
REVIEW

NOVEL INSIGHTS INTO PEDIATRIC ALLERGY AND IMMUNOLOGY

Kounis Syndrome: a pediatric perspective

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ABSTRACT

Kounis Syndrome is defined as a hypersensitivity coronary disorder constituted by the association of an acute coronary syndrome with a hypersensitivity, allergic, anaphylactic or anaphylactoid reaction, in a pathophysiologic context involving mast-cells, platelets, eosinophils and various interacting inflammatory cells. Currently, Kounis Syndrome is established in the literature, as accompanied by a plethora of clinical case reports that further elucidate its aspects. To the best of our knowledge, a specific analysis regarding the pediatric data of Kounis Syndrome has never been performed. The aim of this review was to reveal all the pediatric Kounis Syndrome cases in the literature, in an attempt to define its clinical implications in children. Moreover, based on the data of this analysis, a new classification for Kounis Syndrome is proposed, focusing mainly in the presence or the absence of allergic myocardial infarction, as the central clinical feature for the stratification of the patients' clinical manifestations.

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KEY WORDS: Kounis Syndrome; Acute coronary syndrome; Hypersensitivity; Inflammation; Pediatrics.

Kounis Syndrome is defined as a coronary hypersensitivity disorder constituted by the association of an acute coronary syndrome with a hypersensitivity, allergic, anaphylactic or anaphylactoid reaction, in a pathophysiologic context involving mast-cells, platelets, eosinophils and various interrelated and interacting inflammatory cells.^{1,2} Mesenteric, peripheral and cerebral arteries might be involved as well in similar entities to Kounis Syndrome.^{3,4}

Three variants of Kounis Syndrome were described in the literature: type 1 referred as allergic vasospastic angina due to endothelial

dysfunction constituting one of myocardial infarction with non-obstructive coronary arteries (MINOCA)⁵ causes, type 2 referred to allergic myocardial infarction and type 3 known as allergic stent thrombosis with an occluding thrombus (subtype a) or stent restenosis (subtype b).^{1,6}

Cardiovascular disorders associated with anaphylactic, allergic, hypersensitivity, or anaphylactoid reactions were initially characterized as acute carditis,⁷ morphologic cardiac reactions or rheumatic carditis of unknown pathophysiology⁸ and were attributed to serum pathology.⁹ The allergic angina syndrome, as a coronary spasm represent-

ing a manifestation of endothelial dysfunction or microvascular angina leading to allergic acute myocardial infarction, was described about 30 years ago¹⁰ and in 2005 was named by American researchers as the Kounis Syndrome.¹¹ In 1950, Pfister *et al.*¹² reported for the first time a case of a 49-year-old male patient with myocardial infarction and urticaria post treatment with penicillin. Kounis *et al.*¹⁰ described the full concept of the pathophysiology underlying vasospastic angina and myocardial infarction correlated to an allergic reaction in 1991. Braunwald *et al.*¹³ classified allergic angina as a dynamic coronary occlusion condition, mediated by a vasospastic mechanism. Kounis *et al.* published the first comprehensive review on the syndrome in 2006.¹⁴ Biteker *et al.*¹⁵ published for the first time a pediatric case series in 2009.

Since these first steps, awareness of this syndrome increased worldwide, as demonstrated the escalation of epidemiological study published.¹⁶⁻¹⁹ Abdelghany *et al.*² recently reviewed all the Kounis Syndrome cases in published papers so far. However, to the best of our knowledge, a specific analysis on pediatric data was never performed.

Data sources and search strategies

A systematic literature search was performed in Medline through Pubmed. We used default search keywords connected to pediatric Kounis Syndrome. Case reports, original studies and review articles in English were identified up to May 15, 2020. No additional databases' filters were used. The result of the databases search and the following article selection is shown (Figure 1). After removing duplicate publications, 28 total papers were identified. A further screening was performed basing on articles' titles, abstracts or full-texts to identify all the cases of pediatric Kounis Syndrome. Publications with duplicated cases were excluded. As a result, 8 papers were eligible for the inclusion. To deepen our search, a reference lists screening of the articles was performed, and another eligible paper was found and included. At the end of the process, that was carried out by three researchers (MG, AA and LS), 9 papers were selected, reporting

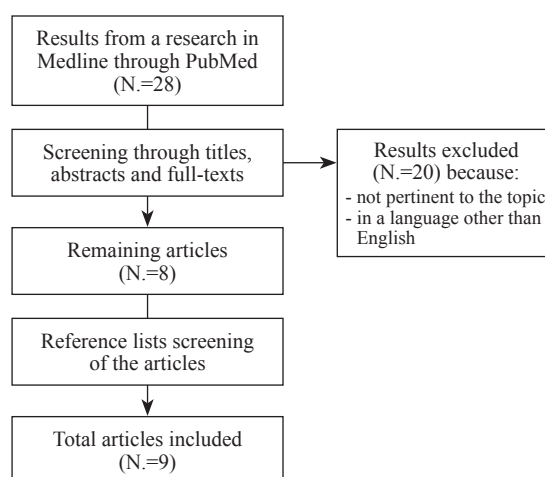


Figure 1.—Flow-chart reporting the research process.

