Review

Familial aggregation in giant cell arteritis and polymyalgia rheumatica: a comprehensive literature review including 4 new families

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ABSTRACT

Objective. *To review personal and published observations of giant cell (temporal) arteritis (GCA) or polymyalgia rheumatica (PMR) with familial or conjugal aggregation and emphasise on epidemiological, clinical and genetic features of such cases.*

Methods. *We pooled data obtained from all cases of GCA or PMR with familial aggregation recruited in the department since 1976 and those from reports of familial or conjugal GCA or PMR published in the French-English literature since 1970.*

Results. *During the study period, we diagnosed 460 patients (128 with isolated PMR, 227 with isolated GCA, 105 with PMR/CGA). No conjugal couples were observed in the whole series. No familial cases were identified among PMR patients, whereas the prevalence of familial GCA was 1 in 83 (1 in 250 to 500 expected by chance), as we identified 4 patients (brother-brother, sister with history of affected sister, and daughter with priory affected mother). An additional pair of sisters with TA, recruited several months after diagnosis, is also presented. Pooling data from 85 patients (74 with GCA) including our patients, representing 32 families and 8 conjugal pairs, enabled us to draw the following observations: 1) partial or full agreement in the clinical picture (GCA, PMR, or GCA/PMR) was observed in 96% of the siblings pairs, suggesting a common pathogenic mechanism; 2) five kindred were described in whom at least three members were affected; 3) the lag between manifested diseases in familial or conjugal pairs averaged 5.7 years, with synchronous or close disease occurrence in only 26% of the pairs; 4) 18 of 32 assessed patients (56%) carried the DR4 antigen.*

Conclusion. *Our survey on familial aggregation of GCA and PMR accumulated data pointing to a genetic predisposition. However, environmental contagious factors could have trigger synchronous disease onset in up to one-fourth of the cases.*

Introduction

Giant cell arteritis (GCA) is a fascinating illness, from an epidemiological point of view (1, 2). Indeed, there is seemingly a paradox between the late onset of the disease (at age 70-75 on average) and the well demonstrated implication of genetic factors (1-6).

The concept of an environmental aetiology of GCA relies both on experimental immunological data (2) and observations of a seasonal disease pattern in Olmsted county, Minnesota (United States) and Israel (6-9) but not in Northwestern Spain (10), or apparent fluctuations in a cyclic pattern (7-9), sometimes linked with epidemics (11). An association between infection and the onset of the temporal arteritis syndrome has also been suggested in a case control study (12). Finally, a multicenter, prospective case-control study demonstrated that re-infection with human parainfluenza type 1 virus is associated with the onset of biopsy-proven GCA (6). However, despite accumulating indices pointing toward an infectious aetiology, direct evidence of active viral or bacterial infection in temporal artery biopsies in patients with GCA is lacking (13-22). Likewise, a study showed no association between altitude and the incidence of GCA in a defined population (23).

Conversely, the genetic epidemiology of GCA is supported by solid facts. The disease appears more common in individuals with Nordic descent (24). Certain histo-compatibility HLA antigens, most notably HLA-DR4, are significantly more prevalent in GCA patients than in controls (25-28). There is also growing evidence that GCA is governed by multiple genes encoding host defence molecules (29). Genetic factors seem to be implicated not only in the susceptibility, but also in the severity and outcome of GCA (30, 31). Finally, large kindred with multiple affected members and/or sibling sharing the whole HLA phenotype have been described (32-39). However, such reports are scarce and often incomplete or have mixed indistinctly cases of GCA, biopsy-proven or not, and PMR, although these entities share distinct patterns of HLA class II association (40), as well as other potentially involved genetic polymorphisms (41). Little is known, therefore, on incidence and prevalence of familial/conjugal aggregation of GCA and PMR as separate entities.

Herein we present our personal experience on familial aggregation of GCA and isolated PMR, with pooling of our cases with all published familial and conjugal cases. This study was conducted with the aim of reinforcing knowledge on this rare presentation of GCA/ PMR and discussing findings from an etiological viewpoint.

