Blau Syndrome and Related Genetic Disorders Causing Childhood Arthritis

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Blau Syndrome (BS) is an inheritable disorder characterized by granulomatous polyarthritis, panuveitis, and exanthema. It was described by Edward Blau in 1985, the same year in which Douglas Jabs reported a very similar family. Clinically indistinguishable from early onset sarcoidosis (EOS), both are now known to share a mutated form of caspase recruitment domain-15 (CARD 15), a protein involved in activation of nuclear factor kappa B which is in turn an up-regulator of pro-inflammatory cytokine transcription. An association between BS and EOS was suspected for years given the striking similarities of the core triad (arthritis-uveitis-dermatitis) and a common emerging pattern of systemic involvement. Hence, the familial form (BS) and the sporadic form (EOS) are almost certainly the same illness/defect, inherited in the first and acquired in the second as a result in most cases of a de novo mutation. Another form of granulomatous arthritis with uveitis, Crohn's disease, has also been associated with mutations in CARD 15 (albeit at a different domain) and despite similar phenotypes there are obvious differences including gut inflammation and pyoderma gangrenosum in Crohn's disease. This paper will review the clinical characteristics of these three disorders and their association with mutations in the CARD 15 gene.

Introduction

Granuloma formation, the histopathologic hallmark of a number of infectious and non-infectious inflammatory diseases still awaits full elucidation. It is clear, that granuloma formation requires an orderly process of recruitment of inflammatory cells. Most infectious processes associated with granuloma involve intracellular micro-organisms, require T-cell presence for their orchestration, and up-regulation of tumor necrosis factor (TNF) and interferon-γ (IFN-γ) [1]. The best-studied infections associated with granulomas are caused by *Mycobacteria*, *Brucella*, *Lysteria*, and fungi [2]. A special group with particular interest to pediatricians in which granulomatous inflammation is seen are the immune-deficiencies of which the best known to present this complication is common variable immune-deficiency [3]. Histologically those lesions appear adjacent to mucosal surfaces and within lymphatic nodes. The other classic example is chronic granulomatous disease where cutaneous and visceral granulomata are a distinct clinical finding. One is tempted to speculate that unusual or non-virulent micro-organisms are responsible for this complication. Among the idiopathic inflammatory conditions there are some in which vasculitis is required such as Wegener's granulomatosis and Churg-Strauss syndrome and in others while vasculitis is not required still can be observed [4]. The latter group includes sarcoidosis and Crohn's Disease.

A necrotic (caseating) center, surrounded by macrophages and an outer layer of mononuclear cells are characteristic of *Mycobacterium tuberculosis* infection. Giant cells are multinucleated, result from cell membrane fusion of three to 12 macrophages (foreign-body type-Langham cell), and are a characteristic histologic finding. If their nuclei are lined up resembling epithelium they are called epitheloid cells. Central necrosis is not seen in sarcoidosis (non-caseating granuloma).

Finding of granulomata in synovial tissue is unusual and can be seen in association with some of the aforementioned infections, foreign body synovitis and sarcoid arthritis (both the adult and early onset sarcoidosis [EOS]) (Fig. 1). This paper will focus on entities that not only share the presence of granulomatous inflammation in their target organ (including synovium) but also mutations in the encoding region of a central mediator of both apoptosis and inflammation known as caspase recruitment domain 15 (CARD 15). Additionally, it is worth remarking that Blau Syndrome (BS) and EOS belong to the select group of rheumatic diseases for which a specific mutation has been described. Interestingly these two are the most "rheumatic" of all, suggesting a particular arthritogenic effect of this mutation and a relevant pathway to be investigated by those interested in elucidating the mechanism of chronic inflammatory arthritis.

Clinically the arthritis of BS and EOS is similar to the polyarticular form of juvenile rheumatoid arthritis, with which they are often confused, although the striking presence of non-caseating granulomata in the synovial tissue of BS and EOS suggest a basic different mechanism.

