Blau Arteritis Resembling Takayasu Disease with a Novel NOD2 Mutation

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ABSTRACT. Objective. To put forward a new concept — Blau arteritis, a form of large-vessel vasculitis phenotypically related to Takayasu disease but genetically and clinically part of an expanded phenotype of Blau syndrome.

Methods. We provide a clinical description of a new case and summarize previously published cases of arteritis associated with Blau syndrome. Genetic testing was performed by direct sequencing of exon 4 of the NOD2 gene.

Results. The case described and those reviewed from the literature demonstrate the emerging phenotype of Takayasu-like arteritis in patients with Blau syndrome. Although most patients described to date depict an otherwise classic Blau syndrome phenotype, the current case was atypical in that the predominant features were arteritic. A novel substitution, G464W, in a highly conserved position near the nucleotide oligomerization domain of the NOD2 protein is also described.

Conclusion. Blau arteritis can be observed in the context of both typical and atypical (incomplete) Blau syndrome. The associated mutation in the NOD2 gene raises the question of the potential importance of this gene among patients with “primary” forms of Takayasu arteritis. (First Release Aug 1 2012; J Rheumatol 2012;39:1888–92; doi:10.3899/jrheum.120156)

Key Indexing Terms:
BLAU ARTERITIS TAKAYASU DISEASE NOD2 MUTATION LARGE-VESSEL VASCULITIS

Blau syndrome is a monogenic granulomatous disease characterized in its most typical form by a triad of exuberant polyarthritis, uveitis, and granulomatous dermatitis. It is caused by single amino acid substitutions at or near the NACHT domain of NOD2. Although its systemic expression is well recognized after the descriptions of the expanded phenotype of Blau syndrome, large-vessel vasculitis remains one of its serious and yet underrecognized manifestations if not actively sought by the treating physician.

We describe an 8-year-old girl with symptomatic Takayasu-like arteritis and cardiomyopathy against the background of Blau syndrome with a G464W substitution in NOD2. We reported a similar case in 1989, while others have observed arteritis among children with both sporadic and familial Blau phenotype before the mutation was known (Table 1). We also review the clinical features of Blau arteritis based on cases published before and after the discovery of the mutation in 2001. The mother of this patient was encouraged to see an adult rheumatologist and ophthalmologist for additional investigation, but she declined further medical care, citing constraints of distance and cost.

MATERIALS AND METHODS
A girl, now 11 years old, from rural India, presented to us for the first time at 18 months of age, with bilateral knee effusions of a few months’ duration in the absence of rash, uveitis, or systemic features. From the age of 1 month she had had recurrent and unexplained episodes of fever. Her antinuclear antibody result was negative. With a working diagnosis of oligoarticular juvenile arthritis she was administered intraarticular steroids, to which she responded well. She was lost to followup for almost 6 years thereafter. At the age of 8 years, she presented with gradually progressive dyspnea and palpitations of 3 months’ duration. She had not thrived, and at this stage she weighed 17.2 kg and her height was 113 cm. There were no systemic features but joint examination showed “boggy synovitis” of the right elbow and knee. Cardiovascular examination showed an irregular pulse with a pulsatile precordium and evidence of congestive heart failure. A rhythm strip on electrocardiography showed ventricular extra beats. The echocardiogram revealed dilated ventricles, generalized hypokinesia with an ejection fraction of 20%, mild tricuspid and aortic regurgitation, and abnormal echogenicity within the wall of the left ventricle. With oligoarticular arthritis in a setting of dilated cardiomyopathy, elevated erythrocyte sedimentation rate, and family history of recurrent unexplained fevers in her mother, a diagnosis of early-onset sarcoidosis was considered. Her eye examination continued to be normal and all biopsies requiring sedation were deferred because of poor cardiac function. Oral methotrexate 10 mg/m² and corticosteroids 2 mg/kg were initiated in addition to decongestive treatment consisting of digitalis, diuretics, and captopril. She showed a gradual but steady improvement in effort tolerance, although her ejection fraction on electrocardiography did not mirror her clinical improvement. One and a half years later on a routine followup she was found to be hypertensive. Her carotid pulsations were decreased and a renal bruit was detected. Antihypertensive treatment was instituted and a computed...
tomography angiogram followed by digital subtraction angiography showed
generalized narrowing of aorta, carotids, and left subclavian and renal arter-
ies (Figures 1A, 1B, 1C). Cerebral circulation was maintained normally with
diffuse collaterals. Her condition is currently well controlled on a combina-
tion of methotrexate and low-dose oral corticosteroids with antihypertensive
drugs, and her last echocardiogram demonstrated an ejection fraction of 55%.
She is able to walk 5 km to and from her school. Throughout this time her
renal function has remained stable and angiotensin-converting enzyme levels
have been within normal levels.