11 pediatric cases of Kounis Syndrome. Details from these cases were exported in a data sheet, summarized and carefully analyzed.

Pediatric Kounis Syndrome case reports

Kounis *et al.*²⁰ described a case with the characteristics of Kounis Syndrome in a 12 years-old boy with ulcerative colitis who developed severe chest pain after oral administration of 5-aminosalicylic acid. During the pain there were no dynamic ischemic changes except inverted T-waves in the lateral chest leads. Cardiac enzymes, troponins, C-reactive protein (CRP) and brain natriuretic peptide (BNP) were normal.

Biteker *et al.*²¹ reported a case of Kounis Syndrome in a 13-year-old previously healthy boy. He developed a mild pruritic skin rash and thoracic pain started 10 minutes after the ingestion of an oral dose of amoxicillin/clavulanic acid. His electrocardiogram demonstrated an acute inferior/lateral myocardial infarction (ST elevation in II, III, aVF, V4, V5 and V6 leads), and inferior wall hypokinesia was reported on echocardiogram. Blood levels of troponin I (2.1 ng/mL), creatine kinase-muscle/brain (CK-MB, 30 IU/L) and serum tryptase (31 µg/L; n.v. 5.6-13.5 µg/L) were increased, with normal total serum immunoglobulin E (IgE) and negative serum amoxicillin-specific IgE. Coronary angiography revealed normal coronary arteries. He was treated with antihistamines and prednisolone for 5 days with

normalization of cardiac markers and resolution of electrocardiographic abnormalities.

The same group published a paper in 2009,²² in which they described the latter boy in addition to other 3 Kounis Syndrome cases.

The first patient was a 9-year-old previously healthy girl. She was stung several times by honeybees on the head and neck and then she developed an erythematous rash over the face, neck, and arms and chest pain radiated to the neck. Electrocardiogram revealed inferior acute myocardial infarction (elevation of ST segment in II, III, aVF, V5 and V6 leads), while echocardiogram demonstrated a hypokinesia of the inferior wall and a mildly impaired left ventricular function with ejection fraction of 50%. The blood samples showed increased levels of troponin I (4.3 ng/mL), CK-MB (342 IU/L), serum tryptase (45 µg/L, n.v. 5.6-13.5 µg/L) and total IgE (190 IU/mL, n.v. 0-100 IU/mL). The coronary angiography was normal. The patient was treated with oral antihistamines and prednisolone with subsequent resolution of electrocardiographic and echocardiographic alterations and normalization of serum markers. Intradermal skin test with bee venom performed on the volar side of the forearm of the patient was considered positive.

The second case was referred to an 11-year-old previously healthy boy, who developed chest pain, palpitations and pruritus few minutes after the oral ingestion of amoxicillin/clavulanic acid. Electrocardiogram and echocardiogram revealed anterior acute myocardial infarction, with elevation of ST segment in V2 and V5 and anterior wall hypokinesia, respectively. The coronary angiogram was completely normal. Troponin I, CK-MB, total IgE and tryptase levels were increased (5.0 ng/mL, 780 U/L, 780 U/mL and 42 µg/L, respectively) and serum amoxicillin-specific IgE were positive. The patient received a treatment with corticosteroids, ketotifen and histamine H2 receptor antagonists with resolution of all pathological findings in few days, without any other complication.

The last patient was a 10-year-old previously healthy boy, who developed chest pain and pruritic erythematous rash immediately after being stung by wasps on his head and forearms. His electrocardiogram was compatible with inferior/

lateral acute myocardial infarction with elevation of ST segment in II, III, AVF, V5 and V6 leads, while transthoracic echocardiogram and coronary angiography were normal. On blood examinations there were increased levels of troponin I (1.1 ng/mL), CK-MB (42 IU/L), serum tryptase (33 µg/L) and total IgE (321 IU/mL). The patient was treated with oral antihistamines and prednisolone with complete recovery. Intradermal skin test with wasp venom performed on the volar side of the forearm of the patient was considered positive.

Parent *et al.*²³ described Kounis Syndrome in a 2-year-old boy during surgical repair of atrial septal defect with autologous pericardium. Frequent atopic clinical manifestations were reposted in his previously medical history, including eczema and hives as a reaction to certain foods and "emotional stress." Cefazolin, midazolam, fentanyl, rocuronium and then continuous inhaled isoflurane were administered pre-operatively. Afterwards, 4-6 hours post cardiopulmonary bypass, the patient developed desaturation with increased oxygen requirements due to pulmonary edema, along with diffuse ST segment depression on 12-lead electrocardiogram and increased levels of troponin I (18.3 ng/mL). Given the deterioration of cardiorespiratory status, re-intubation along with additional administration of rocuronium and fentanyl was performed. In acute phase, an echocardiogram demonstrated moderate decrease of the biventricular systolic function. The patient developed significant ST segment elevation, hypotension, severe bradycardia necessitating cardiopulmonary resuscitation, pulmonary edema, before coronary angiography. Afterwards, return of spontaneous circulation was achieved and coronary angiography was performed on extra corporeal membrane oxygenation (ECMO) support, that revealed a diffuse and significantly decreased dimensions of right and left coronary artery systems, without apparent response to nitroglycerin. Thus, the first diagnostic hypothesis was coronary congenital hypoplasia. After 3 days, ECMO was switched to biventricular assist device (BiVAD). Extracardiac complications such as anuric renal failure requiring hemodialysis, compartment syndrome of his right calf, bilateral watershed cerebral in-

