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NOD2-Associated Pediatric Granulomatous Arthritis (PGA):

an Expanding Phenotype. A Study of an International Registry and a National Cohort

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Abstract

Objective—To study the phenotypic characteristics of the largest to date cohort of patients with Pediatric Granulomatous Arthritis (PGA) and documented NOD2 mutations.

Methods—Merged data from two prospective cohorts and systematic review of medical records of interest.

Results—Forty-five individuals with PGA (23 sporadic and 22 from familial pedigrees) and documented NOD2 mutations were identified and are the basis of this report. In this series, 18 patients have the R334W-encoding mutation, 18 the R334Q, four the E383K, three the R587C, one the C495Y and one the W490L. The majority of patients manifested the typical triad of dermatitis, uveitis and arthritis. Conversely, in 12 patients, the following “atypical” manifestations were found: fever, sialadenitis, lymphadenopathy, erythema nodosum, leukocytoclastic vasculitis, transient neuropathy, granulomatous glomerular and interstitial nephritis, interstitial lung disease, arterial hypertension, pericarditis, pulmonary embolism, hepatic granulomatous infiltration, splenic involvement and chronic renal failure. In addition, 4 individuals with an asymptomatic carrier status of a disease causing mutation were documented.

Conclusion—NOD2-associated PGA can be a multi-systemic disorder with significant visceral involvement. Treating physicians should be aware of the systemic nature of this condition since some of these manifestations may entail long-term morbidity.

Introduction

Pediatric Granulomatous Arthritis (PGA) encompasses two diseases with an identical phenotype, the autosomal dominant Blau Syndrome (BS) and Early Onset Sarcoidosis (EOS), a sporadic condition. The finding of identical mutations on exon 4 of the *NOD2* gene afforded strength to the notion that these diseases are actually the same (1-3). BS was described both as a triad of granulomatous “boggy” polyarthritis, uveitis and papulo-erythematous rash by Blau (4) and as a polyarthritis with uveitis, without rash but with cranial neuropathy by Jabs (5). EOS has been known since the 1970s and like BS is characterized by granulomatous boggy synovitis, uveitis and rash indistinguishable from BS albeit without family history (6). Before the discovery of *NOD2* mutations there have been sporadic reports of organ involvement beyond the typical triad for both BS and EOS (7-14), challenging the initial notion of a restricted phenotype (15). More recently as a result of our systematic analysis of the phenotype our group (16) and others (17) have been able to confirm most of the already described and some previously unknown clinical features among individuals with confirmed *NOD2* mutations (18,19). We present in this report an account of those clinical manifestations drawn from a population of 45 individuals resulting from the merger of the International PGA Registry and a Spanish cohort (16,17).

Subjects

Subjects with atypical manifestations were identified from the PGA International Registry and DNA repository in existence since 2005 and the Spanish cohort from the Systemic Auto-inflammatory Diseases Unit at Hospital Clinic (Barcelona, Spain) through a genetic testing referral system. Contributors who cared for patients of interest were asked to submit to the principal investigator (CDR) de-identified detailed narratives of patients' history to capture details not included in the database.

The inclusion criteria for the International Registry required the presence of granulomatous inflammation in tissue biopsy and either arthritis, uveitis or rash. The individuals from the Spanish cohort were selected from the genetic testing referral system database if they presented "Blau mutations" in the NOD2 gene.

Methods

Genomic DNA extraction

For the International PGA Registry, genomic DNA was obtained directly from collaborating sites or was extracted from blood samples (or in 1 case from a buccal swab sample). Blood samples were processed using standard salting out elution techniques. The buccal swab was processed using the G1N10 Gene Elute Mammalian Genomic DNA Miniprep Kit (SigmaAldrich, St. Louis, MO) according to the manufacturer's instructions with the addition of increased total lysing volume (360 ul) which included increased proteinase K volume (30ul) in order to completely cover the buccal swab, and with decreased elution volume (60 ul) to obtain more concentrated DNA. For the Spanish cohort, genomic DNA from whole blood samples was isolated using the QIAmp DNA Blood Mini Kit (QIAgen, Germany) according to the manufacturer's instructions.