Blau Syndrome: History and Clinical Aspects

In 1985, two independent reports emerged describing two separate families with autosomal dominant granulomatous

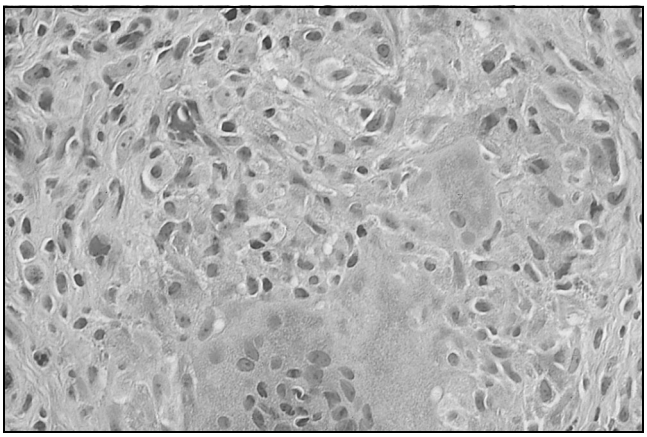

Figure 1. Synovial biopsy specimen depicting non-caseating giant cell granuloma.

arthritis. Douglas Jabs described a three-generation family with four affected members. Clinical manifestations included non-caseating granulomatous synovitis, uveitis, and cranial neuropathies including sensory hearing loss and transient sixth nerve palsy [5•]. Pertinent negative findings included lack of antinuclear antibodies, rheumatoid factor, and skin rash. That same year, Edward Blau reported a four-generation family with 11 affected members. Clinical manifestations included non-caseating granulomatous synovitis and tenosynovitis, granulomatous uveitis (macroscopic slit-lamp finding denoting clumpy precipitates), and papulosquamous skin rash with associated dermal non-caseating granulomas [6••]. Pertinent negative findings included lack of fever, chest radiograph abnormalities, and antinuclear antibodies. When a third family, involving a mother and two daughters, was reported in 1990 with the same triad, reported by Blau, of polyarthritis, iritis, and granulomatous papulosquamous rash, "Blau Syndrome" was confirmed as a distinct clinical entity [7].

Specific clinical features of Blau syndrome set it apart from other forms of granulomatous diseases and chronic childhood arthritis. The disease is autosomal dominant in nature, with an observed element of "anticipation", or worsening of symptoms in succeeding generations [8]. Arthritis is unremitting and polyarticular with associated synovial and tenosynovial "cysts", described as such because the exuberance of the swelling of affected joints and tendons (Figure 2A). Multidigit contracture of the interphalangeal joints, or campylodactyly, is reported. Camptodactyly is not seen congenitally, suggesting an inflammatory process leading to this deformity. Uveitis could be anterior, posterior, or panuveitis, and can be granulomatous or non-granumlomatous. It tends to be severe and associated with a myriad of complications including glaucoma, vitritis, retinal detachment and cataracts with consequent decrease in visual acuity. The characteristic biomicroscopic aspect of precipitates in a "clumpy", rather than diffuse distribution is known as granulomatous uveitis, which should not be confused with the histologic granuloma which in turn can be found in conjunctival biopsy. Hence, the uveitis of BS is macroscopically and histologically granulomatous. The skin rash is described as papulo-erythematous, and typically presents early in the course of disease [8]. It is usually observed in trunk and extremities and is mildly scaly and may become tan colored. Characteristically, it waxes and wanes and tends to fade away after 1 to 2 years (Figure 2B).

It was involvement of the "classic triad" of joints, skin, and eyes in Blau syndrome that set it apart from other reported familial granulomatous diseases, including the family reported by Jabs [5•] with cranial nerve involvement and an earlier family, reported by Rotenstein *et al.* [9], who had the classic triad with additional involvement of granulomatous vasculitis with fever and hypertension. Later, two reports of the serendipitous finding of visceral granulomata imposed doubts to the narrow definition of BS. In 1996, liver granulomata in the proband of a family with four affected members were found [10] and in 1998, renal interstitial granulomata were described in the mother of the proband in an affected family of three [11]. The phenotypically restricted form of BS (synovitis-uveitis-dermatitis) gave way to the idea of an expanded phenotype and BS is now viewed by most as a systemic disease.

Early Onset "Sarcoid" Arthritis

Clinically indistinguishable from Blau Syndrome, except for lacking the autosomal dominant transmission, EOS was recognized in the 1960s but the first detailed description is owed to North *et al.* [12]. The name stemmed from the non-caseating granulomas found on dermal, synovial, and conjunctival histology. The disease is manifested by granulomatous boggy polyarthritis and tenosynovitis, uveitis, and rash. Extension of the disease to involve large vessel vasculitis (granulomatous?) has also been reported [13–15] as well as granulomatous infiltration of the heart, lung, kidney, and liver [16] in terminal stages of the disease.