farcts associated with seizure activity and acute respiratory distress syndrome requiring mechanical ventilation occurred during his hospitalization. One month after recovery, echocardiogram and coronary angiography were performed and showed normal systolic biventricular function and normal right and left coronary artery without significant stenosis, respectively. The child was taken back to the operating room for BiVAD removal and, despite the preemptive perioperative nitroglycerin infusion, again developed ST changes on electrocardiography (ECG). Laboratory tests demonstrated further increased levels of troponin I (2.5 ng/mL), serum tryptase (10 ng/mL, n.v. <1 ng/mL) and serum total IgE (152 IU/mL, n.v. <60 IU/mL), while histamine levels were normal. At this time Kounis Syndrome was suspected, and the patient started a treatment with antihistamines and mast-cell stabilizers. From the review of the procedures, it was highlighted how both isoflurane and rocuronium were used for every anesthesia, that could have been the triggers of the reaction.

Ilhan *et al.*²⁴ described a 16-year-old previously healthy boy with the diagnosis of Kounis Syndrome. He developed chest pain immediately post oral ingestion of amoxicillin/clavulanic acid along with typical inferolateral ischemia on 12-lead electrocardiogram performed during the chest pain (T-wave inversion in III and aVF leads and ST segment elevation on I, II, III, aVF, V5 and V6 leads). No data are available about laboratory tests carried out. Echocardiogram and coronary angiography did not show abnormalities. Initially, a myocarditis diagnosis was considered but finally Kounis Syndrome was identified during the follow-up and it was recommended to the patient to strictly avoid the use of beta-lactam antibiotics in the future.

Yaman *et al.*²⁵ described a Kounis Syndrome in a 15-year-old previously healthy boy. He was bitten by a black widow spider on the right side of the neck and post 5-6 hours from the bite, he developed acute respiratory distress and generalized pain. A S3 cardiac sound was present on cardiac examination along with bilateral fine crackles up to upper zones on respiratory examination. The patient was admitted to the intensive care unit and he was treated with diuretics, and va-

sodilators such as nitroglycerine and morphine. Electrocardiogram revealed sinus tachycardia and ST segment depression in inferolateral leads (II, III, aVF, I, aVL, and V3-V6). Echocardiogram showed mildly dilated left ventricle with global hypokinesia and ejection fraction of 22%, a pulmonary artery systolic pressure of 35 mmHg and pericardial fluid in the area near to the right ventricle. Laboratory results revealed increased levels of troponin I (1.8 ng/mL, n.v. <0.04 ng/mL) and CK-MB (83 ng/mL, n.v. <5 ng/mL). After the second hospitalization day, optimal medical treatment for chronic heart failure was initiated. During the fourth day of treatment, urticaria like pruritic lesions were noticed in both gluteal regions. The patient was discharged with ACE-inhibitor and beta-blocker treatment, that was stopped after 3 months because of normalizations of all echocardiographic findings.

Terlemez *et al.*²⁶ described Kounis Syndrome in a 14 years-old boy with a previous clinical history of allergic rhinitis. In his familial history, trimethoprim/sulfamethoxazole and bee sting allergy were reported (mother and grandfather, respectively). He presented severe chest pain, shortness of breath and an erythematous widespread rash in the upper area of the neck and body 6 hours post the intravenous administration of the second metronidazole dose, that was prescribed together with trimethoprim/sulfamethoxazole for watery diarrhea. When electrocardiogram was performed, it showed ST segment elevation in the inferior leads (II, III and aVF). Laboratory tests revealed increased levels of troponin I (18.05 ng/mL) and CK-MB (36 ng/mL). Data on serum tryptase were not available. A treatment with morphine, nitroglycerine, calcium channel blocker and salicylic acid was started, with immediate disappearance of the clinical manifestations. Coronary angiography was normal. Therapy with calcium channel blocker and aspirin, administered at antiaggregant dose, was continued for 2 months without any additional complication.

