

Paediatric mastocytosis: a systematic review of 1747 cases

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Summary

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Paediatric mastocytosis was previously considered to be a benign and spontaneously regressing disease. However, this evolution is impossible to predict. To clarify the characteristics and course of paediatric mastocytosis, we performed a literature review of 1747 cases published between 1950 and April 2014. Lesions occurred before the age of 2 years in 90% of cases, and presented as urticaria pigmentosa (75% of cases), mastocytoma (20%) or diffuse cutaneous mastocytosis (5%). The male-to-female ratio was 1.4. KIT D816V mutation was detected in 34% of 215 tested patients. Clinical regression (complete or partial) occurred in 67% of cases and stabilization in 27%. However, the outcome was fatal in 2.9% of patients.

What's already known about this topic?

- The clinical and genetic features and outcomes of mastocytosis differ for the adult and paediatric forms.
- Since paediatric mastocytosis was linked to mutations in c-Kit in 2010, it has been considered a clonal disease.
- In 1963, Caplan reported that spontaneous regression occurs in the majority of cases of paediatric mastocytosis, and no predictive factors have been identified.

What does this study add?

- This extensive review points out that the outcome in some paediatric cases is fatal, that KIT mutations are rarely studied and that predictive factors are still unknown.
- We suggest that long-term follow-up of children is necessary and that prospective studies are warranted to evaluate the prognostic value of sequencing KIT.

Mastocytosis refers to a heterogeneous group of clinical disorders characterized by abnormal accumulation of mast cells in various tissues.^{1–3} In about two-thirds of cases, mastocytosis begins in childhood.⁴ In its typical form, childhood-onset mastocytosis is characterized by cutaneous involvement, most commonly urticaria pigmentosa (UP, also called maculopapular mastocytosis), mastocytoma and, less frequently, diffuse cutaneous mastocytosis (DCM).⁵ The different clinical and histological features are summarized in Figure 1.

Adult mastocytosis is a clonal disease frequently associated with KIT D816V mutations, causing abnormal mast cell accumulation and activation.⁶ Paediatric mastocytosis is a regressive disease and as such was previously considered to be nonclonal.⁶ In fact, by performing full KIT sequencing, we found a high frequency of KIT mutations located mainly (44% of cases) outside exon 17,^{7,8} demonstrating that paediatric mastocytosis is also a clonal disease. This finding raised the important question of whether the disease truly regressed. Previous studies reported that paediatric mastocytosis is a benign disease with a substantial clinical improvement, or that spontaneous regression before

puberty may be observed.^{9–24} Although rare, systemic forms can occur in children.^{19,22} In these cases, the disease may remain active throughout adolescence, with a risk of systemic disease in adulthood. Finally, some rare but very severe forms of mastocytosis, such as mast cell sarcoma (MCS) and mast cell leukaemia (MCL), are reported in children.^{25–36} Factors predicting the course and severity of childhood-onset mastocytosis have not yet been completely identified. In order to clarify the presentation, genetics and clinical course of paediatric mastocytosis, we performed a literature analysis of all published studies on paediatric mastocytosis.

Materials and methods

Bibliographical search strategy

The search strategy is outlined in Figure 2. A search of Medline via PubMed and Embase was undertaken using 19 search strings: 'cutaneous mastocytosis' AND 'children' or 'childhood' or 'infants', 'urticaria pigmentosa' or 'mastocytoma' or

