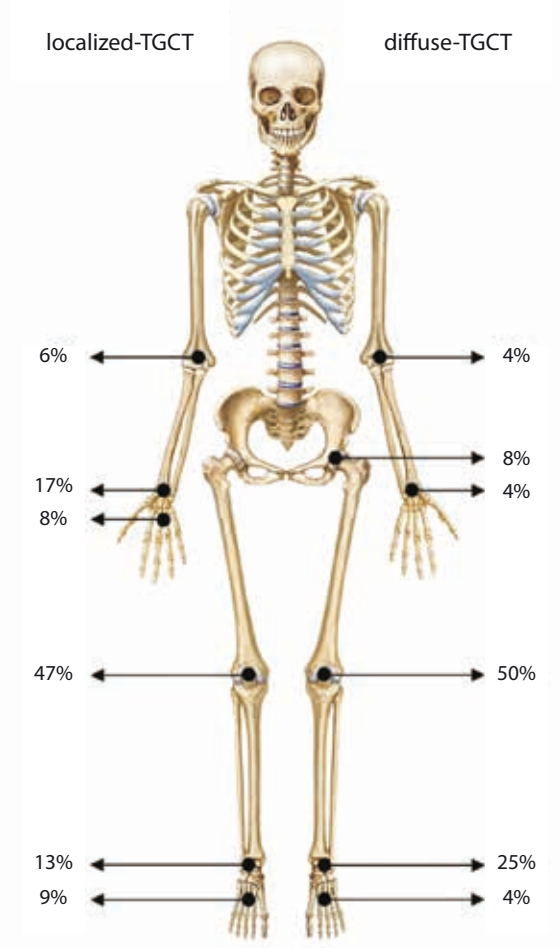

Figure 3 Skeleton showing TGCT localization in children extracted from a Dutch incidence study, excluding digits[3]. In diffuse TGCT, one patient was classified as "other"; he was treated for TGCT in his vertebral column.

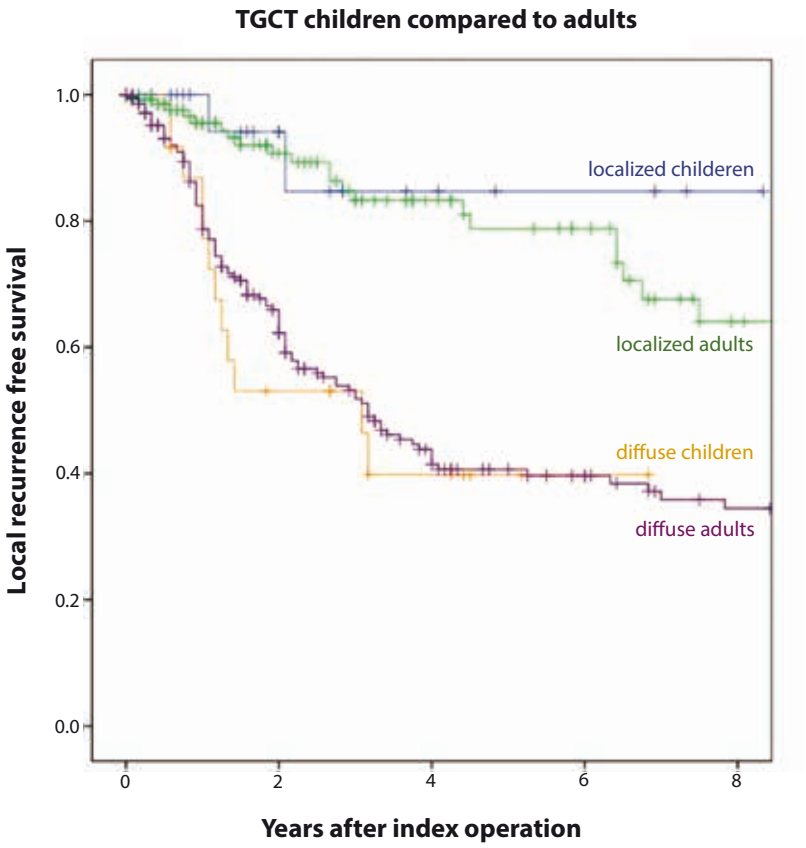

Figure 4 Local recurrence-free survival curve of localized and diffuse TGCT (Kaplan-Meier), excluding digits. Time zero is the time of the primary surgery. All patients were surgically treated; patients treated with wait-and-see treatment are excluded. In the adult graph, two patients died and were censored at the time of death if a recurrence had not occurred.