There has been much debate in the literature about the relationship between sarcoidosis and EOS. In contrast to the adult form of sarcoidosis, EOS is seen typically in children younger than 5 years of age, with a paucity of constitutional symptoms, namely fever, lymphadenopathy, malaise, and fatigue. There is an obvious lack of hilar adenopathy but pulmonary infiltrates has been seen in both. The chronic arthritis of sarcoidosis is rare and tends to affect the lower extremities in an oligoarticular pattern and the ankles are almost always affected [17]. In contrast with adult sarcoidosis, the polyarthritis of EOS is progressive and relentless, resulting in severe joint deformities, despite treatment. Uveitis can be anterior, posterior, or both and is usually a significant source of morbidity, with long-term visual impairment. A summary of all clinical manifestations is presented in table form in comparison with those of sarcoidosis (adult form) as it presents in pediatrics (Table 1).

The clinical similarities of EOS and Blau syndrome have been noted for decades, yet the autosomal dominant transmission of Blau syndrome kept the two diseases considered as separate entities. This idea was challenged in

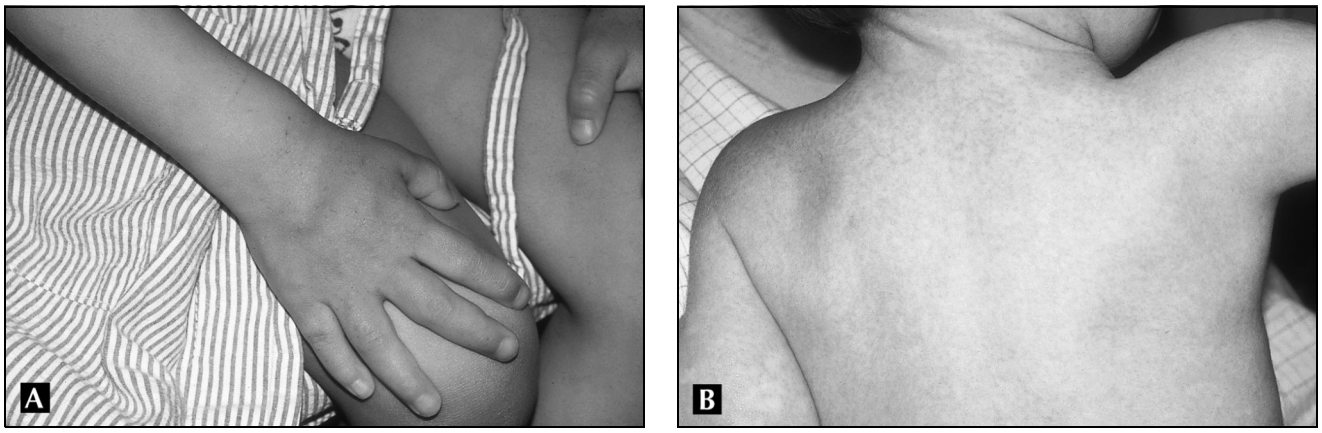

Figure 2. A, Exuberant synovial and tenosynovial "cysts" in Blau Syndrome. **B,** Papuloerythematous skin rash of Blau Syndrome.

Table 1. Adult and early onset forms of sarcoidosis in children

	Adult sarcoidosis in children	Early onset sarcoidsis and Blau syndrome
Onset	8 to 15 years	Below 5 years
Race and gender	Primarily black and Japanese	Equal gender and race
Geographic distribution	Worlwide. In the United States 80% is in the southeast	Worldwide
Systemic symptoms	Systemic involvement of fever, hilar lymphadenopathy, hepatosplenomegaly, malaise, fatigue	Paucity of systemic symptoms at onset. Later dissemination is seen in EOS and in systemic familial granulomatosis.
Arthritis	Less common ~ 30%, either acute with Löfgren's or chronic	Polyarticular boggy synovitis and tenosynovitis
Rash	Erythema nodosum, lupus pernio, vasculitis	Scaly ichthyosiform maculopapular orange/tan rash. Erythema nodosum also seen
Eye disease	Acute uveitis, pseudotumor, optic neuritis	Granulomatous panuveitis
Vasculitis	Palpable purpura (granulomatous) of small vessels. Large pulmonary arteries by encroaching pulmonary granulomas.	Large vessel vasculitis (Takayasu-like). Described in EOS and in BS with involvement in EOS of aortic arch, renal and abdominal aorta.
Lung	Interstitial lung disease early	Interstitial lung disease with cardiac and CNS dissemination as a terminal event
Nervous system	Aseptic meningitis, myelitis, VII nerve palsy	IV and VI cranial nerve palsies.
Bone	Osteitis, myositis	Not described yet
Kidney	Tubulo-interstitial nephritis	Interstitial nephritis
Prognosis	Main morbidity—pulmonary fibrosis	Main morbidity—joint deformity and visual impairment

BS—Blau Syndrome; CNS—central nervous system; EOS—early onset sarcoidosis.