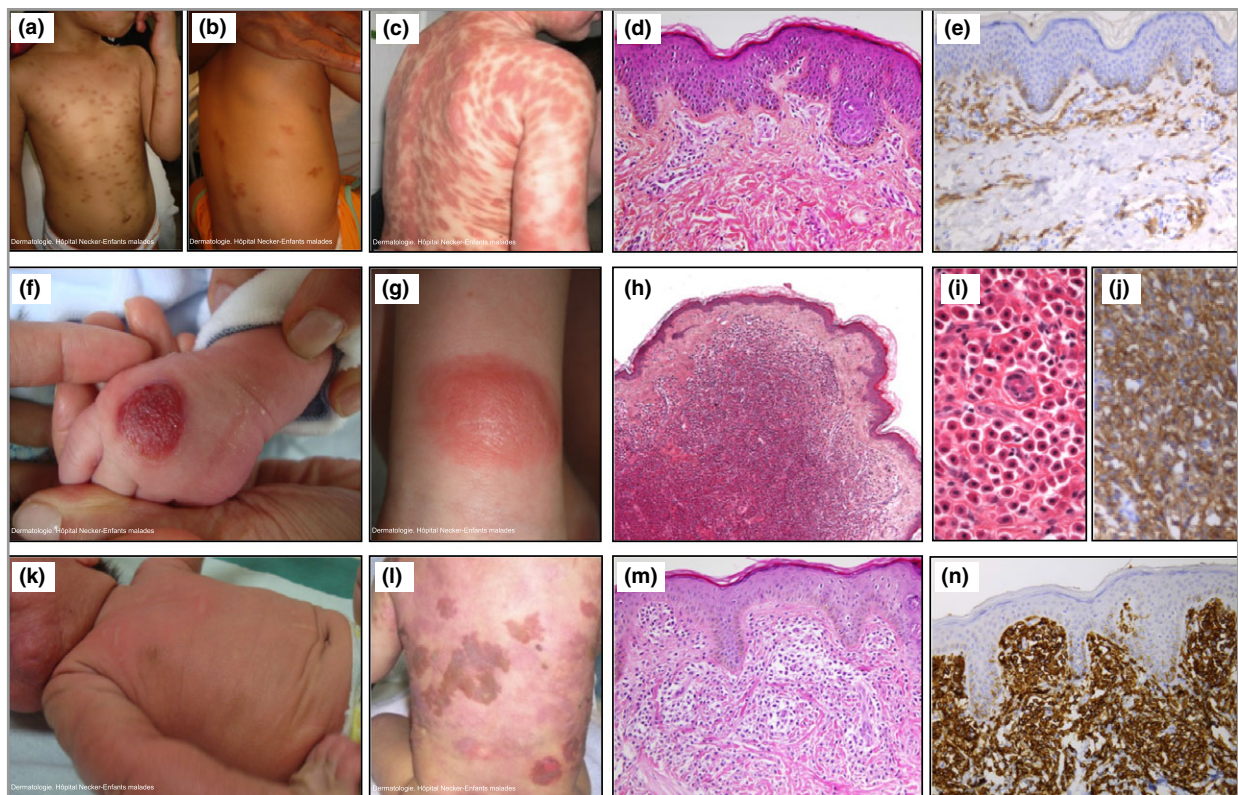


Fig 1. Clinical features and histological findings in childhood mastocytosis. Diagnosis of mastocytosis in children is often obvious and skin biopsy is rarely performed. The histological diagnosis of cutaneous mastocytosis must consider the increased number and proportion of mast cells compared with other inflammatory cells. Mast cells can be rounded, cuboidal, fusiform or histiocytic-like. Eosinophils may be observed in all mastocytosis subtypes. The epidermis may be hyperpigmented in urticaria pigmentosa (UP) and diffuse cutaneous mastocytosis (DCM), while it is normal in mastocytoma. (a–e) UP: (a) maculopapular UP; (b) plaque-type UP; (c) extensive UP with plaques and macules; (d) skin biopsy ($\times 40$): increased number and proportion of mast cells around the vessels or scattered into the dermis, dilatation of the capillaries of the superficial dermis; (e) c-Kit staining. (f–j) Mastocytoma: (f) mastocytoma localized on the hand; (g) mastocytoma localized on the forearm; (h, i) skin biopsy: abundant and diffuse infiltration of mast cells throughout the dermis. Mast cells are always recognizable, with a large, pink and granular cytoplasm and a round, dense, central nucleus; (j) c-Kit staining. (k–n) DCM: (k) diffuse infiltration of skin; (l) extensive bullous lesions associated with infiltration on the back; (m) skin biopsy: diffuse dermal infiltration of mast cells associated with some fibrosis and dilated capillaries; (n) c-Kit staining.

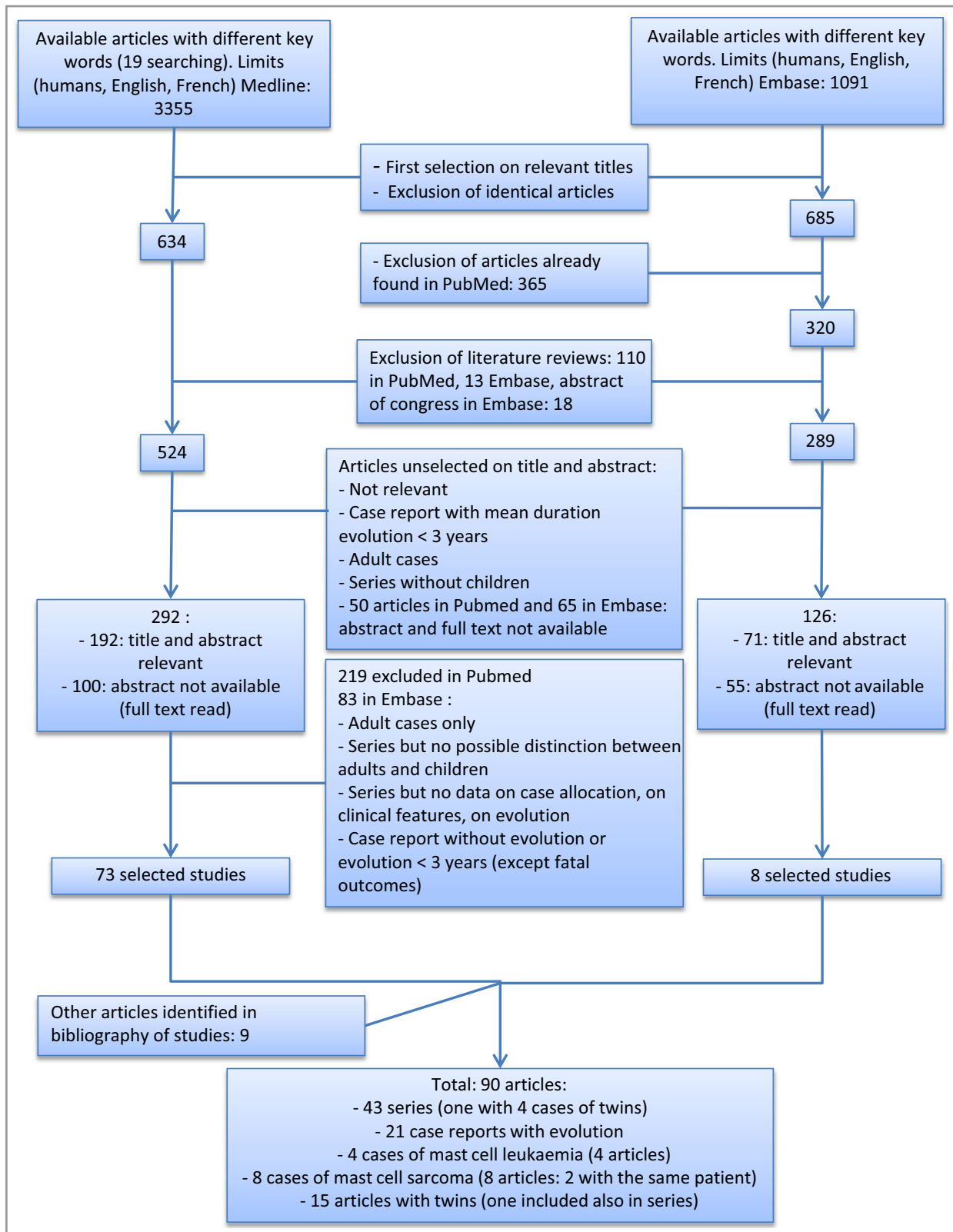


Fig 2. Flowchart of the bibliographical search strategy.