Castellano-Martinez *et al.*²⁷ described a 10-year-old boy with a possible diagnosis Kounis Syndrome, post an intravenous bolus of atropine administration before an upper endoscopy in the context of chronic abdominal pain inves-

tigation. Immediately after that, he became pale, hypotensive and sweaty. He had received a previous well-tolerated atropine infusion during anesthetic induction for cholesteatoma surgical resection 2 years before. ECG-monitor showed severe bradycardia with ventricular escape rhythm, that resolved spontaneously in 30 seconds. After the resumption of spontaneous circulation, a 12-lead electrocardiogram was performed and revealed ischemic changes in the inferior wall, with ST segment depression and inverted T-wave in II, III and aVF. Blood examinations showed increased levels of troponin I (0.29 ng/mL). A 24-hours Holter-ECG, ergometry, transthoracic echocardiogram, cardiac angiomagnetic resonance imaging and angiocomputed tomography were further performed with normal results.

Dogan²⁸ described a case of Kounis Syndrome in a 17-years-old previously healthy boy, occurred 30 minutes after oral ingestion of branched-chain amino acid supplement for muscle growth. The patient developed pruritus, facial rash, palpitations and chest pain. His electrocardiogram performed on admission to the hospital showed ST wave elevation on inferolateral leads (II, III, AVF, V4, V5 and V6). Transthoracic echocardiogram showed inferior wall hypokinesia, while his coronary arteriography was normal. Laboratory tests revealed increased troponin I (3.3 ng/mL; n.v. 0.01 ng/mL) and CK-MB (45 IU/L, n.v. 0-25 IU/L), while total IgE were mildly increased (156 IU/L, n.v. 0-100 IU/L). Serum tryptase was measured as well (51 µg/L) and other laboratory tests such as BNP, complete blood count, cholesterol levels, infectious and coagulation workup were normal. The patient was treated with oral

antihistamines, desloratadine for 2 weeks, and steroids, prednisolone for 5 days, with excellent recovery of his clinical manifestations.

Results

In this review all the pediatric Kounis Syndrome cases reported in the literature, specifically 11, were presented (Table I, II, III).²⁰⁻²⁸

Male was the mostly prevalent gender in 10/11 patients (90.9%). The median age of the patients was 12.0 years, ranging from 2.0 to 17.0 years.

In 4/11 patients (36.4%) of the patients it was possible to identify other significant medical conditions in the past medical history, such as ulcerative colitis, atrial septal defect and atopy, preexistent allergic rhinitis and chronic abdominal pain in the context of cholesteatoma. Notably, in 2/11 patients (18.2%) there was a concomitant atopic disease or atopy.

Regarding the trigger of the reaction, drugs were identified as the main factors (7/11 patients, 63.6%) followed by stings/bites (3/11 patients, 27.3%) and foods (1/11 patients, 9.1%). Among drugs, antibiotics were recognized as the leading triggers (4/7 patients, 57.1%): amoxicillin/clavulanic acid in 3/4 patients (75.0%) and metronidazole in another patient (1/4 patients, 25.0%). Non antibiotic agents were described as well as mesalamine (1/7 patients, 14.3%), atropine (1/7 patients, 14.3%) and rocuronium, isoflurane (1/7 patients, 14.3%). Among stings/bites, honeybee stings (1/3 patients, 33.3%), wasp stings (1/3 patients, 33.3%) and black widow spider bites (1/3 patients, 33.3%) were found as triggers. Among

TABLE I.—Sex, age, past medical history and triggers of the reported pediatric patients with Kounis Syndrome.

References	Sex	Age (years)	Past medical history	Triggers
Kounis <i>et al.</i> 2008 ²⁰	M	12	Ulcerative colitis	Mesalamine
Biteker <i>et al.</i> 2009 ²¹	M	13	Healthy	Amoxicillin clavulanate
Biteker <i>et al.</i> 2009 ²²	F	9	Healthy	Honeybee sting
Biteker <i>et al.</i> 2009 ²²	M	11	Healthy	Amoxicillin clavulanate
Biteker <i>et al.</i> 2009 ²²	M	10	Healthy	Wasp sting
Parent <i>et al.</i> 2011 ²³	M	2	Atrial septal defect, atopy	Rocuronium, isoflurane
İlhan <i>et al.</i> 2013 ²⁴	M	16	Healthy	Amoxicillin clavulanate
Yaman <i>et al.</i> 2015 ²⁵	M	15	Healthy	Black widow spider bite
Terlemez <i>et al.</i> 2015 ²⁶	M	14	Allergic rhinitis	Metronidazole
Castellano-Martinez <i>et al.</i> 2018 ²⁷	M	10	Cholesteatoma, chronic abdominal pain	Atropine
Dogan 2018 ²⁸	M	17	Healthy	Branched-chain amino acid supplement

TABLE II.—*Cardiologic workup performed on reported pediatric patients with Kounis Syndrome, their cardiovascular involvement and complications.*

