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EDITORIAL

Adapting HUVAC Vasculitis Registry to a Country-wide online registry system: Turkish Vasculitis Study Group Prospective Database, TRVaS

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Vasculitides are relatively rare diseases that can affect various organ and tissue systems. Vasculitides can lead to mortality as well as various morbidities. Collaboration with various departments is crucial in the diagnosis, differential diagnosis, and management of the disease. Primary vasculitides, as defined in the Chapel Hill Consensus, are primarily characterized by vasculitides involving large, medium, and small vessels, along with specific subtypes. Additionally, primary vasculitides may exhibit varying patterns of involvement based on different characteristics such as geographic regions, ethnicity, and gender. For example, in the Far East, ANCA-associated vasculitides are frequently seen in the form of microscopic polyangiitis, whereas in our region and Northern Europe, granulomatous polyangiitis is more common. Furthermore, the types and frequencies of vasculitides in childhood and adulthood can differ.

It is evident that, as vasculitides are classified as rare diseases, retrospective data will be limited in determining their epidemiological basics, diagnosis, treatment, and courses. Prospective patient registry systems can provide more comprehensive and descriptive data. In this regard, aiming to increase collaboration among departments in the diagnosis, follow-up, and treatment of vasculitis patients and to establish effective representation and partnerships on national and international platforms through a regular registration system, the Hacettepe University Vasculitis Research Centre (HUVAC) was established in May 2014, and prospective patient registration commenced. The period leading up to the establishment of our center has been discussed in the context of our ANCA-associated vasculitides Workshop volume [1].

HUVAC patient records have provided one of the first significant epidemiological data for our region. The differences in the distribution of vasculitides between childhood and adulthood have been updated as the number of patients has increased. Figure 1 presents the diagnosis and frequency distribution of 2046 adult and 536 pediatric vasculitis patients registered at our center as of June 2023.

Another important point to highlight is the involvement characteristics of the same vasculitides may vary between children and adults. In a study conducted at our center, evaluating 88 adult and 330 pediatric IgA vasculitis cases, spondyloarthritis was only observed in the adult group. At the same time, relapses were more common in pediatric patients. Most pediatric patients did not require additional treatment, whereas more than half of the adults required immunosuppressive therapy. Additionally, this study is the first to examine the use of biological therapy in IgA vasculitis [2].