Patients and methods

Characteristics of the series and data collection

We included in the study all consecutive cases of GCA or isolated PMR diagnosed during the past 31 years in the internal medicine department of a university hospital that cares for the Limousin, a region situated in the centre of France which comprises a population of 720,000 inhabitants. As our department is likely to recruit no more than one-third of total regional incident GCA cases and only a small proportion of total regional PMR incident cases, observed prevalence data of familial GCA and PMR cannot be extrapolated for the general population. Ninety-four percent of the patients were recruited before steroid treatment, the remaining cases being already treated for up to one month at the time of admission. Regarding GCA patients, only cases fulfilling at least three of the American College of Rheumatology criteria (42) were included in the study. The diagnosis of GCA was pathologically established according to usual criteria (43, 44). Pre-treatment clinical, laboratory and pathological data were recorded prospectively at the time of diagnosis by a senior internist using in each patient a specifically designed, comprehensive, questionnaire that includes a precise history and 174 items. Patients were treated according to the same protocol using prednisone at a dosage depending on the presence or absence of ischaemic symptoms or threat to vision (45). PMR was diagnosed using Bird's criteria (46) or Chuang's criteria (47), regardless of associated GCA. When isolated, PMR was ascertained if no other conditions mimicking this entity were diagnosed either initially and in the follow-up (48, 49). Recovery from GCA or PMR was defined as no clinical or laboratory relapses for at least 9 months after the cessation of treatment.

In two families, the affected sibling or parent had been followed elsewhere. Since full information on GCA features at onset, TAB results, and outcome could be obtained from each patient's attending internist, both case histories were pooled with those of our patients. However, we excluded these patients from calculations on incidence of familial GCA /PMR.

Genetic studies

Immunogenetic studies were not performed routinely in our patients with GCA or PMR but were carried out in GCA patients with familial aggregation, all of whom were recruited after 1991, when molecular typing of HLA-DR and DQB became available at our hospital. Typing was performed by polymerase chain reaction amplification using sequence-specific primers.

Literature survey and data analysis

We retrieved from French and English language all case reports of familial or conjugal GCA or PMR published since 1970 using a Medline search. Only well described, unquestionable, cases of GCA or PMR were included in the study. Patient clinical, pathological and epidemiological characteristics and immunogenetic studies were extracted from each case report and pooled with data obtained from our cases. We assessed the degree of agreement existing in the clinical picture within a familial or conjugal pair. Isolated GCA or PMR in both cases was quoted "full agreement", GCA+PMR in one case and GCA or PMR in the other one was quoted "partial agreement", and isolated GCA in one case with isolated PMR in the other case was quoted "no agreement". In kindred with more than 2 affected members, patients were compared two abreast.

Results

Personal observations – frequency of familial aggregation in PMR and GCA

No familial cases were observed among 128 patients diagnosed with pure PMR. Of 332 patients diagnosed with GCA (257 biopsy-proven, 105 with associated PMR) recruited during the same period, 4 familial cases (one pair of non-twin siblings, a woman with affected sister, and a woman with a history of affected mother) were found, representing thus 1 in 83 patients. An additional pair of sisters with GCA is presented apart since these patients were recruited 6 months following diagnosis and do not belong, therefore, to the inception cohort. Table I depicts the clinical, laboratory and genetic features, and outcome of these 6 patients and affected relatives. During the 31-year study period, no conjugal pairs were recruited among the 460 patients.

In three kindred, no other sibling, first degree family members, spouses, ore close friends had recognised GCA or PMR. In the second family, Bo Y. recalled a history of biopsy-proven GCA in her sister-in-law (born in 1922) and husband (born in 1921). We had later confirmation that, in this married couple unrelated by blood, GCA developed within one year of each other, in 1995 and 1996, respectively. In the fourth family, De D., the half-sister of Ri L., also

Table I. Personal observations of familial clustering of giant cell arteritis: summarized features.

