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. (J Rheumatol First Release Aug 1 2012; 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[1]. It is caused by single amino acid substitutions at or near the NACHT domain of NOD2[2]. Although its systemic expression is well recognized after the descriptions of the expanded phenotype of Blau syndrome[3,4], 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[5], 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[2]. 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.

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Accepted for publication May 25, 2012.

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/m^2 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

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

No. with Vasculopathy	Blau Phenotype	Vascular Phenotype	Substitution	Publication	Familial vs Sporadic
2/4	Classical	Large-vessel	Predated testing	1982[11]	F (4 affected)
1	Classical	Renovascular hypertension	Predated testing	1986[12]	S
1	Classical	Takayasu arteritis	Predated testing	1990[5]	S
1	Classical	Aortitis	Predated testing	1996[13]	S
2 pedigrees	Not reported	Large-vessel vasculitis	R334W and R334Q	2002[14]	F

tomography angiogram followed by digital subtraction angiography showed generalized narrowing of aorta, carotids, and left subclavian and renal arteries (Figures 1A, 1B, 1C). Cerebral circulation was maintained normally with diffuse collaterals. Her condition is currently well controlled on a combination 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.

Genetic testing. 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 ACG GCC AGT GGC TGC ACT TGC TGT GGG CT; (2) B4.1R: CAG GAA ACA GCT ATG ACC TAT CTG TAG TGG TCT TTG GG; (3) B4.2F: TGT AAA ACG ACG GCC AGT ACC TCA AGG GCT TCT CTG AA; and (4) B4.2R: CAG GAA ACA GCT ATG 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 manufacturer's recommendations, followed by electrophoresis of the amplicons on an ABI 3100XL Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

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. Table 2 depicts the published NOD2 mutations associated with Blau phenotype to date.

DISCUSSION

We describe a case of a young girl with Takayasu-like aortoarteritis, 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. Alignment of amino acid sequences of NOD2 from mice and humans showed that this amino acid at position 464 is highly conserved.

Although it could be argued that this girl's phenotype is incomplete for Blau syndrome, we have observed wide phenotypic variation in our registry, including a mutation-carrying pedigree with affected and unaffected members. In addition, although uveitis is frequent, 40% of patients lack this feature[6].

Takayasu arteritis is an idiopathic large-vessel vasculitis affecting elastic arteries including the aortic arch and its primary 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 characterized by the presence of noncaseating giant cell granuloma in the vessel wall[7], 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 overexpression of nuclear factor-κB (NF-κB) and subsequent transcription of proinflammatory cytokines, as suggested by immunehistochemistry in granuloma tissue of both Blau and Crohn's[8]. 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 arteritis[9]. Recent work on a large cohort of patients with Takayasu arteritis failed to show variations in the TNF promoter among 110 unrelated Han Chinese[10], 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 1985[1]. Although the emerging phenotype of Blau arteritis includes predominant involvement of the aorta and renal arteries[11,12,13], fully developed Takayasu phenotype has been observed in both the current case and one reported previously, in which stenosis of the primary branches of the aortic arch was documented[5]. In the 10-pedigree report by Wang, *et al*, 2 families showed vascular involvement[14]. Unfortunately, no details are provided on the clinical features[14]. More recently, isolated involvement of the coronary sinus was reported by a surgical group in a patient with existing Blau phenotype[15]. Again, the authors did not provide details about the clinical features or mutation analysis, or histological findings on the excised valvular tissue[15].