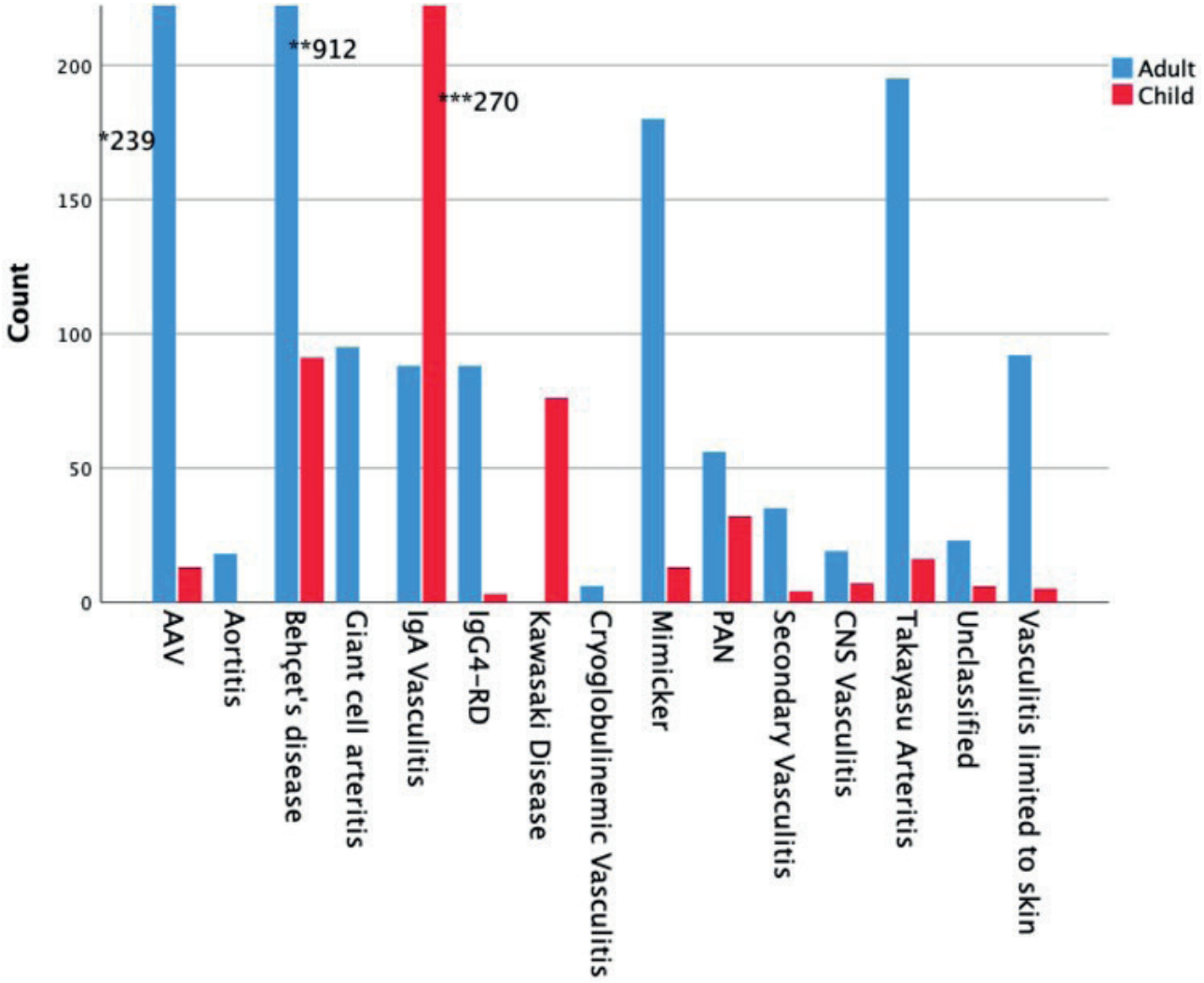

Figure 1. As of June 2023, the distribution of adult and pediatric patients registered in our HUVAC database center.
*n=239 for adult patients with AAV, ** n=912 for adult patients with Behçet's disease, ***n=270 for child patients with IgA vasculitis

In addition to the development of research and projects to track and discuss the current vasculitis literature and to raise awareness about vasculitis, an annual Vasculitis workshop has been organized since 2017. In the COVID era, an online workshop was held in 2020 on ANCA-associated vasculitides. The following year, focusing on Giant Cell Arteritis and Polymyalgia Rheumatica, took place in 2021 in a face-to-face format. Speech summaries and papers from both workshops have been published in the Acta Medica journal [3,4]. Based on the high level of interest and positive feedback received for both workshops, in 2022, a workshop titled 'Chapel Hill Consensus Conference on Less Talked Vasculitides: What Are They? What Are They Not? Real-Life Case Examples' was organized, focusing on vasculitides classified under the 'Rarely Seen Vasculitides' category in the Chapel Hill classification.

Thanks to the increasing prevalence of web-based platforms in our lives during the pandemic, starting from the end of 2020, HUVAC has transitioned to a web-based infrastructure for patient records through a protocol established with Vanderbilt University [5]. While the HUVAC registry continues to evolve, it does have some limitations. Hacettepe University, due to its location and nature, receives referral patients from various regions of Turkey. It is known that the involvement and disease course of the patients who apply for treatment are more severe. Therefore, data obtained from a single center may overlook the milder cases of vasculitides, which represent a heterogeneous patient group.

Therefore, in order to comprehensively and in greater detail investigate Turkey as a country where reflections of Eastern Mediterranean populations

can be observed in the perspective of vasculitis, data of vasculitis patients and mimickers seen in Internal Medicine and Rheumatology clinics in different cities were collected through a web-based RedCap system under the umbrella of the Turkey Vasculitis Study Group (TRVaS) after obtaining necessary approvals and system definitions. The project began with an inventory page for all vasculitis types in 2021, involving six centers. By 2022, TRVaS expanded to include 23 centers, including pediatric rheumatology clinics.