NOD2 gene mutational analysis

All 12 exons and intronic flanking sequences of *NOD2* gene were amplified by polymerase chain reaction (PCR). PCR products were treated with ExoSAP-IT (USB Corp., Cleveland, OH; International Registry cohort) or purified using the QIAquick PCR Purification Kit (QIAgen, Germany; Spanish cohort). Bidirectional fluorescence sequencing was performed using an ABI BigDye Terminators v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) and run on an ABI 3100 automatic sequencer (Applied Biosystems, Foster City, CA). In addition to direct sequencing, denaturing high-performance liquid chromatography (WAVE instrument, Transgenomic Inc., Omaha, NE) was utilized to screen samples from the International Registry for polymorphisms in exons 1, 2, 8, 9, and 12.

Statistical analysis

For comparisons between wild-type NOD2 versus NOD2 mutated patients and between mutated individuals with and without expanded phenotype, non-parametric statistics (Mann-Whitney U test) and Chi-square or Fisher exact test were used as indicated.

Results

From their inception 128 individuals have been entered to the International Registry spanning all pediatric granulomatous diseases and 12 to the Spanish cohort. The combined number of 45 affected individuals (22 from familial pedigrees and 23 sporadic cases) with documented NOD2 mutation has been identified and is the basis of this report. In addition, 26 had a granulomatous inflammatory disease with wild-type NOD2. Finally four asymptomatic individuals with NOD2 mutation were documented. The remaining

individuals were either asymptomatic relatives of affected patients or the samples are pending.

NOD2 mutation positive individuals

In this series, the largest to date, 18 subjects carried the mutation encoding R334W, 18 the R334Q, four the E383K, three the R587C, one the C495Y and one the W490L (Table 1). There were 21 females and 24 males. Average age of onset was 30 (3-216) months and the age at recruitment ranged between 4-49 years for the International group and 4-48 years for the Spanish cohort. The large majority of patients (34 out of 45) exhibited the complete classical triad of rash, uveitis and arthritis originally described with the disease (4). We found one patient in the Spanish series and one in the International Registry without arthritis, two without rash, and 10 without documented uveitis at the time of inclusion. In all but two patients with a skin and synovial biopsy respectively, from the International Registry, epithelioid granulomas were documented on biopsy tissue. All four Spanish patients with a biopsy available showed granulomatous inflammation. None showed positive Antinuclear Antibodies or Rheumatoid Factor in serum.

Demographic and clinical manifestations considered part of the classical phenotype including polyarthritis, uveitis and icthyosiform rash are shown in Table 1. Twelve out 45 patients in this series (29%) presented at least one manifestation either at onset or during the course of the disease that can be considered atypical and will be detailed further. The age at disease onset was not different in patients with an expanded phenotype compared to patients with the classical triad only. The median (range) disease duration at inception in the expanded phenotype group was 227 (54-474) months while for the patients with the classic triad it was 99.5 (20-528) months ($p< 0.05$). Comparison of the relative frequencies of the various mutations between patients with and without expanded phenotype revealed a relative under-representation of R334W in the expanded group ($p<0.05$). The other mutations showed no differences. Similarly there were no differences of either age or gender distribution nor of the prevalence of the clinical components of the classical triad (arthritis-uveitis-dermatitis) between these two groups.

NOD2 mutation negative (wild-type) individuals

Twenty-six individuals presented with a granulomatous inflammatory disease and wild-type NOD2. Their median age at onset was 36 (0-132) months, their age at study entry was 11 (2-42) years. Age at onset and at study entry were not significantly different between patients with wild-type NOD2 compared to patients with NOD2 mutation. Arthritis, eye and skin inflammation were seen in 52%, 64% and 80% of wild-type NOD2 patients respectively, with only two individuals exhibiting the complete classical triad. The prevalence of arthritis was significantly higher in the group with NOD2 mutation ($p<0.0001$), but not the prevalence of uveitis nor cutaneous inflammation. The clinical features in this group was much more variable hence the percentage of patients with “expanded” manifestations was much larger than in the NOD2 mutated group which showed a more restricted phenotype, as expected (81% vs. 29%, $p<0.0001$). These manifestations comprised fever, hepatosplenomegaly, lymphadenopathy as well as lung, kidney, gastrointestinal, bone and CNS involvement. In addition, this group exhibited Mickulicz syndrome and a large variety of skin manifestations including erythema nodosum, lobular panniculitis and cutaneous vasculitis. Only two patients in this group presented the tan-coloured skin rash. Fever, hepatosplenomegaly, lung and CNS involvement were significantly more prevalent in the wild-type NOD2 group compared to the NOD2 mutated patients.