'bullous mastocytosis' or 'congenital mastocytosis' or 'mastocytosis' or 'diffuse cutaneous mastocytosis'/AND 'children', 'mastocytosis series', 'paediatric mastocytosis', 'mastocytosis/

AND c-kit/AND children', 'mastocytosis' or 'urticaria pigmentosa'/AND 'twins', 'neonatal mastocytosis', 'childhood onset mastocytosis', 'mast cells/AND leukaemia/AND children',

'mast cell/AND sarcoma/AND children', 'mast cell sarcoma', 'mast cell leukaemia'. The search was restricted to human cohorts published between 1950 and April 2014 in both English and French. Published full texts were systematically retrieved for the articles selected. If the full text was not available, the article was not included. The bibliographical references of the articles retrieved were screened to identify further studies for possible inclusion.

Inclusion criteria

The paediatric population was defined as patients aged < 18 years. The diagnosis of mastocytosis had to be clearly established based on clinical criteria (lesion type, Darier sign) and histological confirmation in uncertain clinical situations.

The inclusion criteria were evaluated by two investigators (C.M. and S.G.L.) and consisted of series of paediatric mastocytosis involving more than three children with clinical data for each, case reports with at least 3 years of follow-up after the diagnosis, cases of twins and cases of MCS and MCL with childhood-onset disease. Adult mastocytosis with childhood onset diagnosed during the paediatric period and case reports of children who died before 3 years of follow-up were included. Series of the same children mentioned in two studies were included only once.^{26,36–38}

Exclusion criteria

All articles failing to meet the inclusion criteria were excluded: nonrelevant data including case reports with < 3 years of follow-up, series reporting only adult mastocytosis, studies of medical technical or laboratory test findings without clinical data for patients, studies including adults and children in which it was impossible to distinguish between the two, articles including adults with childhood-onset mastocytosis diagnosed in adulthood, and/or articles not supplying data on age. Duplicate articles, literature reviews, pictures, conference abstracts and quizzes were excluded.

Selected articles

In total 90 articles were available. This included 43 series,^{7–22,37,39–64} 21 case reports with outcome data (> 3 years),^{65–85} 15 articles involving twins (one of which was also included in the 43 series), corresponding to 31 cases^{55,86–99} and 12 articles concerning MCL or MCS, corresponding to 12 cases (two concerning the same patients).^{25–36,100,101} A two-generation history of mastocytosis was mandatory for the positive familial history criterion. The 31 cases of twins were not considered as familial mastocytosis.^{55,86–99}

Data extraction and analysis

The following data were extracted from each article: general characteristics of the studies, patient features (number of

patients, age of onset, familial mastocytosis, data on diagnosis, skin biopsy, KIT mutations), tryptase level and outcome. Clinical features included characterization of the cutaneous lesions, Darier sign, dermatographism, itching and blisters, lymphadenopathy and hepatosplenomegaly; and systemic signs: flushing, headache, bone pain, abdominal pain, vomiting and diarrhoea (digestive signs), and anaphylaxis, dyspnoea, syncope and hypotension. According to the World Allergy Organization, anaphylaxis is the sudden release of multiple mediators from mast cells and basophils leading to symptoms in more than one organ system, such as skin symptoms associated with mucosal signs (oedema) or respiratory symptoms, or a sudden drop in blood pressure.¹⁰² To evaluate outcome, we thus defined five categories (according to Valent *et al.*):² (i) complete regression of skin lesions and specific skin-related symptoms; (ii) partial regression, including major regression (disappearance of > 50% of skin lesions and specific skin-related symptoms) and partial regression (disappearance of 10–50% of skin lesions and specific skin-related symptoms); (iii) stabilization: disappearance of < 10% lesions and symptoms, (iv) worsening and (v) fatal outcome.

Results

Epidemiology and age at onset

A male-to-female sex ratio of 1.4 (841 vs. 594) was found in the 1747 childhood cases analysed. In 90% of cases (872 of 973), disease onset occurred before the age of 2 years, and congenital mastocytosis was described in 23% (252 of 1085). One-half (50%; six of 12) of cases of MSC and MCL arose in children aged over 2 years. Familial mastocytosis was described in 4% of cases with at least one first-degree parent with mastocytosis (Table 1).