Table 2 Details of patients with TGCT of large joints in children versus adults, including sex, localization, age, symptoms, first treatment, recurrent disease, and followup[†]

	Children	
Patient variables	**Localized TGCT**	**Diffuse TGCT**
Total number of patients	28	29
Sex		
Male:female ratio	13:15 (1:1.2)	11:18 (1:1.6)
Localization		
Knee	13 (46%)	19 (66%)
Other joints	15 (54%)	10 (34%)
Age		
Median age at diagnosis (years; range)	16 (4-18)	16 (11-18)
Symptoms before diagnosis		
Swelling	24 (86%)	21 (72%)
Pain	12 (43%)	17 (59%)
Limited ROM	3 (11%)	4 (14%)
Median duration of symptoms (months; range)	9 (1-48)	18 (1-72)
First treatment		
Arthroscopic resection	3 (11%)	6 (21%)
Open resection	25 (89%)	22 (76%)
Wait and see	0	1 (3%)
Recurrent disease[†]	**N = 28**	**N = 28**
No recurrence	26 (93%)	17 (61%)
≥ 1 recurrence	2 (7%)	11 (39%)
Followup status		
Disease-free	19 (68%)	16 (55%)
Alive with disease[‡]	4 (14%)	9 (31%)
Death of other disease	0	0
Lost to followup[‡]	5 (18%)	4 (14%)
Median time to followup (months; range)[*]	25 (7-100)	77 (7-144)

Adults		Children versus adults	
Localized TGCT	**Diffuse TGCT**	**p value localized TGCT**	**p value diffuse TGCT**
172	251		
		0.285	0.434
65:107 (1:1.6)	109:142 (1:1.3)		
		0.019	0.207
121 (70%)	189 (75%)		
51 (30%)	62 (25%)		
42 (19-82)	38 (19-72)		
106 (62%)	163 (65%)	0.010	0.510
103 (60%)	157 (63%)	0.129	0.558
13 (8%)	49 (20%)	0.608	0.486
12 (1-240)	24 (1-300)	0.176	0.153
		0.486[+]	**0.289**[+]
7 (4%)	37 (15%)		
147 (85%)	188 (75%)		
18 (11%)	26 (10%)		
N = 154	**N = 225**	**0.280**	**0.407**
132 (86%)	106 (47%)		
22 (14%)	119 (53%)		
		0.840	**0.768**
110 (64%)	121 (48%)		
19 (11%)	94 (37%)		
0	2 (1%)		
43 (25%)	34 (14%)		
36 (6-301)	54 (6-350)	0.127	0.780

[*]Patients lost to followup are excluded for median time to followup; lost to followup is defined as < 6 months followup; [†+]wait and see treatment was not included in calculation of independent t-test; children were included between 1995 and 2015 adults between 1990 and 2015; [‡]patients alive with disease either have wait and see treatment, residual or recurrent disease; TGCT = tenosynovial giant cell tumor.

Discussion

TGCT is most commonly seen in adults in the third and fourth decades of life, but this study confirms that it also affects paediatric patients. The paediatric incidence rate for both localized and diffuse type suggests that it is rare, but we believe it is still common enough to include in the differential diagnosis of both children and adults with nonspecific symptoms like swelling, pain, and limited ROM. We found no differences with the numbers available between children and adults in terms of presenting symptoms, treatments used in the few available case-series, and recurrence-free survival rates. In the era of personalized medicine, future research should define the most effective treatment for TGCT, with its various clinical scenarios, both in children and adults.