**RESULTS**

On genotyping of exon 4 of NOD2 a G464W substitution was
found, confirming a diagnosis of Blau syndrome, with her
mother demonstrating the same mutation and her father
exhibiting the wild-type. Siblings were not tested (Figure 2).
This mutation has not been described in the literature before.

**DISCUSSION**

We describe a case of a young girl with Takayasu-like aor-
toarteritis, cardiomyopathy, arthritis, maternal history of
recurrent fevers, and a G464W substitution in NOD2 in both
mother and daughter. This NOD2 variant is a nonconservative
change that was not observed in 108 control chromosomes.

As all known mutations are located in exon 4, a set of primers
was designed to amplify 2 overlapping fragments covering this region of exon
4, as follows: (1) B4.1F: TGT AAA ACG AGC GGC AGT GGC TGC ACT
TAG TGG TCT TTG GG; (2) B4.2F: TGT AAA ACG AGC GCC AGT GCC AGT
ACC AGC AAA GCT GGT GGC ACA TC. and (4) B4.2R: CAG GAA ACA GCT ATG
ACC ACC AGC AAA GCT GGT GGC ACA TC.

Polymerase chain reaction amplification was performed using Promega
PCR Master Mix, according to the manufacturer’s protocol (Promega,
Madison, WI, USA). Direct sequencing was performed using the BigDye
Terminator v3.1 (BDT v3.1) cycle sequencing kit, according to the manufac-
turer’s recommendations, followed by electrophoresis of the ampcions on an
ABI 3100XL Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Takayasu arteritis is an idiopathic large-vessel vasculitis
affecting elastic arteries including the aortic arch and its pri-
mary branches, in both its thoracic and abdominal segments.
Curiously, as in Blau syndrome, noncaseating granulomas are
consistently found in the inflamed arteries in autopsy studies.
Indeed, the 2 most prevalent forms of elastic artery arteritis —
giant cell arteritis (GCA) and Takayasu arteritis — are char-
acterized by the presence of noncaseating giant cell granula-
mosa in the vessel wall7, a characteristic finding on affected
organs of the 2 NOD2-related diseases, Blau syndrome and Crohn’s disease. This shared morphologic feature raises the
question of a role of NOD2 variants in the pathogenesis of
Takayasu arteritis, GCA, or both. Blau syndrome-associated
mutations produce a gain of function leading to overexpres-
sion of nuclear factor-κB (NF-κB) and subsequent transcrip-
tion of proinflammatory cytokines, as suggested by immune-
histochemistry in granuloma tissue of both Blau and Crohn’s.

Both Takayasu arteritis and Blau syndrome show some
response to tumor necrosis factor (TNF) blockade and TNF
seems to be an important agent in the tissue damage in blood
vessels of patients with Takayasu arteritis9. Recent work on
a large cohort of patients with Takayasu arteritis failed to show
variations in the TNF promoter among 110 unrelated Han
Chinese10, suggesting upstream activation of inflammatory
cytokines through NF-κB as an alternative explanation for the
role of TNF in the pathogenesis of Takayasu arteritis, which
could in turn conceivably involve deregulation of NOD2.

An association between Blau syndrome and large-vessel
involvement can be traced to the period before Edward Blau’s
first description in 19851. Although the emerging phenotype
of Blau arteritis includes predominant involvement of the
aorta and renal arteries11,12,13, fully developed Takayasu phe-
notype has been observed in both the current case and one
reported previously, in which stenosis of the primary branch-
es of the aortic arch was documented3. In the 10-pedigree
report by Wang, et al, 2 families showed vascular involve-
ment14. Unfortunately, no details are provided on the clinical
features14. More recently, isolated involvement of the coro-
nary sinus was reported by a surgical group in a patient with
existing Blau phenotype5. Again, the authors did not provide
details about the clinical features or mutation analysis, or his-
tological findings on the excised valvular tissue15.