Twin cases were reported in 1.8% of the 1747 cases (*n* = 31). Twins were monozygotic in 53% of

Table 1 Epidemiology and clinical features

Sex ratio	1.4 (841 male, 594 female) ^a	
Congenital mastocytosis	23% (252/1085) ^a	
Familial cases	4% (34/926)	
Age of onset	Before 2 years ^b	After 2 years
In series (934 patients) ^a	91% (<i>n</i> = 846)	9% (<i>n</i> = 88)
Cases of twins (27 patients) ^a	74% (<i>n</i> = 20)	26% (<i>n</i> = 7)
MCS and MCL (12 patients) ^a	50% (<i>n</i> = 6)	50% (<i>n</i> = 6)
Clinical presentation (<i>n</i> = 1747) ^c		
Urticaria pigmentosa	74.8% (<i>n</i> = 1307)	
Mastocytoma	19.5% (<i>n</i> = 340)	
Diffuse cutaneous mastocytosis	5.2% (<i>n</i> = 90)	
Telangiectasia macularis eruptiva perstans	0.3% (<i>n</i> = 5)	
Darier sign	91% (562/617)	
Skin biopsy	73% (984/1349)	

MCS, mast cell sarcoma; MCL, mast cell leukaemia. ^aAvailable data. ^bIncluding congenital cases. ^cFive cases of MCS or *de novo* MCL not included.

cases^{87,88,90–93,95,96,99} and not in two cases.^{97,98} Data were not available for five sets of twins.^{55,86,89,94}

Clinical and biological features at diagnosis

Types of mastocytosis presentation at diagnosis are described in Figure 3(a–c) and consisted of UP (74.8%), mastocytoma (19.5%), DCM (5.2%) and telangiectasia macularis eruptiva perstans (TEMP; 0.3%). Skin biopsies were undertaken in 73% of cases, to confirm the diagnosis or within the framework of clinical studies (Table 1).

The type of initial lesions in patients with UP-type lesions was reported in 35% of cases. These were macules (20%), papules (12%), maculopapules (41%), plaques (15%) or nodular-type lesions (12%).^{10–13,22,23,37,46,54,59} In four studies

using the Hartmann and Henz classification,¹⁰³ 63% of patients presented with maculopapular lesions, 21% with plaques and 16% with nodular-type lesions.^{22,23,37,59}

Cutaneous features (Fig. 3e and Table S1) were reported in 70% of cases in the series.^{7,10–16,18–22,37,38,41–44,46,47,54,57,58,63,104} Darier sign was present in 90% of patients. Itching was the most frequent feature (48.0%), followed by bullous lesions (34.5%).

Mast cell release symptoms such as flushing, gastrointestinal symptoms and bone pain were present in 24.5%, 19.5% and 13.7% of cases, respectively, as shown in Figure 3(f) and Table S1. These symptoms were more frequent in patients with DCM (Fig. 3d).^{10,12,15,16,18,21,22,37,38,43,46,47,57,58,63,98,104}

Anaphylaxis was reported in 5.5% of patients,^{7,14,18,37,38,47,63} and in only one patient in the twin cases.^{88,93} However, the