Expanded manifestations in subjects with NOD2 mutation

Fever

The presence of fever was not unusual and may have been underreported, since it tends to be mild to moderate. A total of 7 individuals experienced fever including one with prolonged fever at presentation while the others experienced fever in association with a disease flare. There were no cases of either periodic or hectic fever.

Panniculitis

Three patients showed subcutaneous nodules, all of them had also febrile episodes. A clinical diagnosis of erythema nodosum was made in all of them, although no histologic confirmation was attempted. In one patient (Table 1, #7) there was a single episode observed during a systemic disease flare whereas in the others it was recurrent.

Granulomatous lymphadenopathy

One patient (#7) presented with prominent cervical lymphadenopathy. Due to concerns of lymphoproliferative disease, a biopsy of a posterior auricular node was obtained. Multiple epithelioid granulomas were found on a background of an inflammatory infiltrate with histiocytes and mature lymphocytes. This case has been reported already (8,18).

Liver and Spleen involvement

The same individual (#7) underwent a liver biopsy in order to monitor for methotrexate toxicity. He was found to have multiple hepatic epithelioid granulomas with no evidence of parenchymal inflammation nor organ dysfunction after 12 years of follow up. Another subject (#5) developed liver enlargement; a biopsy obtained during elective abdominal surgery showed non-caseating granulomas.. Asymptomatic liver and spleen involvement (# 27 and # 40) manifested as hepatosplenomegaly was observed in two cases and in both considered an inconsequential physical finding. There was no liver nor splenic histology available in any of these two patients.

Salivary gland involvement

Intense granulomatous infiltration of the salivary gland was detected serendipitously with a posterior cervical lymph node biopsy of this child (#7). To this point he had not developed xerostomy nor lacrimal gland involvement.

Leukocytoclastic vasculitis

One patient (#27) developed recurrent nonspecific maculopapular and urticarial rash. Due to the persistence of single urticarial lesions, a biopsy was performed which revealed classical leukocytoclastic vasculitis with no hemorrhage and prominent nuclear dust. Episodes resolved after institution of anti-TNF therapy. This patient has been reported elsewhere (19).

Pneumonitis

One patient (# 6) presented acutely with fever and adenopathy. Chest CT revealed mild upper mediastinal but no hilar adenopathy. Unexpectedly several small areas of ground glass opacity were noted in the medial segment of the right middle lobe and bilateral lower lobes of the lung parenchyma. A repeat scan a few months later after intensification of corticosteroid therapy revealed resolution (18).

Granulomatous glomerulonephritis and interstitial nephritis

Patient #27 had a six-year history of classical BS when she developed leukocyturia, increased serum creatinine and mild (1g/24 hrs) proteinuria. A renal biopsy revealed epithelioid granulomas in 3/9 glomeruli and severe interstitial granulomatous inflammation. Renal function and urinary microscopy normalized after four infusions of Infliximab (19). Two additional subjects (#40 and # 43) have stable chronic renal insufficiency.

Arterial hypertension

Two young patients (# 9 and # 23) presented with asymptomatic arterial hypertension soon after diagnosis. In both, additional investigations demonstrated normal renal function and urinary microscopy and negative digital angiograms of the renal arteries. Both are currently on combination therapy including beta-blockers and angiotensin converting enzyme inhibitors.

Patient #40 was already hypertensive at the time of diagnosis at 22 months of age. Currently he suffers from chronic cardiomyopathy and chronic renal failure. One additional patient (#7) has recently developed high blood pressure and was started on ACE inhibitors like in his sibling (#9); work-up has been negative although angiogram was not performed.

Pericarditis

Two children (# 27and # 36) developed acute pericarditis suspected by chest radiograph in one and confirmed by echocardiography in both. In the two cases the episode was a single occurrence, associated with a febrile/systemic flare which subsided with medical management.