Between the diagnosis of cardiomyopathy in our case and
the clinical finding of arteritis there was an 18-month asymp-

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**Table 1. Summary of published cases with Blau syndrome and large-vessel vasculitis.**

<table>
<thead>
<tr>
<th>No. with Vasculopathy</th>
<th>Blau Phenotype</th>
<th>Vascular Phenotype</th>
<th>Substitution</th>
<th>Publication</th>
<th>Familial vs Sporadic</th>
</tr>
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<tbody>
<tr>
<td>2/4</td>
<td>Classical</td>
<td>Large-vessel</td>
<td>Predated testing</td>
<td>198211</td>
<td>F (4 affected)</td>
</tr>
<tr>
<td>1</td>
<td>Classical</td>
<td>Renovascular hypertension</td>
<td>Predated testing</td>
<td>198612</td>
<td>S</td>
</tr>
<tr>
<td>1</td>
<td>Classical</td>
<td>Takayasu arteritis</td>
<td>Predated testing</td>
<td>199015</td>
<td>S</td>
</tr>
<tr>
<td>1</td>
<td>Classical</td>
<td>Aortitis</td>
<td>Predated testing</td>
<td>199613</td>
<td>S</td>
</tr>
<tr>
<td>2 pedigrees</td>
<td>Not reported</td>
<td>Large-vessel</td>
<td>R334W and R334Q</td>
<td>200214</td>
<td>F</td>
</tr>
</tbody>
</table>
tomatic period. In addition, the patient had normal blood pressure and peripheral pulses at the onset of the cardiac disease. While one could interpret the 2 manifestations (cardiomyopathy and arteritis) as separate expressions of Blau syndrome, in retrospect it is likely that clinically silent aortoarteritis was occurring during those 18 months. The association between

Figure 1. Digital subtraction angiography. Arrows show stenosis of the descending portion of thoracic aorta (A), left common carotid artery (B), and left renal artery (C).
carditis and subclinical aortoarteritis in the context of a NOD2 mutation as observed in this case should alert clinicians of the possibility of concomitant “silent” arteritis. Moreover, digital angiography should be considered in patients with NOD2 mutations who develop cardiomyopathy; further vascular damage, if found, could be ameliorated or even averted with aggressive pharmacologic therapy. The existence of this association should as well alert clinicians caring for patients with Blau syndrome about this potentially lethal and commonly silent form of arteritis. Careful examination of the peripheral pulses at regular visits and a low threshold for noninvasive imaging may be advisable. Testing for NOD2 mutations should be considered in pediatric patients presenting with large-vessel vasculitis and systemic features, particularly in the context of other family members with inflammatory disease. Finally, further research is warranted on the relationship between NOD2 variants and primary forms of granulomatous large-vessel vasculitis, for which no genetic causes have been found to date.

ACKNOWLEDGMENT

We are grateful to Tammy M. Martin, PhD, for keeping records of published NOD2 mutations associated with Blau syndrome and for providing the data for this publication.

REFERENCES

1. Blau EB. Familial granulomatous arthritis, iris, and rash. J Pediatr
Table 2. NOD2 mutations published to date. The NOD domain (nucleotide oligomerization domain) spans from amino acid 293 to 463. The LRR domain (leucine-rich repeat domain) spans from position 767 to 1032. No mutations have been described within the LRR region to date.

<table>
<thead>
<tr>
<th>Nod2 Amino Acid Substitution</th>
<th>First Reported (reference number)</th>
</tr>
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<tbody>
<tr>
<td>R334W</td>
<td>2</td>
</tr>
<tr>
<td>R334Q</td>
<td>2</td>
</tr>
<tr>
<td>D382E</td>
<td>16</td>
</tr>
<tr>
<td>E383G</td>
<td>17</td>
</tr>
<tr>
<td>E383K</td>
<td>18</td>
</tr>
<tr>
<td>L469F*</td>
<td>2</td>
</tr>
<tr>
<td>G481D*</td>
<td>19</td>
</tr>
<tr>
<td>W490L*</td>
<td>6</td>
</tr>
<tr>
<td>ELL (498–500)V**</td>
<td>20</td>
</tr>
<tr>
<td>C495Y*</td>
<td>3</td>
</tr>
<tr>
<td>H496L*</td>
<td>16</td>
</tr>
<tr>
<td>M513T*</td>
<td>16</td>
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<tr>
<td>M513R*</td>
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<tr>
<td>R587C*</td>
<td>3</td>
</tr>
<tr>
<td>T605N*</td>
<td>22</td>
</tr>
<tr>
<td>T605P*</td>
<td>16</td>
</tr>
<tr>
<td>N670K*</td>
<td>16</td>
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</table>

* Substitutions near the NOD domain; ** 6-base deletion.