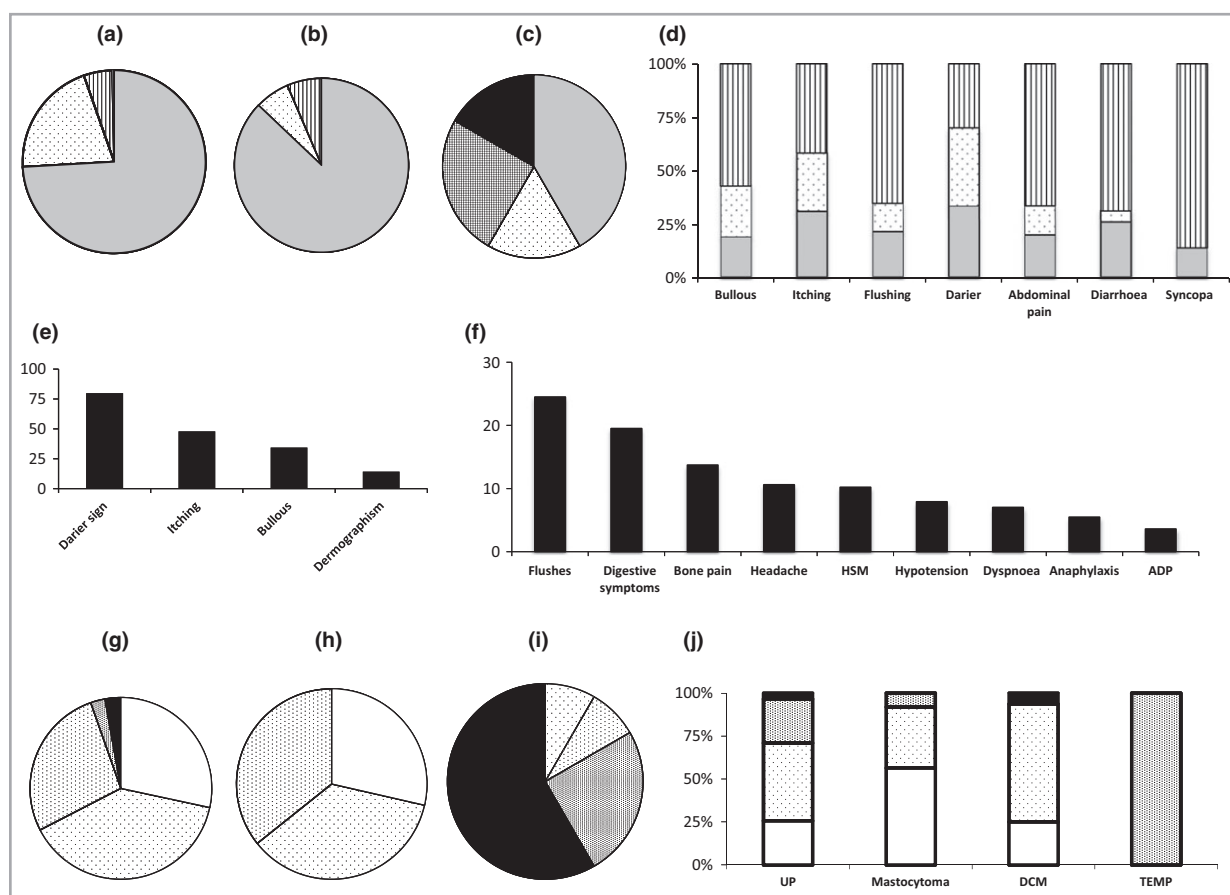


Fig 3. Paediatric cutaneous mastocytosis, clinical features and outcome. (a–d) Grey, urticaria pigmentosa (UP); dots, mastocytoma (M); lines, diffuse cutaneous mastocytosis (DCM); black, data not available; hatched, *de novo* cases. (a–c) Paediatric cutaneous mastocytosis at onset. (a) Distribution in series and case reports ($n = 1704$): UP 74.8%, M 19.5%, DCM 5.2%, TEMP 0.3%. (b) Distribution in twin cases ($n = 31$; the two sets of twins reported in a series⁵⁵ are included only in the twin cases): UP 87%, M 6%, DCM 6%, TEMP 0%. (c) Distribution of cases of mast cell leukaemia and sarcoma ($n = 12$): UP 42%, M 17%, DCM 0%, TEMP 0%, *de novo* 25%, data not available 17%. (d) Correlation between clinical features and type of cutaneous mastocytosis. (e, f) Clinical features in 26 series. (e) Mastocytosis-related cutaneous symptoms; (f) mastocytosis-related systemic symptoms (ADP, adenopathy; HSM, hepatosplenomegaly). (g–j) White, complete regression (CR); scattered dots, partial regression (PR); moderate-density dots, stabilization (S); high-density dots, worsening (W); black, fatal outcome (FO). (g–i) Paediatric mastocytosis outcome. (g) Progression in 621 children (series and case reports). CR 28.2%, PR 39.1%, S 27.1%, W 2.7%, FO 2.9%. (h) Twin cases progression ($n = 14$). CR 29%, PR 36%, S 36%, W 0%, FO 0%. (i) Progression of mast cell leukaemia and mast cell sarcoma ($n = 11$). CR 0%, PR 9%, S 9%, W 27%, FO 55%. (j) Correlation between outcome and type of mastocytosis in 348 children in series.

criteria for anaphylaxis were rarely described in these studies. Data on personal or familial history of atopic dermatitis or asthma were available for 507 patients, and positive in 14% ($n = 73$).^{10–14,16,21,42,48,55,70,88} Caplan found 47% of cases with a familial or personal history of atopy, unlike Azaña *et al.*,^{10,12} who reported only 6% of patients with atopy.

Tryptase levels were available for 403 patients.^{7,8,19,22,26–34,37,38,55–59,63,75–77,80,83,98} Alvarez-Twose demonstrated that serum tryptase levels $> 20 \text{ ng mL}^{-1}$ were correlated with extensive skin involvement, but not always associated with systemic forms.²² Tryptase levels were substantially elevated in MCS and MCL (seven of 10 cases). No correlation between prognosis and tryptase levels was identified.

Genetic data

KIT mutations were reported in 12% of cases ($n = 215$). Mutations in exon 17 including D816V were detected in 34% of patients.^{8,19,22,52,53,56,61,64,71,73,75} Mutations outside exon 17 were found in 18% of cases (Del419, F522C, ITD502–503, K509I, M541L, L852L).^{7,27,29,31,35,55,64,77} In 48% of cases, KIT mutational status was mentioned as wild-type.^{7,8,19,22,26,30,31,33,37,49,52,53,55,56,61,64,82,83,96} Whole KIT gene sequencing data were only rarely available for those cases with wild-type genotype (29 of 103, 28%).^{7,8,30,31,55,64,83} Details on KIT mutations are reported in Table S2.

The KIT mutation was reported in 9% of twin cases ($n = 6$).^{55,96} Interestingly, the M541L KIT variant, which is considered to be a polymorphism of the KIT gene in adult mastocytosis, was found in two pairs of twins.⁵⁵

A correlation between KIT mutation and disease outcome was not clearly established (36 of 548, 6.6%),^{19,26,27,29,30,33,56,61,71,73,75,77,83} making it impossible to draw conclusions. We were also unable to correlate KIT mutation data with UP subtype (maculopapular or plaque type).^{22,37}

Outcome

Outcome data were available for 621 cases (36%; Fig. 3g–i).^{9,10,12,13,15–19,21,25–34,37–40,47,50,56,61,65–85,95} Clinical outcome was described by three teams.^{2,10,16,19}

The complete regression rate seems to increase with age. After a median follow-up of 6 years (range 1.5–55), and exclusion of fatal outcomes, complete regression was observed in 29% of cases. Indeed, the median follow-up in both series and case reports was 5.5 years (range 2.2–20). In the series of Uzzaman *et al.*¹⁹ and Sotlar *et al.*,⁶¹ complete regression was observed in 68% of cases ($n = 15$) and in 45% of cases ($n = 20$) at a median follow-up of 20 and 15.3 years, respectively. Partial regression was observed in 39% and stabilization in 27% of all patients for whom outcome data were reported ($n = 621$).

Worsening was observed in 2.7% ($n = 17$) of patients and was most common in cases of UP, with various clinical signs including isolated cutaneous worsening ($n = 8$),^{10,50} increased

itching and flushes ($n = 1$),¹⁶ duodenal infiltration ($n = 1$)¹³ and systemic mastocytosis ($n = 2$).^{37,83} Worsening cases were rarely observed in DCM: indolent systemic mastocytosis ($n = 1$),⁵⁶ persistence of cutaneous involvement, especially in the skin folds, and development of cutaneous tumours ($n = 1$)⁶⁸ combined with systemic involvement in adulthood.