1986 when it was suggested that both diseases should be included within a spectrum of granulomatous diseases, rather than two distinct entities distinguished by phenotype. They could then be characterized as an inherited and sporadic form of the same disease process, a concept later supported by Blau [18,19]. With the documentation of granulomata in viscera beyond the classic triad of joints, skin, and eyes in Blau syndrome families, this claim became more plausible as we suggested in 1996 [10].

Arthritis Associated with Crohn's Disease

Crohn's disease (CD) is rarely described in the context of granulomatous disorders, since only 40% to 60% of involved intestinal samples and very few dermal and synovial samples have shown granulomas. It remains to be established if CD is one entity or a group of conditions of which one subset is truly granulomatous.

Clinicians interested in pediatric rheumatic disorders, commonly make a diagnosis of CD in children who present with oligoarthritis with or without sacroiliitis. Some of the suggesting findings for CD in addition to arthritis include: uveitis, stomatitis, nodular panniculitis (similar to erythema nodosum), small and medium size vessel vasculitis and pyoderma gangrenosum. Although those extraintestinal manifestations are highly suggestive of CD more commonly it will be an oligoarthritis associated with poor weight and height gain, microcytic anemia, disproportionate elevation of the

sedimentation rate, family history of inflammatory bowel disease, or perianal findings (particularly skin tags), that will put the rheumatologist on the right diagnostic track. A tagged white cell scan or an upper gastrointestinal series with follow-through will confirm the diagnosis unless there is associated diarrhea prompting an endoscopic diagnostic procedure.

There are two forms of musculoskeletal involvement in CD. The most commonly seen is a peripheral small and large joint arthritis with intermittent involvement parallel or not with disease activity in the gastrointestinal track. The other clinical pattern is Crohn's spondylitis with unilateral or bilateral sacroiliac disease and variable association with the HLA-B27 antigen. In fact, this association prompted an interesting line of work leading to a model in which clinical or subclinical disease of the gastrointestinal tract may be the source of joint inflammation for all spondyloarthropathies. The spondyloarthropathy-like findings of the B27 transgenic rat and mouse models once the gut becomes populated with bacteria in the non-sterile environment lent strong support to the gut-joint theory. Further, new developments in imaging techniques in particular MRI, revolutionized the idea of enthesitis and added osteitis as an important component of the skeletal manifestations of the enteropathic spondyloarthropaties. Reviews on the clinical manifestations of CD arthritis are abundant in the literature [20–22].

CARD15

Genetic advancements over the past 10 years have begun to answer some of the questions posed by clinical observations. In the mid 1990s, a susceptibility locus was mapped on the original Blau kindred to chromosome 16 positioned at 16p12-21 [23••]. In 2001, a mutation in the CARD15, also termed nucleotide oligomerization domain protein 2 (NOD2), was found to increase the risk for CD. This locus fell within the susceptibility region mapped by Tromp *et al.* [23••] for BS, and since CD is a granulomatous disease, Miceli-Richard *et al.* [24••] tested this "candidate gene" in four French families with Blau syndrome. Three distinct mutations within the nucleotide-binding domain (NBD) of CARD15, were found and proven different from the ones found for CD which are located in the leucin rich repeat (LRR) domain of the same protein [25,26].

The CARD15 gene encodes a 1040 amino acid protein comprised of two CARDS, a neuronal apoptosis inhibitory protein (NACHT) domain or NBD, and a LRR. The CARD domain structure is found in many proteins that are associated with apoptosis. The NACHT domain is likely to be involved in homodimerization of CARD15 and in binding nucleotides. It is known to function as an ATPase and is found in proteins involved in apoptosis and in transcriptional activation of the major histocompatibility genes. The LRR region is structurally related to the LRR regions of the toll-like receptors, which are molecules of the innate immune system which sense molecular motifs specific to pathogens, such as lipopolysaccharide. The role of CARD15 in inflammatory disease suggests that CARD15 may serve as an intracellular "sensor" of bacteria, and it participates in an inflammatory signaling cascade involving the activation of nuclear factor kappa-B. A comprehensive review of this protein is beyond the scope of this paper, but further information is available [27].

