

Clinical course of granuloma annulare.

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Summary

In order to investigate the duration of granuloma annulare (GA) and its responsible factors, we reviewed the clinical records of 190 cases of GA (118 females and 72 males, whose age ranged between 1 and 14 years at the moment of the first examination) seen in the Unit of Pediatric Dermatology of Bari University between 1975 and 2004. All these patients were invited to answer a questionnaire and some of them were reexamined. According to the clinical records and the responses to the questionnaire, the following parameters were investigated: sex, age at the moment of the first consultation, triggering factors and associated disorders, clinical variants of GA, site of the lesions and family history. We confirmed in our pediatric cases the increased frequency of GA in females (118/190), the more frequent involvement of the dorsal aspect of the foot (66/180 cases) and the more frequent association with insulin dependent diabetes in the localized variant of GA (3/180 cases of insulin dependent diabetes). Moreover, we put in evidence a peak at 3 years in the age of onset of pediatric GA. With regard to the duration of GA and its responsible factors, we established that the average duration of GA in our pediatric population is one year and half. However, we also put in evidence a minority of cases with a longer duration -even more than 20 years-. The latter cases are characterized by a more significant prevalence of females, later age of onset, more widespread lesions and, finally, more frequent autoimmune disorders in the family history.

Key words

Granuloma annulare, clinical course, autoimmunity.

Granuloma annulare (GA) is a chronic relapsing disorder (38) clinically characterized by granulomatous lesions with centrifugal spreading and histologically by focal degeneration of the collagen, which is surrounded by a reactive inflammatory infiltrate. The latter mainly consists of histiocytes with palisade arrangement.

The causal factors of the disease have not been yet clarified. However, its clinical features and pathological findings are quite characteristic and allow to easily recognize GA. From a clinical point of view different variants of GA are

known such as localized GA (3, 4, 5, 6) with single or multiple lesions, generalized GA (10, 24), subcutaneous GA (7, 12, 15, 16, 22), perforating GA (1, 13, 19) and linear GA (29).

A few reports (49) face the problem of the duration of the disease. Due to this reason and given the increased frequency of GA in children and adolescents (37), we reviewed 190 cases examined in the Clinic of Pediatric Dermatology of Bari University, with the aim of studying the clinical and epidemiological features of the disease, particularly its duration and the related factors.



Fig. 1

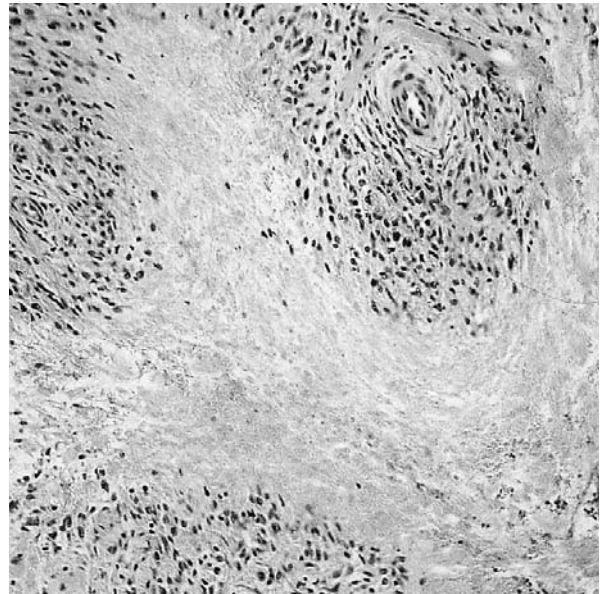


Fig. 2

Fig. 1, 2, 3, 4: Localized granuloma annulare in its more typical localization on the dorsal aspect of the feet (Fig. 1). Fig. 2 (EE 100x) shows the typical pathological findings of focal degeneration of the collagen, surrounded by palisade histiocytic infiltrate. Localized granuloma annulare of the index (Fig. 3) and generalized granuloma annulare (Fig. 4).



Fig. 3



Fig. 4

Patients and methods

In this study the clinical records of 190 patients (118 females and 72 males, aged 1 to 14 years at the moment of the first examination) were reviewed. The patients, who had been examined in the Clinic of Pediatric Dermatology of Bari University between 1975 and 2004, were asked to fill in a questionnaire and some of them were reexamined. According to the clinical records and the responses to the questionnaire, we investigated sex, age at the moment of the first visit, triggering factors and associated disorders, clinical variants of GA, site of the lesions and family history.