Fatal outcome, reported in 18 cases (2.9%), was most frequent in male patients (male-to-female ratio of 2). The types of mastocytosis observed were DCM ($n = 5$)^{66,71,73,76,80} and UP ($n = 7$), including two cases of systemic mastocytosis, two of UP with extensive congenital blistering, one of systemic mastocytosis with associated haematological nonmast cell disease^{65,67,70,72,75,81,85} and six cases of MCS or MCL.^{25,26,28,30,32,34} Twelve patients developed MCS ($n = 8$) or MCL ($n = 4$) in childhood, either *de novo* ($n = 3$) or secondary to mastocytoma ($n = 2$) or UP ($n = 5$) (Table 2).^{25–28,30,32,34,36,101} The median time from diagnosis of mastocytosis to an aggressive form such as MCS or MCL was 25 ± 18 years.^{27,29,31,32,34,100,101}

The correlation between mastocytosis subtype and disease progression reported in the series (more than three cases) is described in Figure 3(j).^{10,12,15,16,19,21,38,40,50,56,61} Regression, including both complete and partial regression, was more frequent in cases of mastocytoma and DCM than in UP (92%, 94% and 71%, respectively).

Discussion

In this review of 1747 cases of paediatric mastocytosis, we first confirmed the reversal of the sex ratio in childhood disease compared with adults, with a preponderance of male patients (male-to-female ratio 1.4). The age of onset in 90% of cases was before the age of 2 years, and familial forms represented 4% of cases. The simultaneous development of the disease in monozygotic twins suggests an inherited genetic susceptibility to mastocytosis. However, other situations such as an absence of medical history and discordant twin cases are also reported, which argue against a monogenic inherited disease. The two situations may coexist. With only a few exceptions, KIT mutations are not detectable in germinal cells in familial cases.

The clinical presentation was most commonly UP (74.8% of cases), followed by mastocytoma (19.5%). Some small spontaneous regressive mastocytomas may therefore be underdiagnosed. We highlight the rare frequency of DCM and TEMP among children. TEMP is more frequent in adult mastocytosis.¹⁰⁵ Data concerning a history of atopy or allergic disorders for both patients and family are rare.

Paediatric mastocytosis was previously considered to be a benign and self-limiting disease, and an analysis of the literature shows that regression (partial or complete) occurs in 67% of children. However, although regression was observed in two-thirds of patients, it is important to point out that the condition was still progressive or had stabilized in the remaining third. In a recent analysis, Barnes *et al.*⁶³ suggested that a high number of maculopapular lesions ($P = 0.02$) and the

Table 2 Main features of cases of mast cell leukaemia (MCL) and mast cell sarcoma (MCS) with a previous history of paediatric mastocytosis

Study	Diagnosis	Sex	Age at onset of mastocytosis	Type of mastocytosis at onset	Age of diagnosis of sarcoma or leukaemia (years)	KIT mutation	Death (age in years)	MCL evolution
Chott 2003 ²⁶	MCS	Female	8 years	<i>De novo</i>	8	Not detected	Yes (10)	Yes
Brcić 2007 ²⁸	MCS	Male	4 years	<i>De novo</i>	4	Not mentioned	Yes (5)	Yes
Georgin-Lavialle 2013 ³⁰	MCS	Male	10 years	UP	25	WT	Yes (25)	No
Ryan 2013 ³¹	MCS	Female	12 years	<i>De novo</i>	12	WT	No	No
Ryan 2013 ³¹	MCS	Male	1 years	UP	19	Del419	No	No
Bautista-Quach 2013 ³³	MCS	Male	11 months	NA	1	WT	No	No
Auquit-Auckbur 2012 ³²	MCS	Male	Neonatal	Mastocytoma	40	Not performed	Yes (42)	No
Kim 2013 ³⁵	MCS	Female	15 years	NA	15	L799F	No	No
Waters 1957 ²⁵	MCL	Male	9 months	UP	5	Not performed	Yes (5)	
Akin 2004 ²⁷	MCL	Male	5 months	UP	25	P522C	Not mentioned	
Mital 2011 ²⁹	MCL	Female	12 months	UP	53	Dup502–503	Not mentioned	
Chantorn 2012 ³⁴	MCL	Female	5 years	Mastocytoma	23	Not performed	Yes (23)	

UP, urticaria pigmentosa; NA, not available; WT, wild-type.

number of skin symptoms ($P < 0.01$) were statistically significant predictors of the number of systemic symptoms. Moreover, preliminary sex-ratio data potentially suggest that male puberty could play a role in mastocytosis regression. Indeed, the sex ratio in adults with mastocytosis diagnosed during infancy/childhood (male-to-female ratio 0.47) is biased towards women.⁷ It has also been suggested that progression could be correlated with lesion size.¹⁰³ Maculopapular cutaneous mastocytosis with small lesions in children and adults appears to resolve spontaneously only rarely, and could be classified as indolent systemic mastocytosis. Conversely, plaque-type cutaneous mastocytosis, with large lesions and solitary mastocytomas characteristic of paediatric mastocytosis, does not progress but tends to disappear. However, in the review, data on follow-up were variable.