References	Troponin I	CK-MB	ST	Echocardiography	Coronary angiography	Allergic myocardial infarction/complications
Kounis <i>et al.</i> 2008 ²⁰	Normal	Unknown	Inverted T waves (lateral leads)	Unknown	Unknown	Unknown
Biteker <i>et al.</i> 2009 ²¹	2.1 ng/mL	30 IU/L	Elevation (inferior leads)	Abnormal	Normal	Allergic myocardial infarction
Biteker <i>et al.</i> 2009 ²²	4.3 ng/mL	342 IU/L	Elevation (inferior leads)	Abnormal	Normal	Allergic myocardial infarction
Biteker <i>et al.</i> 2009 ²²	5.0 ng/mL	780 IU/L	Elevation (anterior leads)	Abnormal	Normal	Allergic myocardial infarction
Biteker <i>et al.</i> 2009 ²²	1.1 ng/mL	42 IU/L	Elevation (inferolateral leads)	Normal	Normal	Allergic myocardial infarction
Parent <i>et al.</i> 2011 ²³	18.3 ng/mL, then 2.5 ng/mL	Unknown	First elevation, then depression	Abnormal	First coronary angiography: diffuse small dimension of right and left coronary arteries; after one month: normal coronary angiography	Allergic myocardial infarction, severe bradycardia necessitating cardiopulmonary resuscitation, pulmonary edema
İlhan <i>et al.</i> 2013 ²⁴	Unknown	Unknown	Elevation (inferolateral leads)	Normal	Normal	Unknown
Yaman <i>et al.</i> 2015 ²⁵	1.8 ng/mL (n.v. <0.04 ng/mL)	83 ng/mL (n.v. <5 ng/mL)	Depression (inferolateral leads)	Abnormal	Unknown	Allergic myocardial infarction, acute heart failure, pulmonary edema
Terlemez <i>et al.</i> 2015 ²⁶	18.05 ng/mL	36 ng/mL	Elevation (inferior leads)	Unknown	Normal	Allergic myocardial infarction
Castellano-Martinez <i>et al.</i> 2018 ²⁷	0.29 ng/mL	Unknown	Depression (inferior leads)	Normal	Unknown	Allergic myocardial infarction
Dogan 2018 ²⁸	3.3 ng/mL (n.v. 0.01 ng/mL)	45 IU/L (n.v. 0-25 IU/L)	Elevation (inferolateral leads)	Abnormal	Normal	Allergic myocardial infarction

foods, branched-chain amino acid supplement for muscle growth was reported (1/1 patient, 100.0%) (Table I).²⁰⁻²⁸

The time span between the exposure to the trigger and Kounis Syndrome initiation was not clearly described in 2/11 patients (18.2%). In the remaining patients, the clinical manifestations developed either early, less than 30 minutes in 6/9 (66.7%) patients, or later, 4-6 hours from the exposure to the trigger in 3/9 (33.3%) cases.

Regarding clinical manifestations, chest pain was recorded in 9/11 patients (81.8%). Signs and

symptoms compatible with an allergic reaction were found in 7/11 patients (63.6%).

From the diagnostic point of view, ECG abnormalities were described in 11/11 patients (100.0%). Among them, ST segment and T wave changes constituted the most common electrocardiographic alterations, including ST elevation in 7/11 patients (63.6%), ST depression in 2/11 patients (18.2%), ST elevation followed by depression in a patient (9.1%) and inverted T waves in another one (9.1%). There was no information about the territory of ischemia based on electro-

TABLE III.—Allergological workup performed on reported pediatric patients with Kounis Syndrome.

References	Serum tryptase	Allergological diagnostic workup
Kounis <i>et al.</i> 2008 ²⁰	Unknown	Unknown
Biteker <i>et al.</i> 2009 ²¹	31 mcg/L (n.v. 5.6 – 13.5 mcg/L)	IgE 45 IU/mL (n.v. 0-100 IU/mL), IgE anti-amoxicillin negative
Biteker <i>et al.</i> 2009 ²²	45 mcg/L (n.v. 5.6 – 13.5 mcg/L)	IgE 190 IU/mL (n.v. 0-100 IU/mL), intradermal skin test with bee venom positive
Biteker <i>et al.</i> 2009 ²²	42 mcg/L	IgE 780 IU/mL (n.v. 0-100 IU/mL), IgE anti-amoxicillin positive
Biteker <i>et al.</i> 2009 ²²	33 mcg/L	IgE 321 IU/mL (n.v. 0-100 IU/mL), intradermal skin test with wasp venom positive
Parent <i>et al.</i> 2011 ²³	10 ng/mL (n.v. <1 ng/mL)	IgE 152 IU/ml (n.v. <60 IU/mL)
İlhan <i>et al.</i> 2013 ²⁴	Unknown	Unknown
Yaman <i>et al.</i> 2015 ²⁵	Unknown	Unknown
Terlemez <i>et al.</i> 2015 ²⁶	Unknown	Unknown
Castellano-Martinez <i>et al.</i> 2018 ²⁷	Unknown	Unknown
Dogan 2018 ²⁸	51 mcg/L	IgE 156 IU/L (n.v. 0-100 IU/L)

graphic alterations in 1/11 patients (9.1%). In the remaining patients inferolateral, inferior, anterior and lateral leads have been involved in 4/10 (40.0%), 4/10 (40.0%), 1/10 (10.0%) and 1/10 (10.0%) of the patients, respectively.