In the current system, patients diagnosed with any vasculitis can be registered in the system. An inventory form is filled out for these patients, which includes demographic information, information related to vasculitis diagnosis (vasculitis type, diagnosis date, affected organ/system, genetic and histopathological examinations, serological markers in some vasculitides, treatments used until the registration date), and data regarding comorbidities. Additionally, there is a disease-specific form for ANCA-associated vasculitides.

In addition to routine patient records, project proposals created by researchers are evaluated by the steering committee. Forms specific to approved projects are generated, and centers are invited for data entry.

In last two years, several disease-specific and disease-based project forms were added to the TRVaS database. Herein, we will provide the novelties in the TRVaS database.

1. AAV disease-specific form

There is a form specific to AAV on the TRVaS database, which was created to record the basic characteristics and information of patients diagnosed with ANCA-associated vasculitis. This form is open for data entry of all centers. In this form, data is collected under the following headings: demographic characteristics such as age, gender, and date of birth; anthropometric measurements; habits such as smoking, alcohol; AAV-specific variables such as AAV type, date of diagnosis, date of symptom onset, antibody status, organ involvement at presentation and during the course, activity and damage indices, immunosuppressives used in remission and maintenance, and relapse status; accompanying comorbidities. It is planned to collect longitudinal data by introducing the visit form by the end of this year.

2. AAV Project forms

2.1. External validation of DCVAS ANCA vasculitis criteria

A separate form was created for the external validation of the classification criteria developed by the DCVAS group specifically for ANCA-associated vasculitides. Preliminary data from this project were presented at the 2023 EULAR Congress. In this study, which included a total of 820 AAV, 47 PAN, and 76 IgA vasculitis patients, using 2022 ACR/EULAR Classification Criteria, improved sensitivity and specificity for GPA and sensitivity for EGPA were observed. Additionally, half of the unclassified AAV patients could be classified as either GPA or MPA. These criteria functioned well for the discrimination of patients with AAV from other small/medium vessel vasculitides such as PAN and IgA vasculitis. In total, over 80% of the patients with AAV were accordingly classified parallel to the clinical diagnosis in each GPA/EGPA/MPA group [6]. The final data of the study are in the publication phase.

2.2. Metabolic Syndrome among patients with AAV

This form was opened within the scope of the "Multicentre Study of the Prevalence of Metabolic Syndrome in Patients with ANCA-Associated Vasculitis (AAV)". Many recent studies have emphasized the increased cardiovascular disease (CVD) risk in AAV patients [7,8]. While most AAV patients develop hypertension, diabetes mellitus and dyslipidemia, the mechanisms of accelerated atherosclerosis in AAV patients are not fully understood. Vascular inflammation, arterial wall injury and immunosuppressive drugs may contribute to the acceleration of atherosclerosis [9]. Metabolic syndrome (Met S) is a cluster of CV risk factors, including insulin resistance syndrome, obesity, hyperglycemia,

hypertension, hypertriglyceridemia and low HDL, and is associated with an increased risk for CVD and type 2 diabetes mellitus [10]. To date, there are limited data on Met S and related factors in patients diagnosed with AAV [11]. In a study conducted at Marmara University, 37 patients diagnosed with AAV were investigated and it was observed that the frequency of metabolic syndrome increased in patients with AAV [12]. Based on this study, it is planned to initiate a study involving the Vasculitis Centres that have come together within the Turkish Vasculitis Database (TRVaS), which aims to evaluate AAV patients in Turkey in a multicentre manner. With this multicentre study including a larger number of patients, it is aimed to investigate the frequency of Met S in AAV patients and to examine the link between clinical and laboratory parameters of AAV and Met S to reveal the effect of Met S in the etiology of CVD occurring in AAV patients.

2.3. Identification of Osteoporosis in AAV

It has been shown that the frequency of osteoporosis and osteopenia increases in AAV patients [13]. Chronic inflammation is present in AAV patients and pulse steroid treatment can be used in induction and followed by maintenance steroid treatment [14-16]. The AAV-osteoporosis association may be explained using immunosuppressive therapies, especially glucocorticoids, or directly by inflammation or impaired renal function [17]. It is predicted that the development of osteoporosis may be accelerated by various factors such as these in AAV patients. In our country, a small-scale study examining FRAX score in AAV patients was conducted and it was shown that the risk of fracture increased compared to healthy controls [18]. This study was designed as a retrospective study on adult AAV patients in TRVaS to determine the prevalence and predictive factors of osteoporosis in AAV patients in Turkey. Early data will be discussed at the National Rheumatology Congress in 2023.