There are some limitations to this study. In our systematic review, many case-series included data from children with TGCT in embedded studies that also contained adults' data. When data on children was not separately described, these children were not included in the overview (*Table 1*). The determined incidence rate is a conservative estimate, because our search was based on the nationwide network and registry of histo- and cytopathology in The Netherlands[23]. Patients with TGCT without a biopsy or treatment were not represented in this pathology-based cohort. By standardizing incidence rates, they could be extrapolated to other populations. However, generalizability of the standardized incidence rate depends on the age-specific population structure of the country compared with the WHO population. Included patients had histologically proven TGCT by a dedicated musculoskeletal pathologist (UF, HB, AS, JB). However, patients were not centrally reviewed for this study. Neither functional outcome nor quality of life was evaluated. For TGCT treatment, only surgical treatment was evaluated. Future, comparative studies on treatments should determine what should be done for patients (children and adults) with TGCT. Although surgery is the mainstay, other treatments are used, and future research needs to define what the best approaches are for the various clinical scenarios in which this disease presents. In our patients, children with the localized type frequently lacked longer term followup, mainly as a result of absence of clinical symptoms (17 censored in the first 2.5 years; *Figure 4*). Smaller patient numbers with the diffuse type sometimes lacked longer followup (nine censored in the first 2.5 years).

TGCT does not seem to be an adults-only disease and should be considered in the differential diagnosis in children with (chronic) monoarticular joint effusion. Our systematic review identified mainly small, heterogeneous TGCT case-series in children. Future studies might consider including children with TGCT to allow for optimalization of the treatment protocol in both children and adults.

The standardized paediatric TGCT incidence rate of large joints was 2.42 and 1.09 per million person-years compared with an overall incidence rate of 10.2 and 4.1 per million person-years in localized and diffuse types, respectively[3]. To date, the incidence rate for chronic monoarthritis in children and adolescents is unknown. Savolainen et al. calculated an incidence rate of 64 per 100,000 for all types of arthritis in children (< 16 years) in a defined population in Finland[24]. Although TGCT in children probably accounts for only a small percentage of all types of arthritis, it should still be considered in the differential diagnosis.

Symptoms in children seemed similar to those in adults (*Table 1*). Nonspecific symptoms accompanied by pain and diffuse joint swelling with thickening of the synovial capsule and/or joint effusion resulted in limited movement in approximately half of the patients. Studies in adults add mechanical symptoms, instability, and stiffness[5, 25].

A systematic review (without age limitations) in 2013[5] reported average recurrence rates for localized TGCT in the knee after open resection (4%) and after arthroscopic resection (6%) in contrast to diffuse type after open resection (14%) and after arthroscopic resection (40%) at a mean followup of 108 months. Patel et al.[25] presented 214 patients with knee TGCT of all ages with a recurrence rate of 9% in 100 localized patients and 48% in 114 patients with diffuse TGCT after a mean followup of 25 months (range, 1-168 months). Palmerini et al.[26] reported 294 patients with TGCT of all ages in all joints with a local failure rate of 14% in localized and 36% in diffuse type after a median followup of 4.4 years (range, 1-20 years). The sole primary disease or patients with a first relapse were included. The current paediatric case-series showed comparable recurrence rates of 7% in localized and 39% in diffuse type after a mean followup of 55 months (range, 7-350 months). TGCT is a rare condition in adults and it is even less common in children. Nonspecific symptoms often contribute to a delay in establishing a diagnosis. TGCT should be considered in chronic monoarthritis both in adults and in children. Recurrent disease after surgical treatment of this orphan disease seems comparable between children and adults. With targeted therapies now being developed[27], future research should define the most effective treatment strategies for this heterogeneous disease.

Supplementary data

Supplementary data are available in the online version of this article:
https://dx.doi.org/10.1007/s11999.0000000000000102

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