There were no echocardiographic data available in 2/11 patients (18.2%). In the remaining patients, abnormal echocardiogram was reported in 6/9 patients (66.7%). In 4/6 patients (66.7%) with echocardiographic abnormalities, the area of ECG abnormalities matched with the area of the impaired wall motility. In the remaining cases, in 1/6 patients (16.7%) it was found a moderately decreased systolic biventricular function and in 1/6 patients (16.7%) a global left ventricular hypokinesia was reported.

No coronary angiography data were available in 3/11 patients (27.3%). In the remaining cases, either normal coronaries were present in 7/8 patients (87.5%) whereas in 1/8 patients (12.5%) diffuse, small caliber coronary arteries were described, followed by their normalization after one-month follow-up.

Laboratory workup was carried out in all but 1/11 patients (9.1%). Serum troponin I was the most requested test (9/11 patients, 81.8%; with a median value of 3.3 ng/mL, ranging from 0.3-18.3 ng/mL), followed by serum CK-MB (7/11 patients, 63.6%; 5/11 patients, 45.5%, measured as IU/L, with a median value of 45 IU/L, ranging from 30 to 780 IU/L) and serum tryptase (6/11 patients, 54.5%; with a median value of 37.5 µg/L, ranging from 10.0 to 51.0 µg/L).

Allergic myocardial infarction was evident in 9/11 patients (81.8%). Severe cardiac complications were demonstrated in 2/9 patients (22.2%): among these, 2/2 patients (100.0%) presented acute heart failure with pulmonary edema, with one of them with severe bradycardia necessitating cardiopulmonary resuscitation (Table II).²⁰⁻²⁸

There was no specific reference to allergic diagnostic workup in 5/11 patients (45.5%). In the remaining patients, serum total IgE levels were measured and among the patients with amoxicillin/clavulanic acid induced anaphylaxis, in 2/3 patients (66.7%) serum specific IgE to amoxicillin were performed, and in 1/2 patients (50.0%) proved to be positive. Among patients with stings/bites, intradermal skin test with specific venom was performed on the volar side of the forearm of 2/3 patients (66.7%) and it was considered positive because longest wheal diameter resulted greater than 5 mm after 15 minutes in all patients (2/2, 100.0%) (Table III).²⁰⁻²⁸

There were no treatment data available in 3/11 patients (27.3%). In the remaining patients, 6/8 (75.0%) received a treatment with antihistamines. Among these, 5/6 patients (83.3%) received a combined treatment with corticosteroids and 1/6 patients (16.7%) was treated with mast-cell stabilizers. In the remaining patients, 2/8 (25.0%) were treated with cardiovascular drugs such as vasodilators, ACE-inhibitors, beta blockers, calcium-channel blockers, diuretics and aspirin as well as morphine.

Discussion

Kounis Syndrome is considered a rare clinical entity, especially in pediatrics. However, even if the number of case reports across the world is quickly rising, it still rarely diagnosed and still underestimated.¹⁶⁻¹⁹ Southern Europe, particularly Spain, Italy, Greece, Turkey, are the countries where Kounis Syndrome has mostly been encountered. We suppose that climate and environmental conditions, pollen cross reactions, Hymenoptera exposures, snake bites, overconsumption of medicines, or inadequacy of preventive measures and increased awareness among physicians about the existence of Kounis Syndrome are some factors that possibly contribute to this variation. To the best of our knowledge, our review is the first that tried to elucidate Kounis Syndrome clinical aspects in children, further revealing some specific characteristics.

Kounis Syndrome presents more commonly in male children with age of 12 years old, in the absence of concomitant atopic disease or atopy. Drugs were acknowledged as the most frequent trigger, especially antibiotics and specifically amoxicillin/clavulanic acid. In the majority of patients, the clinical signs and symptoms were acute, in less than 30 minutes, manifesting most commonly as chest pain and signs/symptoms compatible with an allergic reaction. From the electrocardiographic point of view, ST-T changes were reported as the most frequent alterations, especially the ST elevation. The patients most frequently demonstrated abnormal echocardiogram and allergic myocardial infarction, while coronary angiography was negative in all but one of the patients, presenting a decreased dimension of left and right coronary system and the most severe complications. Despite the lack of data regarding long-term outcomes, except

from some isolated cases, the prognosis seems favorable, even if an intensive treatment in the acute phase may be necessary. Regarding laboratory workup, serum troponin I, followed by serum CK-MB and serum tryptase were mainly requested. No specific diagnostic allergic workup was performed in most cases, while there was not standardized in others, rendering unclear its clinical meaning. Antihistamines were the most used drugs.