Patient	Age	Interval between onset	Clinical picture	TAB result	Treatment duration (mo)	Relapses (n)
Family 1						
brother (Au. R.)	62	11 yr	cranial arteritis	pos	14	no
brother (Au. E.)	67		cranial arteritis + PMR	pos	42	yes (1)
Family 2						
sister (Ve. M.)	56	14 yr	cranial arteritis + PMR, then ULAV	pos	60	yes (2)
sister (Bo. Y.)	67		cranial arteritis + PMR	neg§	70+	yes (3)
Family 3						
mother (Du. E.)	75	23 yr	masked TA	pos	30	no
daughter (Vi. H.)	76		cranial arteritis with PVL	pos	17	no
Family 4						
sister (Ri. L.)	75	20 mo	cranial arteritis	pos	10+	no
sister (De. E.)	76		cranial arteritis	pos	30+	yes

§Concurrently associated with chronic myelomonocytic leukemia, which did not evolve into overt leukemia.
TAB: temporal artery biopsy; TA: temporal arteritis; PMR: polymyalgia rheumatica; ULAV: upper limb artery involvement; PVL: permanent visual loss.

had GCA, whereas her brother and 2 sisters had remained unaffected. Within all familial pairs, the patients had lived separately since adulthood. HLA typing yielded A1.29; B44.53; DRB1*0401.*07; DQB1*02.*03, and A1.-; B51(5).8; DRB1*O3.*11, DQB1*02.*03, respectively, in the only kindred (half-sisters) for which it was available.

Pooled personal cases and literature survey – familial cases

We found 19 published reports of GCA or PMR with familial aggregation (32-39, 50-61). Four authors presented more than one affected family (37, 38, 51, 52). Including our personal reports, 70 patients representing 32 kindred were thus reviewed. Individual case histories involved 40 GCA, 24 overlap GCA/ PMR, and 6 isolated PMR. Polymyalgia symptoms were thus present in 43% of the cases. There was full or partial agreement in the clinical picture in 96% of familial pairs. Forty-three out of 54 assessed GCA patients (80%) exhibited a positive TAB result. The mean patient age at GCA onset was 70.3 years (54-80 years) and 74.3% were female. The disease onset lag within a familial pair averaged 6.3 years in 31 assessable pairs, but did not exceed 5 months in 22.6% of these.

Fifty-eight siblings including 43 women were reported in 26 unrelated families (32-39, 50-58). The patient's age ranged from 54 to 80 years (mean 70.3 years). The disease onset lag within a sibling pair averaged 51 months (0-168 months) in 25 assessable pairs and was less than 5 months in 6 pairs (38, 50, 51, 56, 57). Polymyalgia symptoms were recorded in 43.3% of the patients. There was full agreement in the clinical picture in 18 sibling pairs, partial agreement in 10, and no agreement in one (58). Five kindred with multiple affected siblings were reported (33-35, 38, 39) including one large kindred with 4 affected and 5 unaffected siblings (33). Six unrelated parent/sibling pairs were reported (52, 59-61), with full agreement in the clinical picture in 3 pairs and partial agreement in 3. HLA typing was performed in 34 siblings including 14 sibling pairs. Seven pairs (50%) shared the whole HLA phenotype or at least the same class II antigens, as shown in Table II. HLA-DR_4 (or DRB1*04) was found in 18 of 32 assessed patients (56.3%).

Table II. Sibling pairs with giant cell arteritis or polymyalgia rheumatica and identical HLA (or at least the whole class II) typing.

Author (ref)	Relationship (age at onset, yrs.)	Interval between onset	Features of GCA	HLA typing
Kemp (32)	Sister (75)	5 yrs	TA (TAB pos)	A9,w26;B12,27;Cw3,w5
	Sister (72)		TA (TAB pos)	A9,w26;B12,27;Cw3,w5
Kvernebo (33)	Sister (71)	1 yrs	TA (TAB pos) + PMR	A1,3;B8,27;Cw4
	Brother (78)		TA (TAB neg)	A1,3;B8,12;Cw4
Petit (34)	Brother (64)	3 yrs	TA (TAB ?)	A2, B8, DR4
	First cousin (73)		PMR, then TA (TAB ?)	A2, B8, DR4
Ninet (35)	Brother (65)	13 yrs	TA (TAB neg) + PMR	A28, CW3, B15, DR4
	Sister (74)		TA (TAB pos)	A28, Cw3, B15, DR4
	Sister (74)		TA (TAB pos) + PMR	A28, Cw3, B15, DR4
Wernick (36)	Sister (72)	4 yrs	TA (TAB pos)	A1,64;B8,62;DR3,4 (DRB1 O401)
	Brother (66)		TA (TAB pos)	A1,64;B8,62;DR3,4 (DRB1 O401)
Schwizer (37)	Sister (73)		TA (TAB pos)	A3,28;B55,60;Cw3; DR4,13;DQ1,3
	Sister (73)		TA (TAB neg) + PMR	A3,28;B55,60;Cw3; DR4,13;DQ1,3
Fietta (38)	Sister (79)	4 mo.	TA (TAB pos) + PMR	A24,26;B38,55;DRB*11,*14;DQB1*05,*07;DRB3
	Sister (75)		TA (TAB pos) + PMR	A24,26;B38,55;DRB*11,*14;DQB1*05,*07;DRB3