Cranial neuropathies

This subject (# 38) had an episode of transient (few weeks) unilateral facial palsy as well as an inflammatory optic neuropathy secondary to panuveitis.

Pulmonary embolism

One adult patient (#10) with a typical BS phenotype developed chest pain. An acute pulmonary embolism of the right pulmonary artery was demonstrated. Investigations to exclude a prothrombotic state or hypercoagulability disorder were negative. The patient, who had no previous risk factors other than contraceptive, continues after 1 year on anticoagulants with no recurrence.

Asymptomatic carrier state

Four members of a family carrying substitution E383K exhibited no symptoms or signs of disease (not shown in Table 1). Although three of them are still younger than 4 years, one is an adult male aged 40 years. Two mutation positive members of this pedigree exhibited the classical phenotype (polyarthritis, uveitis and rash). A more detailed report of this family is in preparation.

DISCUSSION

Our report is the first to provide a detailed description on the expanded phenotype of PGA, exclusively among patients with documented NOD2 mutations, hence endorsing the notion that PGA may constitute a systemic granulomatous inflammatory disorder.

In 1985, Jabs and Blau reported two separate multiplex families showing a similar clinical phenotype including early onset polyarticular “boggy” synovitis, severe pan-uveitis and an

autosomal dominant pattern of inheritance. The family reported by Blau also presented with a tan-colored maculopapular rash, absent in Jabs' report while the latter included cranial neuropathy (4,5). All patients characteristically showed non-caseating granulomas on tissue biopsy. The BS phenotype was also reported subsequently in a family by Pastores et al (15). The initial idea that this disease entailed a restricted phenotype was later challenged by the publications of 2 families: one with associated liver granulomatous involvement and another with renal granulomatous disease (7,8). Most authors currently accept cranial neuropathies, systemic involvement (fever) and arteritis as part of the disease spectrum. Hence the family reported by Jabs (5) and earlier families reported by Hafner (9) and by Rotenstein (10) could be considered to fall within the BS spectrum. The phenotype of the sporadic form of the disease, formerly known as early onset (childhood) sarcoidosis has itself been expanded to include large vessel vasculitis (11-13) and visceral involvement including granulomatous infiltration of the lungs, heart, liver and kidneys (14).

Cranial neuropathy had been identified in association with BS before genetic analysis was available (5). We were able to confirm this complication in our series in one instance with a patient that suffered from transient facial nerve palsy. The same patient presented an inflammatory optic neuropathy complicating severe panuveitis.

We observed leukocytoclastic vasculitis presenting phenotypically as urticarial vasculitis being part of the spectrum of PGA. Large vessel vasculopathy reported in mutation positive patients by Wang (20) and before by others (11-13) was not observed in this series.

This study expanded the cutaneous manifestations of the disease. The dermatitis described as a maculopapular rash with ichthyosiform desquamation and dermal granulomas was documented in 40/45 subjects, hence without a doubt it is a cardinal manifestation. This study confirmed that recurrent erythema nodosum-like panniculitis as well as cutaneous small vessel vasculitis are also part of the spectrum.

Lymphadenitis (excluding hilar adenitis) and interstitial pneumonitis have not been previously reported in PGA associated with NOD2 mutation. In addition, sialadenitis, hepatic and splenic involvements seem to be without clinical consequences at least in the short-term. Hence these manifestations may not require invasive diagnostic procedures when found as an isolated physical finding.

Pericarditis has not been reported in early disease before, in our series it was symptomatic in one and an echocardiographic finding in the other. Cardiomyopathy found in one patient could have be the result of chronic hypertension and not a bona-fide primary manifestation. Pulmonary embolism found in one instance should be regarded with caution since risk factors for pulmonary embolism can be elusive.

Renal disease has been described as interstitial nephritis in a population of patients with childhood sarcoidosis before genetic testing was available (21); here we show one documented case of acute glomerulonephritis with granulomatous involvement of glomeruli and interstitium. We observed two additional cases of chronic renal failure, however without histologic documentation of granulomatous kidney disease.

Hypertension was previously described in association with renal arteritis (10,12). Our findings confirm that systemic hypertension severe enough to require treatment is not uncommon even during the early phases (# 7, #9 and #23) of the disease and should be monitored closely. The mechanism is unclear since the two children who were investigated had normal digital imaging of the renal vasculature, normal renal function and urinary microscopy. Still, we cannot rule out silent granulomatous nephritis as the cause of the observed hypertension.