A balanced approach for the management of both the allergic reaction and cardiovascular involvement in pediatric Kounis Syndrome appears difficult to obtain. In fact, most of the strategies proposed in the literature in the area are based on a few case reports. For this reason, randomized clinical trials are urgently needed to increase concerning the appropriate standard management of this clinical entity. Furthermore, a deeper knowledge of molecular mechanisms underlying Kounis Syndrome appears to be of critical importance, together with the development of novel tests for its diagnosis. Data focused on the allergological workup in Kounis Syndrome are lacking. However, the latter and a joint cardiological workup seem of critical importance to evaluate the patient's cardiac structural and functional status, cardiovascular risk factors as well as the potential triggers of the allergic reaction, in order to prevent Kounis Syndrome events in the pediatric population.²⁹

Conclusions

Three variants of Kounis Syndrome were described in the literature: type 1 referred to allergic vasospastic angina due to endothelial dysfunction⁵ causes, type 2 referred to allergic myocardial infarction and type 3 known as allergic stent thrombosis with an occluding thrombus (subtype a) or stent restenosis (subtype b).^{1, 6}

TABLE IV.—*Proposal for a novel classification for pediatric Kounis Syndrome.*

KS	Angiographic classification	Clinical classification
Type 1	Patients with normal or nearly normal coronary artery	With/without allergic myocardial infarction
Type 2	Patients with pre-existing atheromatous disease	With/without allergic myocardial infarction
Type 3	Patients with allergic stent thrombosis with an occluding thrombus (subtype a) or stent restenosis (subtype b)	With/without allergic myocardial infarction
Type 4	Patients with coronary grafts	With/without allergic myocardial infarction

However, data from the literature demonstrated that Kounis Syndrome may also occur in patients with coronary grafts.^{30, 31} Thus, these patients should be acknowledged as suffering from Kounis Syndrome type 4, also according to a criterion based on progression of the coronary damage from healthy vessels to the presence of stents or grafts (Table IV). There were no published case reports with characteristics compatible with Kounis Syndrome type 3 or 4, in pediatric patients, fact that was reasonable as need for a coronary stent or graft is rare in children.

As abovementioned, a criterion regarding the anatomy of the coronaries, pointed out by the coronarography, is the most important feature in pointing out the difference between different types of Kounis Syndrome, especially for the first two. Specifically, type 1 includes patients with normal or nearly normal coronary artery and their clinical manifestations may range from allergic vasospastic angina to allergic myocardial infarction, in case of progression of coronary artery spasm. On the other side, type 2 includes patients with pre-existing atheromatous disease and their clinical manifestations may range from allergic myocardial infarction to allergic vasospastic angina, in case of absence of plaque erosion or rupture.³² Furthermore, the latter considerations seem to apply also for Kounis Syndrome type 3 and 4.

Thus, the presence of the absence of allergic myocardial infarction, even if connected to the angiographic classification of Kounis Syndrome, appears to be a parallel feature of this clinical entity. This fact seems particularly evident for the patients in pediatric age, who most frequently demonstrated abnormal echocardiogram and allergic myocardial infarction, while coronary angiography was negative in all but one of the patients. Therefore, basing on the data of this analysis, a new clinical classification for Kounis Syndrome is proposed, focusing mainly in the presence or the absence of allergic myocardial infarction, as the central clinical feature for the stratification of the patients' clinical manifestations (Table IV). This novel approach appears to be imperative for pediatric patients, in which coronarography is less frequently performed, but it is valid also for adult patients.

Moreover, the latter new clinical classification may represent an useful resource to simplify the understanding of Kounis Syndrome across all ages, especially before the performance of coronarography.

References

1. Kounis NG. Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. *Clin Chem Lab Med* 2016;54:1545–59.
2. Abdelghany M, Subedi R, Shah S, Kozman H. Kounis syndrome: A review article on epidemiology, diagnostic findings, management and complications of allergic acute coronary syndrome. *Int J Cardiol* 2017;232:1–4.
3. Goto M, Matsuzaki M, Fuchinoue A, Urabe N, Kawagoe N, Takemoto I, *et al.* Chronic atherosclerotic mesenteric ischemia that started to develop symptoms just after anaphylaxis. *Case Rep Gastroenterol* 2012;6:300–8.
4. González-de-Olano D, Alvarez-Twose I, Matito A, Sánchez-Muñoz L, Kounis NG, Escribano L. Mast cell activation disorders presenting with cerebral vasospasm-related symptoms: a “Kounis-like” syndrome? *Int J Cardiol* 2011;150:210–1.
5. Kounis NG, Koniari I, Soufras GD, Tsigkas G, Chourdakis E, Despotopoulos S, *et al.* Kounis syndrome: an additional etiologic factor of myocardial infarction with non-obstructive coronary arteries. *Cardiol J* 2018;25:648–9.
6. Itoh T, Nakajima Y, Morino Y, Kounis NG. Kounis syndrome: new classification. *Int J Cardiol* 2018;256:11.
7. Wadsworth GM, Brown CH. Serum reaction complicated by acute carditis. *J Pediatr* 1940;17:801–5.
8. Rich AR, Gregory JE. Experimental evidence that lesions with basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. *Bull Johns Hopkins Hosp* 1943;73:239–64.
9. Clark E. Serum carditis: morphologic cardiac alterations in man associated with serum disease. *J Am Med Assoc* 1938;110:1098–100.
10. Kounis NG, Zavras GM. Histamine-induced coronary artery spasm: the concept of allergic angina. *Br J Clin Pract* 1991;45:121–8.
11. Rich MW. Is vasospastic angina an inflammatory disease? *Am J Cardiol* 2005;96:1612.
12. Pfister CW, Plice SG. Acute myocardial infarction during a prolonged allergic reaction to penicillin. *Am Heart J* 1950;40:945–7.
13. Braunwald E. Unstable angina: an etiologic approach to management. *Circulation* 1998;98:2219–22.
14. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol* 2006;110:7–14.
15. Biteker M, Duran NE, Biteker FS, Civan HA, Kaya H, Gökdeniz T, *et al.* Allergic myocardial infarction in childhood: kounis syndrome. *Eur J Pediatr* 2010;169:27–9.
16. Desai R, Parekh T, Patel U, Fong HK, Samani S, Patel C, *et al.* Epidemiology of acute coronary syndrome co-existent with allergic/hypersensitivity/anaphylactic reactions (Kounis syndrome) in the United States: A nationwide inpatient analysis. *Int J Cardiol* 2019;292:35–8.
17. Renda F, Landoni G, Trotta F, Piras D, Finco G, Felicetti