2.4. Venous thromboembolism in AAV

There are reports suggesting that venous thromboembolism (VTE) may be a disease involvement or AAV may be a predisposing factor for VTE [19-26]. In the RAVE study conducted in 2019, VTE was detected in 16/197 patients showing, presence of pulmonary hemorrhage, PR3-ANCA positivity, cardiac involvement and presence of erythrocyte silica in urine as risk factors for VTE in AAV patients in multivariate analysis [24]. In another study, the incidence of VTE was calculated as 2.4/100 patient-years [25]. They reported that the incidence of VTE was highest in the first 3 months following diagnosis (20.4/100 patient-years, 95% CI 11.5-29.4), 8.9/100 patient-years (95% CI 0.2-17.6) in 4-6 months, and 1.5/100 (95% CI 0.0-3.5) in 7-12 months. In this study, disease activity and age were reported to be risk factors for AAV-related VTE [25]. In this project, aim is to determine the frequency of all VTE events and subgroups in the cohort of Turkish patients with AAV and to determine the factors associated with VTE development, if any. We also planned to investigate whether there is a difference in AAV subgroups.

2.5. The translation of the AAV-PRO Patient-Reported Outcome Measure into Turkish and its validity and reliability in Turkish translation

In 2018, the AAV- Patient-Reported Outcome (PRO) measures questionnaire, developed by the University of Oxford, which assesses the quality of life of patients with ANCA-associated vasculitis in six subdomains, was translated into Turkish. The Turkish version of this questionnaire can be accessed through this link [27]. Hacettepe University, Gazi University, and İzmir Katip Çelebi University, as data providers for TRVaS, are collaborating on a validity and reliability study of the Turkish version of the AAV-PRO questionnaire. The preliminary data of the study were presented at the 2022 National Rheumatology Congress and the 20th International Vasculitis and ANCA Workshop [28].

3. IgG4 related disease form

In 2022, a form was created for IgG4-related disease, recording disease-related and treatment-related characteristics. This form focuses on both the classification criteria for IgG4-related disease and the IgG4-related Disease Responder Index, and relevant variables are recorded. The initial data for this data form, which includes both adult and pediatric patients, will be discussed at the 2023 National Rheumatology Congress.

4. IgA vasculitis disease specific form

IgA vasculitis (previously known as Henoch Schönlein purpura) is the most common primary systemic vasculitis in childhood. The estimated incidence is 3-26.7 per 100,000 cases [29-31]. It is a small vessel vasculitis characterized by IgA immune deposits in the skin, gastrointestinal tract, and kidney and arthritis/arthralgia. Early recognition of the disease and initiation of correct and effective treatment is important. A study to be conducted in our country on the evaluation of patients diagnosed with IgA vasculitis in childhood and adults (when the patients were diagnosed, clinical course, laboratory data, biopsies if available, presence of comorbidities, and treatment) will increase the knowledge of physicians about the general characteristics of the disease and its distribution according to age, contribute to the determination of the prognostic factors of the disease, and shape the algorithm to be followed in the follow-up of patients. For this purpose, the study group is still working on IgA vasculitis form and planning to open the page by the end of this year.

a. Future Prospects

TRVAS has been invited to join FAIRVASC, a research project of the European Vasculitis Society (EUVAS) and the RITA European Reference Network. Major national registries include the Irish Rare Kidney Disease Registry, the UKIVAS Registry, the French Vasculitis Study Group Registry, the Czech Vasculitis Registry, the Polish Vasculitis Registry POLVAS, the new German/Austrian/Swiss GEVAS Registry, and the Swedish Skåne Vasculitis Inception Cohort, all partners in FAIRVASC. FAIRVASC uses the same data coding system as TRVas and after a bureaucratic procedure TRVaS is soon planned to join FAIRVASC. More information can be found on this website: https://fairvasc.eu.

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