Results

68/190 patients returned the questionnaire sent by letter. 7 of them were reexamined. The

data put in evidence by the clinical records and by the questionnaires were as follows:

Sex. 118 females and 72 males.

The age at the first visit is visible in table 1.

Clinical variants. Among 178 evaluable cases there were 170 cases of superficial GA (37 with single lesions, 118 with multiple lesions and 15 with generalized GA) and 8 cases of subcutaneous GA. 4 of the latter cases were associated to superficial lesions.

Site of the lesions. Among 180 cases the lower limbs were affected in 115 cases, particularly the feet in 66, the hands in 57 cases, the trunk in 9 cases and, finally, the head in 4 cases.

Triggering factors. Only 5 patients reported the onset of GA after particular events, namely tonsillitis with bronchitis and otitis, gastroenteritis, pyoderma, bullous pyoderma, jellyfish sting.

Personal pathological history. The latter was positive for associated disorders in 112 cases. Frequent -more than 3 a year- episodes of tonsil-

Table 1: Age of patients with granuloma annulare at the first visit.

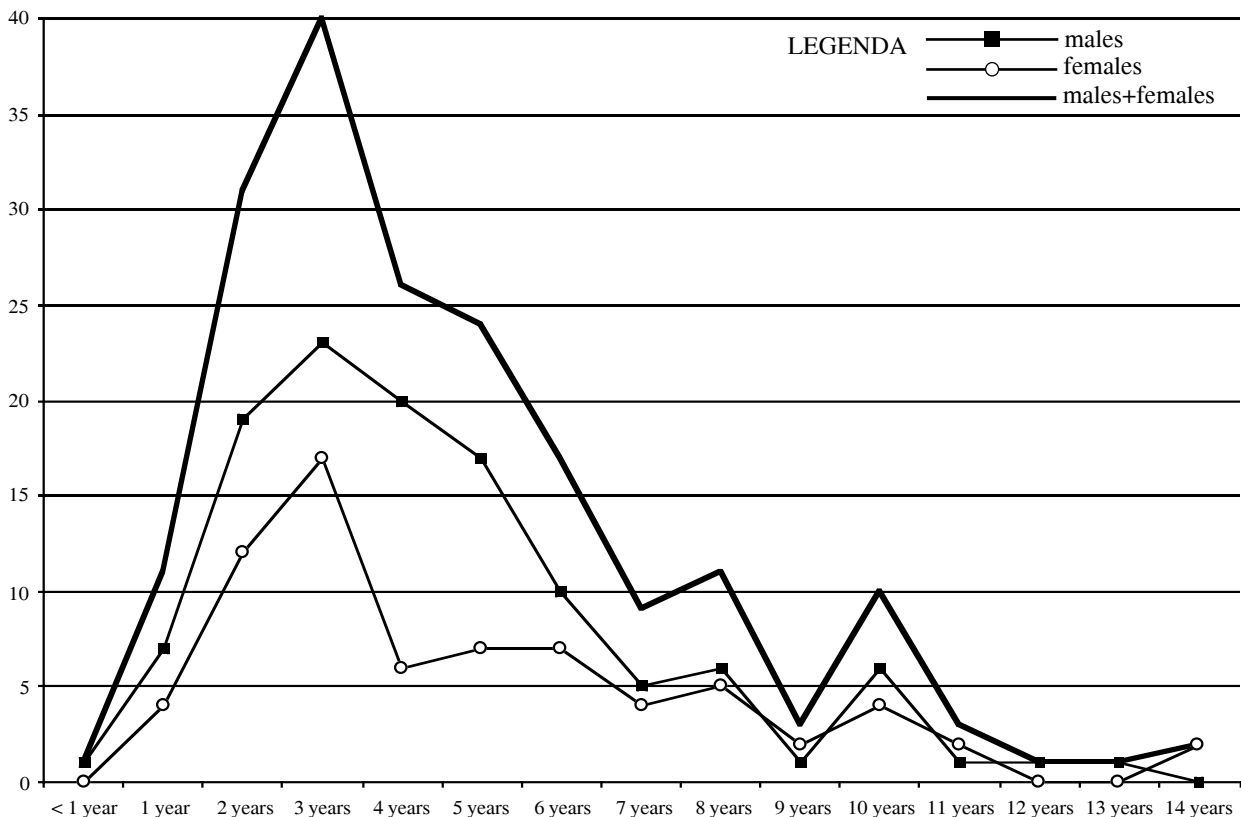


Table 2: Duration of granuloma annulare in 68 patients followed up longer than 10 years.