P, *et al.* Kounis Syndrome: an analysis of spontaneous reports from international pharmacovigilance database. *Int J Cardiol* 2016;203:217–20.

18. Aköz A, Tanboga HI, Emet M, *et al.* A prospective study of Kounis Syndrome: clinical experience and cardiac magnetic resonance imaging findings for 21 patients. *Acta Med Mediter* 2013;9:811–6.

19. Kounis NG, Mazarakis A, Tsigkas G, Giannopoulos S, Goudevenos J. Kounis syndrome: a new twist on an old disease. *Future Cardiol* 2011;7:805–24.

20. Kounis GN, Kouni SA, Hahalis G, Kounis NG. Mesalamine hypersensitivity and Kounis syndrome in a pediatric ulcerative colitis patient. *World J Gastroenterol* 2008;14:7141–2.

21. Biteker M, Duran NE, Biteker FS, Ertürk E, Aykan AC, Civan HA, *et al.* Kounis syndrome secondary to amoxicillin/clavulanic acid use in a child. *Int J Cardiol* 2009;136:e3–5.

22. Biteker M, Duran NE, Biteker F, Civan HA, Gündüz S, Gökdeniz T, *et al.* Kounis syndrome: first series in Turkish patients. *Anadolu Kardiyol Derg* 2009;9:59–60.

23. Parent B, Wearden P, Kounis NG, Chrysostomou C. Kounis syndrome or allergic coronary vasospasm in a two-year-old. *Congenit Heart Dis* 2011;6:499–503.

24. İlhan E, Akbulut T, Gürsürer M. An underdiagnosed syndrome; Kounis syndrome secondary to amoxicillin/clavulanic acid use in a 16 year-old child. *Int J Cardiol* 2013;167:e90–1.

25. Yaman M, Mete T, Ozer I, Yaman E, Beton O. Reversible

Myocarditis and Pericarditis after Black Widow Spider Bite or Kounis Syndrome? *Case Rep Cardiol* 2015;2015:768089.

26. Terlemez S, Eryılmaz U, Tokgöz Y, Uysal P, Coşan A, Bulut Y. Kounis syndrome caused by metronidazole—a case of 14 year-old boy. *Int J Cardiol* 2015;179:222–4.

27. Castellano-Martinez A, Rodriguez-Gonzalez M. Coronary artery spasm due to intravenous atropine infusion in a child: possible Kounis syndrome. *Cardiol Young* 2018;28:616–8.

28. Dogan V. A case of Kounis syndrome associated with branched-chain amino acid supplementation in a 17-year-old boy. *Cardiol Young* 2018;28:1165–7.

29. Giovannini M, Koniari I, Mori F, Ricci S, De Simone L, Favilli S, *et al.* Kounis syndrome: a clinical entity penetrating from pediatrics to geriatrics. *J Geriatr Cardiol* 2020;17:294–9.

30. Kounis NG, Koniari I, Velissaris D, Tzanis G, Hahalis G. Kounis Syndrome—not a Single-organ Arterial Disorder but a Multisystem and Multidisciplinary Disease. *Balkan Med J* 2019;36:212–21.

31. Dazy K, Walters D, Holland C, Baldwin J. Anaphylaxis mediated myocardial infarction in a coronary graft: a new variant of Kounis syndrome (a case report). *Int J Cardiol* 2013;168:e84–5.

32. Kounis NG, Cervellin G, Koniari I, Bonfanti L, Dousdampanis P, Charokopos N, *et al.* Anaphylactic cardiovascular collapse and Kounis syndrome: systemic vasodilation or coronary vasoconstriction? *Ann Transl Med* 2018;6:332.

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