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

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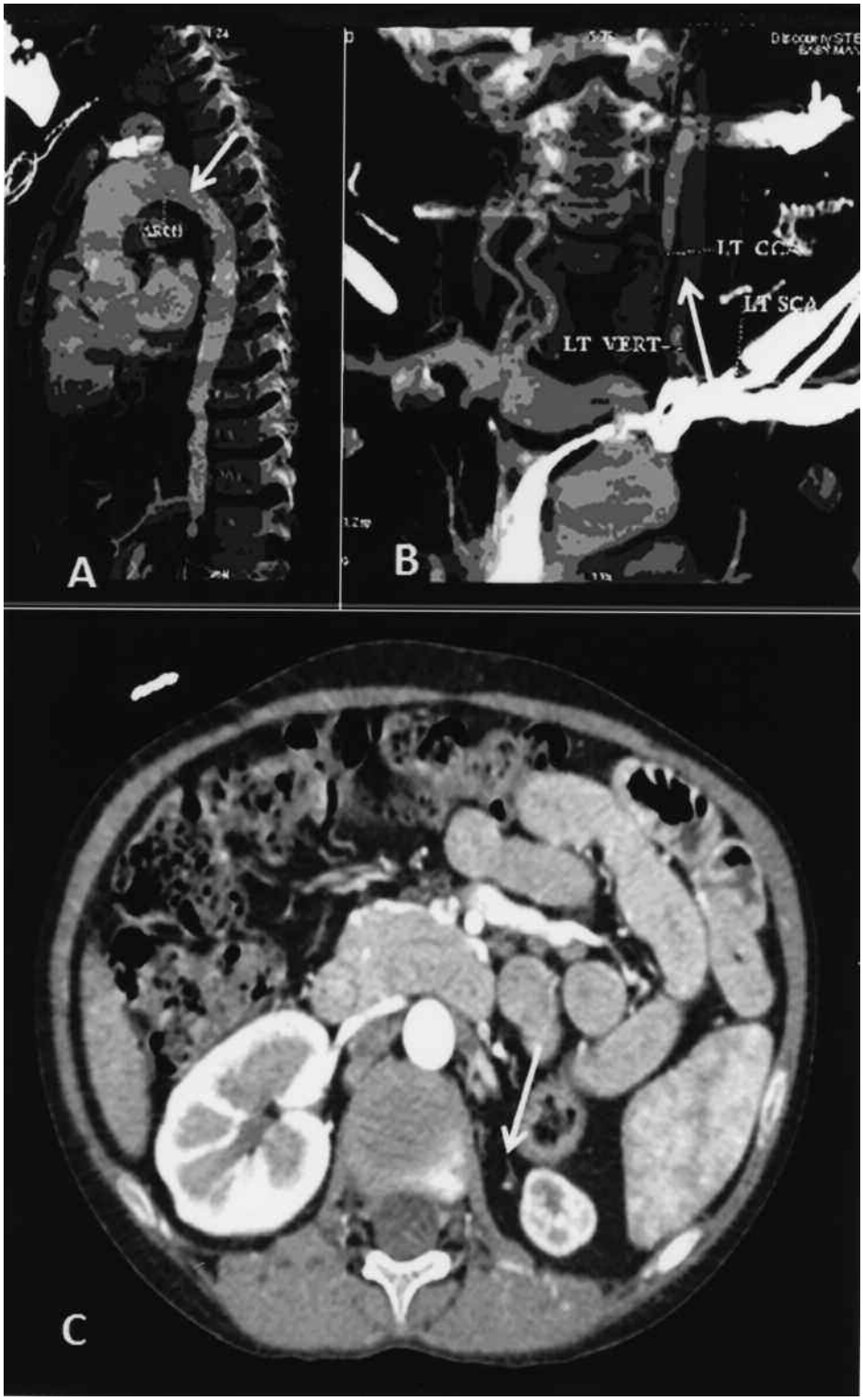

Figure 1. Digital subtraction angiography. Arrows show stenosis of the descending portion of thoracic aorta (A), left common carotid artery (B), and left renal artery (C).