The expanded manifestations were noted both in sporadic and familial cases, and seemed to cluster in a subset of patients constituting more than one fourth of the cohort. This may suggest the presence of additional phenotype-influencing genes in NOD2-associated PGA as has been demonstrated for other auto-inflammatory diseases (22). In addition, the longer disease duration in patients with an expanded phenotype implies that the classic triad may evolve in a greater proportion of patients with longer follow-up and that additional features may emerge with time.

In our cohort we observed some patients that were diagnosed at a later age, hence genetic analysis of NOD2 mutations could be considered not only among children but also in adults with a suspicious phenotype.

A comparison of clinical manifestations between patients with and without NOD2 mutations revealed that arthritis, uveitis and skin rash are not exclusively seen in the presence of NOD2 mutations although the characteristic triad is significantly more common in NOD2 mutated individuals. Conversely although we found extended manifestations in the NOD2 mutated group, their frequency was significantly higher among individuals with wild-type NOD2. Still, the presence of overlapping clinical features supports the hypothesis that additional genetic factors may contribute to the phenotype in pediatric granulomatous inflammatory diseases.

Our investigation has some shortcomings, mostly related to the retrospective character of the clinical data collection. First there may be an underestimation of the exact frequency of certain subclinical manifestations found as a result of unrelated investigations. Among those sialadenitis, granulomatous liver disease and pericarditis should be noted. Second, in the absence of histologic demonstration of granulomas, a causal link for the NOD2 mutation and some of the atypical manifestations such arterial hypertension, cardiomyopathy, chronic renal failure and pulmonary embolism cannot be proven.

From the strong association of NOD2 with granulomatous inflammatory disease and from the knowledge of its role in innate immunity one might be tempted to hypothesize that NOD2 has a pathogenic role in the formation of granulomas. Apart from mutations in the central NACHT domain that are strongly associated with PGA, several mutations and polymorphisms in the N-terminal Leucine Rich Repeat domain are known to confer a susceptibility to Crohn’s disease as well. However as our data demonstrate granulomatous disease even in infants can occur with wild-type NOD2 and mutations can also be silent. The phenotype of individuals with NOD2 mutations is clearly more complex than initially thought, requiring work on potential additional genetic factors capable of modulating the phenotype, although as we showed here this clinical variability may partly be related to the length of disease course.

In conclusion, we have described different new clinical manifestations, and confirmed several previously noted manifestations in patients with PGA and a documented NOD2 mutation by combining two cohorts. The obvious systemic nature of this condition may require yet another consideration for an appropriate name such as Juvenile Systemic Granulomatosis which may describe better the nature of the disease.

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Table 1

Demographic, genetic and clinical information of all symptomatic subjects with *NOD2* mutations from the combined International registry and Spanish cohort*