Table III. Characteristics of 8 conjugal couples with GCA.

Author (ref)	Relationship	Age at onset, yrs	Interval between onset	Features of GCA
Kvernebo (33)	husband	68	6.5 yr	TA (TAB pos)
	wife	69		TA (TAB neg) + PMR
Nielsen (62)	husband	76	1 mo.	PMR
	wife	78		TA (TAB pos) + PMR
Hickstein (63)	husband	78	8 yr	TA (TAB pos) + PMR
	wife	74		TA (TAB neg) + PMR
Kyle (64)	husband	69	2 yr	PMR
	wife	69		TA (TAB neg) + PMR
Garfinkel (65)	husband	78	8 mo.	TA (TAB pos)
	wife	76		PMR
Barrier (66)	husband	78	2.6 yr	TA (TAB pos)
	wife	78		TA (TAB pos)
Galetta (67)	husband	79	simultaneous	TA (TAB pos)
	wife	74		TA (TAB pos)
Faerk (68)	husband	71	simultaneous	PMR
	wife	69		PMR

TA: temporal arteritis; PMR: polymyalgia rheumatica; TAB: temporal artery biopsy.

Conjugal cases

Conjugal aggregation of TA or PMR was reported in 8 pairs without blood relations (33, 62-68), as depicted in Table III. Patient's mean age was 74 years. The disease set up synchronously, or within one year, in 4 married pairs. Four couples had GCA (biopsy-proven in 2) with or without PMR. Full agreement in the clinical picture was seen in 5 couples. Two of 4 assessed conjugal pairs shared some common HLA antigens.

Discussion

We report four new families with GCA of first-degree relatives. We excluded from this study another sister-brother pair, although a familial GCA clustering was strongly suspected in these siblings, who shared the whole class II HLA phenotype (DRB1*15.*07; DQB1*0602.*0202). In fact, both developed unexplained constitutional syndrome with raised acute phase reactants and had a satisfactory outcome under steroid treatment, but the temporal artery biopsy failed to demonstrate GCA in the sister. One patient included in the study had negative temporal artery biopsy and a chronic myelomonocytic leukaemia, raising therefore concerns for the diagnosis of GCA. However, this patient presented with a constellation of features highly suggesting a temporal arteritis/polymyalgia rheumatica overlap, both at onset and during relapses, making the diagnosis of GCA with concurrent malignancy very likely (69).

Evidence against a fortuitous origin of familial GCA

In our study, the observed prevalence of familial clustering of GCA was one in 83 cases (1.2%). This is a minimal estimate, owing notably to the exclusion of a questionable sibling pair, the retrospective study design and the lack of specific genealogy item in our GCA questionnaire. Moreover, it is difficult to trace cases of GCA in the same family as the disease, on the whole, develops late, 70 to 75 years of age. Little is known in the literature on the frequency of occurrence of familial aggregation in GCA. Kemp *et al*. observed 1 familial pair among 50 patients with GCA or PMR (32). Liang *et al*., pooling their own observations with other reported cases, published or not, put forward a similar picture (52). Assuming the prevalence of GCA is unlikely to exceed 50 per 100,000 subjects aged 50 years and older in France, as reported in Germany (70), the likelihood that a patient with GCA will have an affected first-degree relative is 1 in 500. While this estimate has many statistical flaws, it is strikingly different from the figure we calculated in our unselected series of patients. Nevertheless, more precise epidemiological studies are warranted before ascertaining that the familial aggregation of GCA we and others observed is not coincidental. Regarding isolated PMR, the observed prevalence of familial clustering was zero in our inception cohort. Owing to the scarcity of reported cases, contrasting sharply with an observed prevalence of one case in 133 people over age 50 in certain Caucasian populations (71), a chance association is plausible.