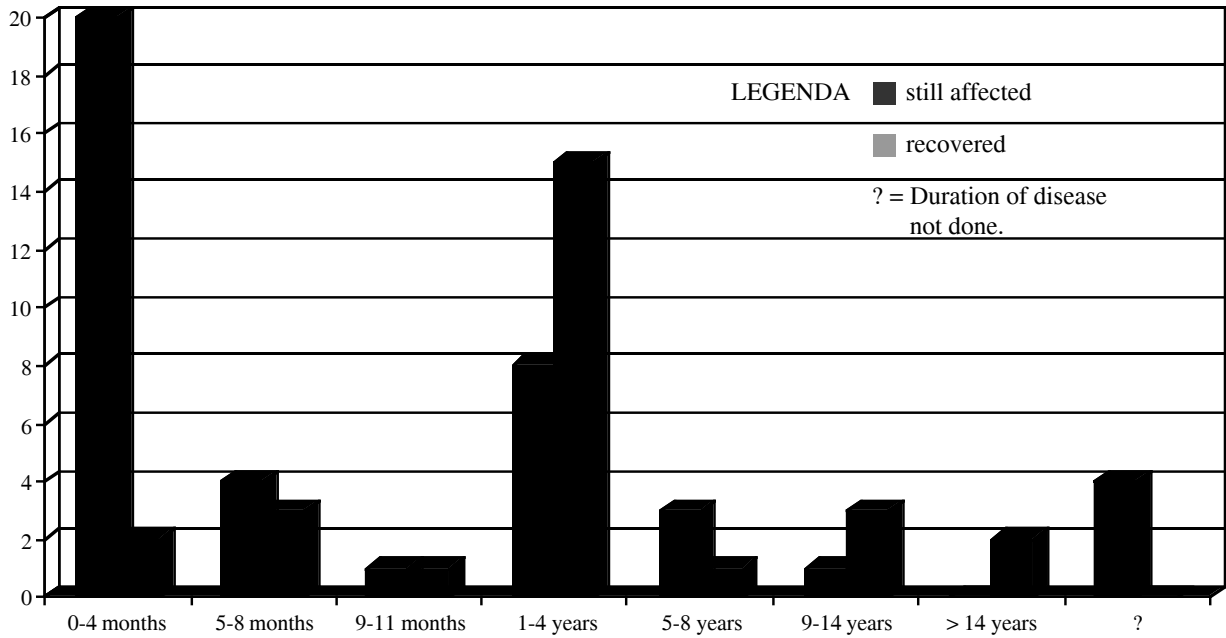
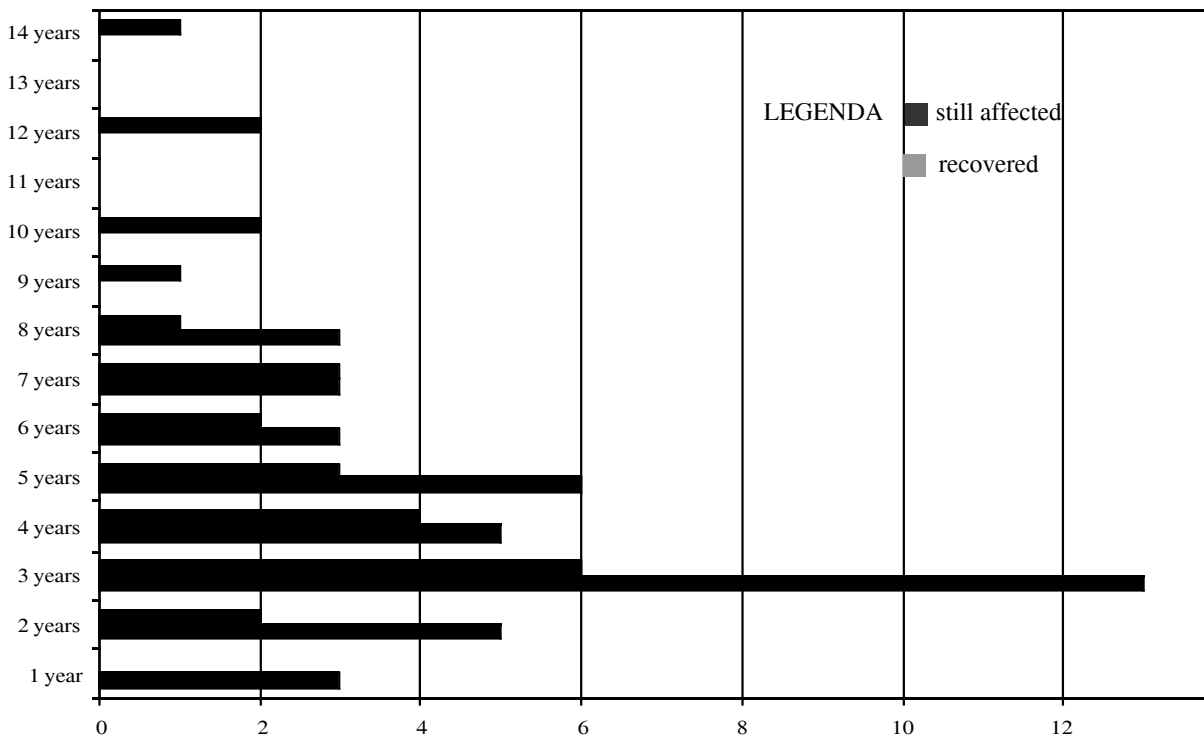