Subject no.	Family no.	Family member †	Sex	Onset age (mos.)	NOD2	Arthritis ‡	Uveitis §	Rash	Extended Phenotype ¶
1	1	PGM	F	?	R334W	Yes	Severe	Yes	None
2	1	Proband	F	5	R334W	Yes	Severe	Yes	None
3	1	Father	M	60	R334W	Yes	Severe	Yes	None
4	1	PU	M	?	R334W	Yes	Severe	Yes	None
5	**2**	**Mother**	**F**	**36**	**R334Q**	**Yes**	**Severe**	**Yes**	**Liver**
6	2	Proband	M	12	R334Q	Yes	Mod.	Yes	None
7	**3**	**Proband**	**M**	**22**	**R334Q**	**Yes**	**Mod.**	**Yes**	**Liver, EN, Fever, Lung, Sialadenitis, Lymphadenitis, AH**
8	3	Sibling 1	M	21	R334Q	Yes	Mild	Yes	None
9	**3**	**Sibling 2**	**M**	**21**	**R334Q**	**Yes**	**Mild**	**Yes**	**AH**
10	**3**	**Mother**	**F**	**168**	**R334Q**	**Yes**	**Mild**	**Yes**	**Pulmonary embolism**
11	4	Proband	M	12	R334W	Yes	Severe	Yes	None
12	4	Mother	F	24	R334W	Yes	Severe	Yes	None
13	5	Sporadic	M	6	R334W	Yes	Mild	Yes	None
14	6	Sporadic	M	50	R334W	No	Mod.	Yes	None
15	7	Sporadic	M	36	R334Q	Yes	Mod.	Yes	None
16	8	Proband	M	12	R334W	Yes	Severe	Yes	None
17	8	Sibling	M	11	R334W	Yes	No	?	None
18	8	Mother	F	24	R334W	Yes	?	No	None
19	9	Sporadic	M	4	R334W	Yes	Severe	Yes	None
20	10	Sporadic	F	12	R334Q	Yes	Mod.	Yes	None
21	11	Sporadic	M	24	R334W	Yes	No	Yes	None
22	12	Sporadic	M	3	E383K	Yes	Severe	Yes	None
23	**13**	**Sporadic**	**M**	**6**	**R334W**	**Yes**	**Mod.**	**Yes**	**AH**
24	14	Sporadic	M	48	E383K	Yes	No	Yes	None
25	15	Sporadic	F	18	W490L	Yes	Mild	Yes	None
26	16	Sporadic	F	11	R334W	Yes	Mod.	Yes	None

Subject no.	Family no.	Family member †	Sex	Onset age (mos.)	NOD2	Arthritis ‡	Uveitis §	Rash	Extended Phenotype ¶
27	**17**	**Sporadic**	**F**	**72**	**R334Q**	**Yes**	**Mod.**	**Yes**	**Pericarditis, glomerulonephritis, fever, leukocytoclastic vasculitis, HSM**
28	18	Sporadic	M	9	R334W	Yes	Mod.	Yes	None
29	19	Sporadic	M	24	R334Q	Yes	Mod.	Yes	None
30	20	Sporadic	M	36	R334Q	Yes	Mild	Yes	None
31	21	Sporadic	F	4	R334Q	Yes	Mild	Yes	None
32	22#	Proband	F	48	E383K	Yes	No	Yes	None
33	22#	PA	F	?	E383K	Yes	Yes	Yes	None
34	**23**	**Sporadic**	**M**	**4**	**C495Y**	**Yes**	**Mod.**	**Yes**	**Fever**
35	**24**	**Proband**	**F**	**48**	**R587C**	**Yes**	**Severe**	**No**	**Fever, ION ¶**
36	**24**	**Sibling**	**F**	**21**	**R587C**	**Yes**	**Mod.**	**Yes**	**Fever, EN, pericarditis**
37	**24**	**Mother**	**F**	**216**	**R587C**	**No**	**No**	**Yes**	**Fever, EN**
38	**25**	**Sporadic**	**F**	**11**	**R334Q**	**Yes**	**Severe**	**Yes**	**Cranial neuropathy**
39	26	Sporadic	F	24	R334Q	Yes	No	Yes	None
40	**27**	**Sporadic**	**M**	**22**	**R334Q**	**Yes**	**Mod.**	**Yes**	**AH, hypertrophic cardiomyopathy, HSM, CRF**
41	28	Sporadic	M	9	R334Q	Yes	No	Yes	None
42	29	Proband	M	20	R334Q	Yes	No	Yes	None
43	**29**	**Mother**	**F**	**18**	**R334Q**	**Yes**	**Mod.**	**Yes**	**CRF**
44	30	Sporadic	F	9	R334W	Yes	No	Yes	None
45	31	Sporadic	F	12	R334W	Yes	No	Yes	None

*Rows in bold font indicate subjects with an extended phenotype. Throughout table, a question mark (?) indicates an unavailable parameter.

†PGM: paternal grandmother; PU: paternal uncle; PA: paternal aunt.

‡All subjects with arthritis exhibited polyarthritis.

§Severe: significant visual loss; Mod.: moderate uveitis indicating presence of complications and preserved vision with correction; Mild: no sequelae.

¶EN: erythema nodosum; AH: arterial hypertension; HSM: hepatosplenomegaly; CRF: chronic renal failure; ION: Inflammatory Optic Neuropathy.

#Four additional family members with mutations but without symptoms have been identified (see Results section).