The mutations discovered by Miceli-Richard *et al.* [24••] in the four Blau syndrome families are within the NBD region of CARD15. This is in contrast to the CD mutations which have been found at or near the LRR region of CARD15 [26]. The three Blau substitutions include an arginine to glutamine at position 334 (Arg334Gln), arginine to tryptophan at position 334 (Arg334Trp), and leucine to phenylalanine at position 469 (Leu469Phe) [24••]. Later work by Wang *et al.* [28] further supported this finding by confirming a CARD15 mutation in five of 10 Blau pedigrees tested. In our experience, of four additional Blau families tested, all affected members carry a CARD15 mutation [29].

Interestingly, in the original report by Miceli-Richard *et al.* [24••], two patients with EOS, with granulomatous involvement of the kidney and/or alveolitis of the lung in addition to skin, joint and /or eye involvement, were tested and found not to carry the CARD15 mutation. This initially suggested that the mutation involved in BS families was not the same as the gene for EOS. This was not supported by further work. Within the past year, two separate reports of the CARD15 mutation in patients with EOS surfaced [30•,31•]. Investigators from Kyoto University and our own group confirmed the presence of the amino acid substitution at position 334 in the two patients tested with EOS. Both patients had polyarthritis, severe uveitis, and rash. Between the two patients, granulomas were found in the synovium, dermis, and lung. Both patients were the sole phenotypically affected member of their families. Analysis of genomic DNA revealed heterozygosity for the mutation of CARD15 at position 334 in both patients. All four parents were tested and were found to be homozygous for the wild type allele at this position, supporting a de novo mutation of CARD15 [30•,31•]. Furthermore, the investigators from Kyoto tested 10 more patients with documented EOS and found a CARD15 mutation in nine of them [32]. These findings lend strong support to the contention first raised by Miller [18] that BS and EOS are the same disease and part of a spectrum of granulomatous arthritides in children.

In addition, further work with adult sarcoidosis did not support a gene defect of CARD15 in patients with this disease. Rybicki *et al.* [33] tested 35 black sibling pairs who had clinically confirmed sarcoidosis, for linkage between the 16p12-q21 interval and sarcoidosis. No evidence for linkage between the Blau syndrome locus and sarcoidosis was found. More recently, Schurmann *et al.* [34] tested 138 families for the known CARD15 polymorphisms associated with CD, as well as 47 patients in multi-case families for the Blau

syndrome gene segment. No Blau mutations or new sequence alterations were found. This further supports the distinction between adult sarcoidosis and EOS.

Arthritic Manifestations of (Adult) Sarcoidosis

Arthritis is not a common manifestation of sarcoidosis. Large series reports around 5% frequency of true arthritis and 10% of articular symptoms among adults with sarcoidosis [35,36]. Clinicians have recognized two patterns of joint involvement. The most common is an acute (mainly ankle) arthritis, associated with acute uveitis, erythema nodosum, and hilar adenopathy also known as Loefgren syndrome [37]. Patients are systemically ill with fever and weight loss. The frequency of granulomatous inflammation in synovium has not been studied. We do not know if this particular subset shows association with mutations in CARD 15 although we do know that such mutation is not present in sarcoidosis in general [33,34].

Very rarely patients with sarcoidosis present with chronic arthritis similar to rheumatoid arthritis in its erosive potential albeit oligoarticular and predominantly affecting the knees. The granulomatous character of the synovitis is unclear. In an early report by Sokoloff and Bunim [38] the disease was described as granulomatous with typical non-caseating granulomas. Palmer and Schumacher [17] more recently performed a systematic investigation with needle biopsy on seven patients with sarcoidosis and arthritis and failed to show granuloma formation in the synovial samples [17].

Pathogenic Considerations and Conclusion

We have described the clinical features of three possibly related rheumatic disorders, EOS, BS, and CD. We also described the arthritis associated with sarcoidosis, the most prevalent of the non-infectious idiopathic granulomatous disorders.