These children were followed up for periods ranging from 1.5 to 55 years, and the characteristics of the lesions, such as their size (small) and type (plaques), are not always mentioned. It is therefore impossible to draw conclusions based on the data in the literature. Only two series had a long-term follow-up.^{19,61} Spontaneous regression should arise before adulthood; however, most series did not monitor the patients into adulthood. Moreover, different patients enrolled in the same study were followed up for different periods of time, making the course of the disease difficult to interpret. For example, in the study by Lange *et al.*³⁷ in patients with a mean age of 4 years, follow-up data (ranging from 1 month to 16 years) were available for each patient ($n = 101$); 32% presented a partial remission and 68% stabilization of the disease. Only six patients were followed to puberty (> 14 years old); complete remission was observed at puberty for two of these patients. This variability was also found by Caplan,¹⁰ and could explain the seven cases of worsening, which were probably due to a shorter duration of follow-up. Furthermore, clinical re-evaluation methods

were not the same in all the studies, ranging from a simple phone call to a complete clinical evaluation. Therefore long-duration prospective studies are warranted to resolve these questions.

When systematically evaluated, serum tryptase levels do not appear to have significant prognostic value in paediatric mastocytosis. However, they do appear to be correlated with the extent of skin involvement.

About 3% of cases of paediatric mastocytosis are aggressive and progress to MCS or MCL and systemic disease with a fatal outcome. The development of such aggressive forms several years after the onset of 'benign' paediatric mastocytosis (mastocytoma, $n = 2$ or UP, $n = 5$) stresses the importance of long-term follow-up for these patients, and reports of a mortality rate $> 50\%$ in patients with MCL and MCS clearly show that paediatric mastocytosis does not always have a benign course.^{27,29–31,33,35,101} Finally, two cases of mastocytosis were associated with ovarian malignant germ cell tumours and a fatal outcome.^{70,75} The combination was described several times with both ovarian and other germ cell tumours, particularly mediastinal tumours.^{70,75,106} These findings could suggest that a common molecular mechanism is responsible for both diseases.

In about 80% of cases, adult mastocytosis is associated with the D816V KIT mutation in exon 17,⁷ whereas 40% of KIT mutations in children occur in exons 8–11,⁸ which are rarely observed in adults. At the present time, there is no evidence to suggest a correlation between the location of the KIT mutations and mastocytosis outcome. Sotlar *et al.*⁶¹ failed to correlate the presence of D816V KIT mutations with clinical outcomes in 20 patients with childhood-onset mastocytosis after a mean follow-up of 11.2 years. In their large study, which was included in our review, Lanternier *et al.*⁷ did not find any link between the presence of the D816V KIT mutation and paediatric-onset indolent systemic mastocytosis, whereas

this combination was statistically significant in the group with adult-onset mastocytosis.

Conclusions

This extensive review of paediatric mastocytosis demonstrates that although more than two-thirds of cases resolve completely or partially after a median follow-up of 6 years, the remainder continue to present with progressive or stabilized disease. In many of the studies the patients had not yet reached adulthood. The clinical presentations, follow-up methods and mastocytosis activation symptom evaluations described are heterogeneous. Studies involving more patients and a longer follow-up time (up to 20 years) are rare and would be highly relevant. Standardized clinical criteria and recommendations for the follow-up of children with mastocytosis are also required. For the purposes of this review, we used the validated World Health Organization classification for cutaneous mastocytosis, but the new classification, which distinguishes between the plaque type and the maculopapular type,¹⁰³ appears to be more appropriate for further studies and requires validation.

Furthermore, biopsies obtained at adulthood could be used to determine whether mast cell infiltration continues to be present in old cutaneous lesions, or whether it is absent in patients with regressive disease. Complete KIT sequencing should also be performed in order to confirm these retrospective data and to delineate childhood-onset mastocytosis and the disease outcome. It may be useful to correlate outcome with KIT mutations to determine whether some types of mutations are linked with a better or worse prognosis. Indeed, it is possible that the heterogeneity of the disease is linked to the different KIT mutations observed in children and adults. Further investigations should focus on this aspect in children in order to understand the pathophysiology of the disease and define appropriate follow-up and treatment methods.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Report of clinical features collected in 26 series, 1184 patients.

Table S2. KIT mutations.

Supplementary Table 1: Report of clinical features collected in 26 series, 1184 patients