Table 3: Healing of granuloma annulare according to the age at the moment of the diagnosis.



litis (in 22 cases), pharyngitis (in 10 cases) and atopic disorders -asthma in 7 cases and dermatitis in other 7 cases- were the most frequent disorders associated to GA. Autoimmune disorders were put in evidence in 5 cases, particularly insulin dependent diabetes mellitus in 3 cases and psoriasis in 2 cases.

Pathological family history. The most frequent disorders in the family history were atopic disorders (24 cases), tiroiditis (19 cases), diabetes (12 cases) and alopecia areata (6 cases). In only one case GA was diagnosed in one family member.

Duration of the disease. Out of the 68 patients questioned after many years -7 of whom reexamined due to doubtful responses- 41 recovered -18 within 1-4 months, 4 within 5-8 months, 1 within 10 months, 8 within 1-4 years, 3 within 5-8 years and 1 within 10 years-. In 4 healed patients the time of healing could not be established. Among the 27 still affected patients GA lasted for 9-14 years in 3 cases, for 19 years in 1 case and for 22 years in another case (Table 2).

Comment

The low percentage of patients who responded to the questionnaire was due to the long time passed in most cases from the first visit and consequent change of address of many patients. Due to this fact, 74 letters returned to the sender without response. Strangely enough, several families did not remember that their relative had suffered from GA and yet denied that they had ever been in the Clinic of Pediatric Dermatology. This probably means that our reassuring words about the benignity of the disease and its lack of relationship with other disorders (2, 9, 14, 17, 18, 20, 27, 32, 41, 45, 46, 47, 48, 51) had had the desired effect. With regard to the sex, females prevail also in our cases (34).

There are not in the literature significant data (34) regarding the age of the first visit in pediatric cases. Our study puts in evidence the highest prevalence between the 2nd and 6th year (138/190 cases with a peak -40 cases- at the age of 3 both in females and males). After this peak the frequency of GA decreases, more rapidly in

males (Table 1). One family reported the onset at birth of the disease. Superficial localized GA with single (31) or multiple (44) lesions was more frequently (118/178 cases) seen, whereas we did not see cases of perforating or linear GA. We observed 15 cases of generalized GA (44).

The latter variant, in contrast with the localized one is characterized by a more difficult diagnosis and, moreover, seems more frequently associated to other disorders, particularly diabetes. Its diagnosis is particularly difficult at the onset when no one lesion has yet acquired the characteristic annular shape. With regard to the comprehensively debated relationship of GA with diabetes, some reports deny the latter, whereas most of them (25, 26, 28, 30, 33, 38, 42) confirm this association, mainly in the generalized variant of GA (25, 26). We found in our 190 cases of GA 3 cases of insulin dependent diabetes, therefore at a slightly lesser extent as compared with the largest study on this topic (35), that found 16 cases of insulin dependent diabetes among 590 cases of GA. However, the latter study includes even adult cases of GA. Interestingly, the 3 cases of insulin dependent diabetes in our series of patients occurred in patients affected by localized GA, confirming the data of other Authors (8, 35, 49).