Early onset sarcoidosis and BS on one hand are polyarticular, symmetrical and highly proliferative, paucierosive symmetrical arthritis with uveitis. The arthritis is unusually resistant to treatment and so is the uveitis. Both present with variable degree of visceral involvement (hepatic and renal) and at a terminal stage show granulomatous dissemination involving myocardium and pulmonary parenchyma but not hilar lymphatic nodes [16]. Large vessel (granulomatous?) vasculitis has been seen in both [9,13–15]. In all, these two conditions can be considered the same disease with a mutated variant of CARD 15 more prevalent in EOS (90%) than in BS (50%). It is to be expected that given the clinical similarities the mutation negative BS patients will eventually show an up or downstream mutation leading to a similar pathogenic process.

It is unclear, but worth studying, the systemic form of BS and EOS in which malignant hypertension, severe systemic features, and vasculitis was associated with the classic BS "core" symptoms of arthritis uveitis and dermatitis originally described by Rotenstein *et al*. [9] in a unique pedigree and by others in several sporadic single report cases.

Unlike EOS and BS arthritis, CD arthritis tends to be oligoarticular, easy to control, affects all ages, and can be associated with sacroiliitis. We know very little about the histology of the synovium in CD. The actual frequency of granuloma in CD synovium may be underestimated since very few histologic studies are available. There are at least two reports of synovial granulomata in CD synovium with one case where the histologic findings in the joint led the investigations to confirm the diagnosis of CD by colonoscopy [39,40]. Intestinal biopsies show non-granulomatous inflammation most of the time with granulomata at onset in about 25% of patients. Two recent studies specifically addressed this issue in light of the association between granulomatous disease and CARD15 mutation. Investigators from Belgium reviewed 161 patient's specimens and found epitheloid granulomas in 68.9% of the specimens with higher incidence in younger patients and distal location (90% of rectal biopsies) [41]. The presence of mutations in CARD15 was not more frequent among the patients with intestinal granuloma. A French group from Rennes reviewed 188 consecutive CD cases. Granulomas were found in 37% of the specimens with 25% at presentation. In this group of patients site was not important but the number of specimens correlated directly with the frequency of granuloma [42]. The relationship between CARD 15 mutation and development of arthritis in CD has not been specifically addressed yet.

Management

There have been no control studies for patients with granulomatous arthritis. Anecdotal experience has shown poor response to nonsteroidal anti-inflammatory drugs for the rheumatic symptoms. These authors have reported excellent response to infliximab (5–10 mg/kg every 4–8 weeks) particularly in the sporadic form, however there is almost always some degree of synovitis particularly in the ankles and wrists [43]. The characteristic contractures of the proximal interphalangeal joints tends to be irreversible although there are relatively mild radiologic changes. The only consistently effective measure to reduce synovial hypertrophy is the use of oral corticosteroids, but of course the side effects of their prolonged use limit their utility. Methotrexate has been ineffective in the author's experience.

The sight-threatening pan-uveitis can be extremely severe and is usually managed with topical, sub-conjunctival, or systemic corticosteroids. We have seen worsening of the uveitis while on infliximab therapy although there is no experience with early intervention with TNF blockers for the uveitis. The author has seen some steroid sparing effect with cyclosporine A at usual doses (2–5 mg/kg/day).

A Final Note on Nomenclature

It is apparent that beyond the histologic similarities between sarcoidosis and the pediatric forms of "sarcoid" arthritis there is not much connection between these entities. Hence, and following the far-seeing advice of Miller [18], the term "sarcoidosis" should be removed from these forms of pediatric arhritides. It is also apparent that the differences between BS and EOS arthritis are probably nonexistent. Hence, these authors echoing Miller's suggestion subscribe to the idea of renaming these conditions pediatric granulomatous arthritis perhaps with the clarification of familial (for those with family history) and sporadic for those without. Even that latter distinction (familial vs sporadic) could be done away with since the mutation in the sporadic form generates new familial (Blau) pedigrees almost certainly since the disease does not abrogate reproductive potential in affected individuals

Conclusions

We believe that more work is needed in search for up or downstream mutations in BS since the frequency of the mutation is only 50% in the largest group of families published to date [28]. In our four families 100% of the affected members carried a mutation while it was absent in all the unaffected members [29]. The systemic forms and the vasculitic forms represent interesting subsets since it is likely that an additional modifying gene is present. Finally, the arthritic forms of sarcoidosis and CD need to be studied more carefully.

Currently an international effort is taking place called the International Pediatric Registry on Granulomatous Arthritis combining development of a clinical data base with genetic testing. With this effort we hope to address some of the most urgent questions and expand on pioneering collaborative research in the field [44].

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