Author	Year	Childrennumber	Patients with clinical features	Darier'ssign	Dermographism	Itching	Bullous	Flush	Digestivsymptoms	Headache	Bone pain	Anaphylaxia	Hypotension	ADP	HSM	Dyspnea
Caplan	1963	84	84	74/84	15/33	54/76	39/84	4/84	na	na	na	na	na	na	na	na
Absoe-Hansen	1964	10	10	10	na	na	na	na	0	na	0	na	na	na	1	na
Coles	1965	14	14	6/8	1	na	na	na	na	na	1	na	na	na	5	na
Brett	1967	11	11	na	na	na	7	2	1	na	3/5	na	na	na	na	1
Vaillaud	1968	4	4	4	2	2	1	0	na	na	0	na	na	na	na	na
Czarnetzki	1981	28	28	na	na	3	na	2	2	na	na	na	na	na	na	na
Kettelhut	1989	8	8	na	na	8	3	6	5	1	na	na	na	0	na	na
Akiyama	1990	14	14	12	na	3	1	0	na	na	na	na	1	na	na	na
Tay	1993	7	7	7	na	7	2	0	0	na	na	0	0	0	0	0
Azana	1994	67	67	62	13	42	17	11	na	na	0	na	na	na	13	na
Loubeyres	1999	49	49	43	na	11	10	na	na	na	na	na	na	na	na	na
Middelkamp	2000	65	65	na	na	30	na	19	17	7	na	na	0	na	na	na
Hannaford	2001	173	173	na	6	5	49	50	na	na	na	0	5	2	3	na
Kanwar	2004	17	17	na	4	17	3	0	0	na	na	na	na	0	0	na
Kiszewski	2004	71	46	43/46	na	29	na	na	9	na	na	na	na	7	11	na
Ben Amitai	2005	180	180	na	na	na	48	19	3	na	na	na	na	na	na	12
Kiszewski	2007	35	16	na	na	8	5	na	2	na	na	na	na	na	3	na
Singalavanija	2008	50	50	50	na	na	8	4	0	0	na	0	0	na	na	0
Lanternier	2008	28	28	na	na	na	na	19	15 (diarrhea)	na	15	7	15	1	9	na
Ahmad	2006	6	6	na	na	na	na	2	2	na	na	na	1	na	na	na
Heide	2009	8	8	4	4	2	5	3	na	na	na	na	na	na	2	na
Uzzaman*	2009	17	17	na	na	15	9	11	7	2	3	na	na	0	0	na
Alvarez-Twose	2012	111	111	na	na	88	61	51	42	na	na	na	4	na	na	na
Lange	2012	4	4	4	na	4	4	2	0	0	na	0	4	0	0	na
Lange	2013	101	100	100	na	68	25	29	22	18	na	6	16	5	10	na
Barnes	2014	67	67	47	na	31	31	23	32	5	7	1	na	na	na	9
Total : 26		1229	1184	466/516 90.3%	45/316 14.2%	417/869 48.0%	328/951 34.5%	257/1049 24.5%	159/815 19.5%	33/311 10.6%	29/212 13.7%	14/256 5.5%	46/558 8.24%	15/417 3.60%	57/559 10.20%	22/315 7.0%

Abbreviations: na: not available *same cohort than the study of Kettelhut 1999

SupplementaryTable 2: *KIT* mutations

Publication (First author)	Year	Children (n=388)	<i>KIT</i> mutation (n=211)	Tissuanalysed	Results
Shah	1998	1	1	Bonemarrow	D816V
Buttner	1998	11	11	Skin	WT*
Sato	1999	2	2	Skin and bone	WT (n=2)*
Kuint	1999	1	1	Blood	D816V
Chott	2003	1	1	Sarcoma	WT**
Sotlar	2003	38	37	Skin	D816V (n=10) D816X (n=6) WT (n=21)
Akin	2004	1	1	Bonemarrow/ blood	P522C
Yanighori	2005	14	14	Skin	D816V (n=7) D816P (n=5) WT (n=2)***
Verzjil	2005	13	13	Skin	D816V (n=2) WT (n=11)**
Lee	2007	1	1	Ovarian tumor/Blood/Bone marrow	D816V
Lanternier	2008	28	26	Skin	D816V (n=11) WT (n=12)**** Del419 (n=2) K509L (n=1)
Foster	2008	10	10	Skin and blood	WT (n=4)**** M541L (n=4) L862L (n=2)
Hoffman	2008	1	1	Skin	Del419Asp
Heide	2009	8	3	Skin	D816V (n=1) WT (n=2)**
Uzzaman	2009	17	3	Bonemarrow	D816V (n=1) WT (n=2)**
Bodemer	2010	65	50	Skin	D816V (n=18) D816Y (n=2) D816I (n=1) Del 419 (n=8) InsFF419 (n=1) Del 417-419InsY (n=1) C443Y (n=1) Exon 9 : S476I (n=1); ITD 501-502, 502-503, 505-508 (n=5) ; K509I (n=5) D572A (n=1) WT (n=7)
Mital	2011	1	1	Bonemarrow	Dup502-503

Alvarez-Twose	2012	111	19	Skin	D816V (n=3) WT (n=16)**
Georgin-Lavalle	2012	1	1	Bonemarrow	WT****
Bautista-Quach	2012	1	1	Sarcoma	WT*****
Ryan	2012	2	2	Sarcoma	WT (n=1)***** Del419 (n=1)
Synakiewicz	2012	1	1	Bone marrow	WT (n=1)*****
Kim	2013	1	1	Sarcoma	L799F (n=1)
Lange	2012/2013	105	2	Bonemarrow	WT (n=2)**
Dequin	2014	9	9	Skin	WT (n=3)***** Exon 9 : Dup 502-503 (n=3) Exon 17 : D816V (n=3)
Total : 25		445/1664 (26.7%)	202/1664 (12.1%)		D816V: 61/202 (30.98%) Other mutation exon 17: 10/202 (4,95%) Exon 8 (Del 419 and Del 417-419InsY): 11/202 (5.45%) Exon 9 (F522C, 501-502, 502-503, 505-508, K509L): 17/202 (6.93%) Exon 10 (M541L) : 18/202 (8.91%) Exon 11 (D572A) : 1/202 (0.50%) Exon 18 (L852L): 2/202 (1.00%) WT: 99/202 (47.52%): WT exon 17: 55/202 (27.23%) WT exon 11 and 17 :13/202 (6.44%) WT exon 8 and 17 :1/202 (0.50%) WT 11, 17 and 18 :2/202 (1.00%) WT complete sequencing :29/202 (12.38%)

Abbreviations: na: not available, WT: wild type. ** Wild type exons 11 and 17 **Wild type exons 17, ***WT exons 11, 17, 18, ***** all exons sequenced, *****WT exons 8 and 17.

Table S1. Report of clinical features collected in 26 series, 1184 patients.

Report of clinical features including dermatological feature and systemic signs of mast cell activation collected in all the series (n=26), in percentage.

Table S2. *KIT* mutations.

Details on *KIT* mutation (number of children concerned, type of mutation found, type of tissue analysed) found in the 25 articles.