The lower limbs, particularly the feet, were more frequently affected also in our cases of localized GA. The dorsal aspect of the feet (Fig. 1) is really the most frequent affected site of localized GA.

With regard to the disorders associated to granuloma annulare in our cases we put in evidence infectious and allergic disorders with a frequency superimposable to that of a normal population of the same age. Only in five cases the time relationship between these events and the onset of granuloma annulare was more close.

The relationship between GA and autoimmune disorders was particularly investigated both in the personal and family history. In the personal history we put in evidence three cases of diabetes mellitus and two cases of psoriasis, whereas in the family history we unveiled only one case of GA, 19 cases of autoimmune thyroiditis (23), 12 cases of diabetes and 6 cases of alopecia areata.

Table 4: Clinical data in 12 cases of granuloma annulare (GA) lasting more than 4 years.

	SEX	AGE OF ONSET (years)	TYPE OF GA	PERSONAL HISTORY	FAMILY HISTORY	DURATION (years)
CASE 17	F	12	generalized		thyroiditis	> 14
CASE 29	F	4	localized (feet, hands)	tonsillectomy		> 19
CASE 34	F	5	localized (foot thigh, ankle)			> 4
CASE 72	M	5	localized (feet, hands)		thyroiditis	> 4
CASE 99	M	2	localized (hand)		thyroiditis	> 8
CASE 104	F	2	localized (feet, hands)		thyroiditis	> 5
CASE 105	F	2	localized (thighs, legs)			> 4
CASE 111	F	8	localized (thighs, legs, foot)		rheumatoid arthritis	4
CASE 129	F	8	localized (hand, thighs, ankle, foot)		alopecia areata	> 8
CASE 147	M	11	localized (hand, heel)			> 13
CASE 167	F	5	generalized			10
CASE 176	F	4	localized (hands, elbows, thighs)	psoriasis	psoriasis	6

Particular attention was paid to the clinical data regarding the duration of the disease. Often physicians after the diagnosis of GA tell the parents that they are facing a benign disorder, self-healing within months or years. We recently observed a case of GA still persisting after 22 years and thus decided to investigate the real duration of the disorder and to search for the factors that are predictive of long duration. We established in 41 healed patients the average duration of the disease. The latter in our cases is one year and half, when non considering the 3 patients recovered in less than two months and the patient recovered in 14 years, but with a follow up of less than 10 years. However, taking into account the still affected patients, we saw that 6/180 cases, namely about 3% of cases, last more than five years, with a case still affected

after 22 years. In these persistent cases the clinical course of granuloma annulare is continuous with subintra relapses for a period of 1-2 years. Later on, the relapses are less frequent and occasional.

Searching for the factors responsible for the duration of the disease, we considered sex, age of onset, extension of the lesions, personal pathological history and family history. With regard to the age of onset of the disease, in the 68 patients who responded to the questionnaire, we saw (table 3) that 21/29 -72%- cases arisen in the first three years recovered, 20/33 -61%-cases arisen between 4 and 8 years recovered, whereas no one of the six cases arisen between 9 and 14 years regressed in an average period of follow up of 5 years. Taking out of our patients 12 cases lasting four years or more (table 4),

three of whom respectively healed after 4, 6 and 12 years and nine of whom still affected with lesions lasting for an average period of 9 years (from 4 to 22), we noticed an even greater prevalence of females -sex ratio 9/3-, a greater extension of lesions -localized GA in a single site in 1 case, multiple localized GA in 9 cases and generalized GA in 2 cases- and a greater prevalence of autoimmune disorders in the family history -7/12 cases, whereas their prevalence in the whole population was 14%- . Finally, a later onset -6 years on average- of the disease was confirmed in the long lasting cases.

In conclusion, in our pediatric cases of GA we confirmed the prevalence of GA in females, the more frequent involvement of the dorsal aspect of the foot and the higher prevalence of insulin dependent diabetes in the localized variant of GA. Moreover, we first showed in the age of onset of GA a peak at the age of 3 in the pediatric cases. With regard to the duration of GA and its responsible factors, we established

that the average duration of GA in our pediatric population is one year and half. However, we also put in evidence a minority of long-lasting cases, even for more than 20 years. This minority of cases is characterized by an even more significant prevalence of females, a later age of onset of the disease, a greater extension of the lesions and, finally, a more frequent family history of autoimmune disorders.

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