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

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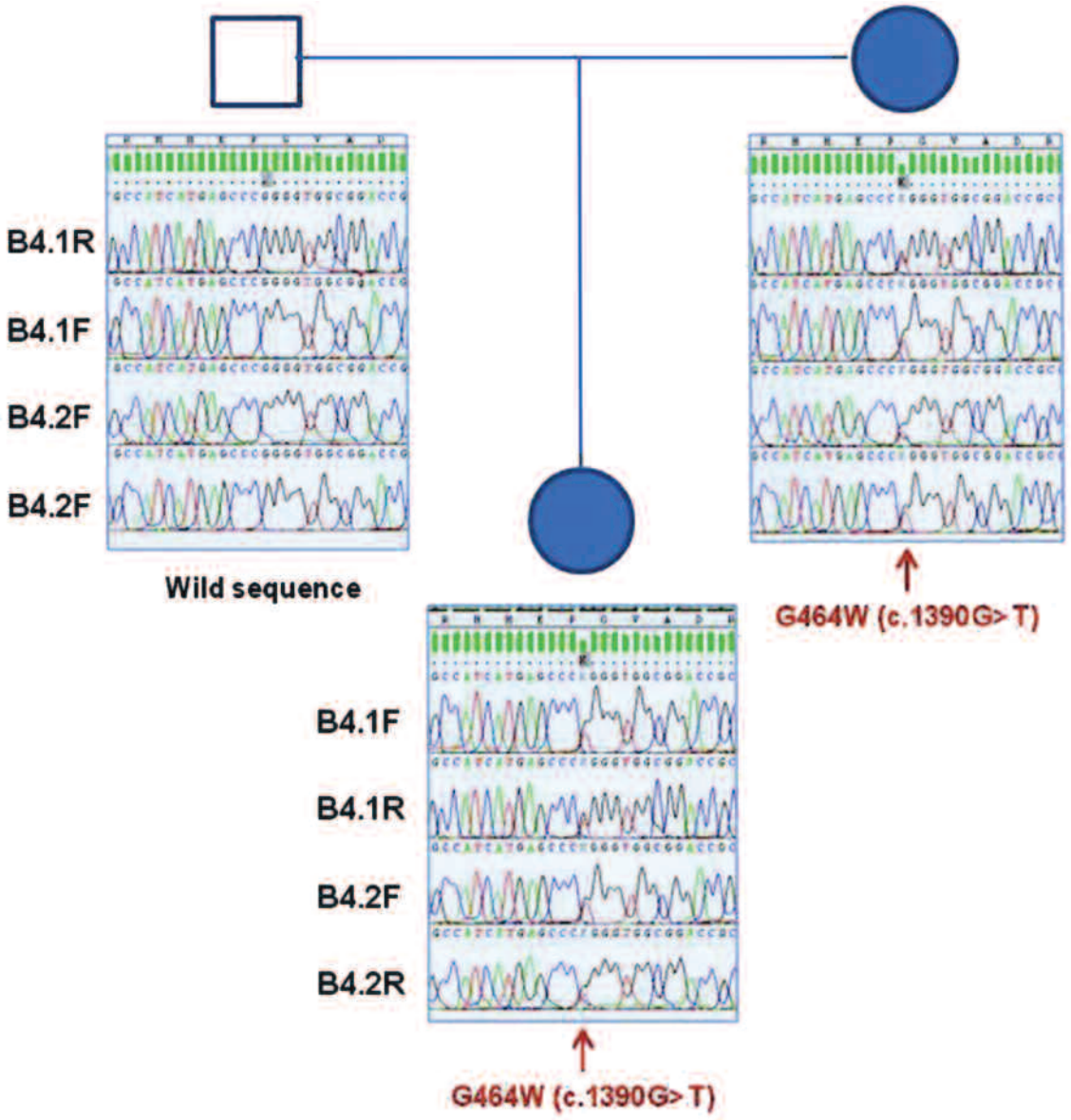

Figure 2. Gene sequencing data show the new G464W mutation (arrow). Two overlapping amplicons (4 reads) were generated in the NOD2 exon 4 regions, where all known mutations are located. Square symbol represents the unaffected father, 2 circles represent the affected mother and daughter.

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.

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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.

Nod2 Amino Acid Substitution	First Reported (reference number)
R334W	2
R334Q	2
D382E	16
E383G	17
E383K	18
L469F*	2
G481D*	19
W490L*	6
ELL (498–500)V**	20
C495Y*	3
H496L*	16
M513T*	16
M513R*	21
R587C*	3
T605N*	22
T605P*	16
N670K*	16

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

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