Our comprehensive survey provided other indirect clues to a non fortuitous origin of familial GCA. First, 16% of reported kindred were multiplex families (33-35, 38, 39). Furthermore, while there are apparently no clinical values distinguishing the familial and non familial forms of GCA and PMR, strikingly, a full or partial clinical concordance within a familial pair was recorded in nearly 100% of the cases. This finding supports the hypothesis of a common determinism in familial clustering of GCA, although we cannot exclude publication biases.

Evidence for genetic factors

As a whole, while many case reports describing familial GCA are available, conclusive data showing a genetic inheritance pattern are still lacking. Nevertheless, the intervention of genetic, rather than environmental, factors is suggested by the fact that the mean interval separating disease onset in sibling pairs averaged 4 years, exceeding 1 year in 16 out of 25 cases. Such a delay precludes reasonably a contagious origin. Surprisingly, GCA in parent and sibling has been reported far less frequently than GCA in sibling pairs (52, 59-61). This might be related, in part, to the disease predilection for elderly subjects, who often show lack of awareness toward, or are not consulted about, their parents' medical history.

The predisposing role of genetic factors is also suggested by the association of GCA with the HLA-DR4 class II serological antigen (or DRB1*04).

Most studies have shown an association of TA with HLA-DRB1*04 alleles (25-28). As regards isolated PMR, however, the HLA class II genetic susceptibility varies from one population to another (21, 34, 35). The interpretation of HLA data in familial GCA in the literature is problematic because of the limited number and heterogeneity of the patients studied. However, it may be relevant that 50% of assessed siblings pairs shared the whole HLA phenotype, or at least the whole class II typing (32-37, 52) and that HLA-DR_4 was found in 56% of familial cases.

The study of large kindred comprising at least two affected members would best substantiate a genetic determinism in familial clustering of GCA, by demonstrating an HLA phenotype that distinguish affected from healthy siblings. In this regard, two exceptional families have been published (33, 35). In the first family, 4 out of 9 siblings developed TA (33). HLA typing, performed in 7 siblings, did not demonstrate differences between affected and healthy ones. In the second family, 3 out of 11 siblings developed TA (35). HLA typing was performed in 9 siblings and yielded A28 CW3 B15 DR4 in 4, including all 3 affected patients, while entirely different phenotypes were found in the 5 latter siblings.

Evidence for environmental factors

Our survey emphasises the relatively frequent simultaneous or close occurrence of GCA or PMR in familial or conjugal pairs (38, 50-52, 56, 57, 62, 67, 68), up to 25% of the cases, but points to the rarity of conjugal involvement. In fact, only 8 married couples with GCA have been reported so far (33, 62-68). However, not all observations of conjugal GCA are published, even in cases of biopsy-proven TA, as exemplified by one of our family histories. Nevertheless, the apparent lack of disease in close associated unrelated by blood is the strongest evidence against a contagious aetiology of GCA. While the simultaneous occurrence of biopsy-proven GCA in a married couple should be viewed as the most striking proof of GCA being a contagious disease, this condition has been reported only once (67).

Ambiguous reports

Some observations appear equivocal, as regards the mechanisms underlying familial clustering of GCA. Kvernebo's report of clustering of 5 cases in close physical contact within one family within a restricted time period, suggests a genetic predisposition to environmental influences (33). Likewise, in some reports of GCA in parent and sibling, the sibling's age at onset of disease decreased by 18 to 20 years, as compared to their affected relative (52, 60) so that simultaneous or close disease occurrence was observed twice (52).

To summarise, from our personal experience and critical survey, familial clustering of GCA, but not PMR, is unlikely to occur randomly. A genetic predisposition is strongly suggested, but reports of conjugal aggregation of both conditions, and the occurrence of the disease within a narrowed time period in nearly one-fourth of the cases, point to an additional role of environmental factors, probably infectious. These findings are consistent with the current concept of GCA as a multi-factorial disease, caused by the complex interaction of age, degenerative vascular disease (72, 73), genetic predisposition, and environmental influences.

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