

Journey of Vasculitis at Hacettepe University: from the Establishment of University to the Hacettepe AAV Workshop, 2020

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Hacettepe University is located in the capital city of Turkey, Ankara. The foundation stone of the university was laid in 1957 with the Child Health Institute and Hospital within Hacettepe, which began its training, education and research activities and public services in 1958 [1]. Hacettepe Science Center was established in 1965 in order to enable the coordination between the academic units within the university.

Professor Muharrem Koksall was the first pathologist and founder of Hacettepe University Department of Pathology [2]. Even the most popular paper of Koksall was published in Nature with topic of extraction of a heparin-like substance from mast cell granules in mouse connective tissue, [3] his case report with post mortem control describing aneurysm of the lower branch of the left pulmonary artery could be accepted as one of the first papers of Hacettepe team regarding vascular pathologies in English literature [4].

Although the first establishment was as Child Hospital, under the leadership of Professor M.Seref Zileli, adolescent and adult patients started to be evaluated around 1965's. Integrated educational systems in Medicine, increasing practical interventions (internship) and awareness of public health were the descriptive differences of Hacettepe University Faculty of Medicine [5]. Multidisciplinary management and clinicopathological conferences were the mostly reflection of integrated systems. A pathologically confirmed Good-pasture syndrome case is can be given as an example of this multidisciplinary management [6].

Pathology department was first established as a unit of Ankara University Doğramacı Pediatric Health Institute in 1958. Its official establishment in Hacettepe University was by Muharrem Köksall in 1963. Formalin fixed paraffin embedded tissues have been archived since 1958. Ever since, tissues taken from the patients with the clinical diagnosis of vasculitis are morphologically addressed for the features of inflammation of vessels according to diameter of the vessel and/or type of inflammatory reaction. Universally accepted specific diagnostic histologic features are sought and each diagnostic category is named according to the updated classification of vasculitides. Clinical features like the organ of involvement are complementary information leading to the specific diagnoses. Electron microscopy or immunohistochemistry are not the principal methods used since vasculitis is a morphological diagnosis.

Meral Calguneri established Rheumatology Department at 1990's. after her Rheumatology fellowship at Leeds University. As the most prevalent vasculitis in Turkey, Behcet's syndrome is the mostly studied and published vasculitidis at Hacettepe. One of the pioneer papers regarding vascular involvement in BS is from Behcet study group of Hacettepe, already has over 400 citations [7]. Major step of addition of benzatin penicilline for Behcet treatment has been based on studies from Hacettepe [8,9]. Besides, unique contributions regarding the Interferon-alpha treatment for FMF-PAN patients, treatment schema for granulomatosis polyangiitis, clinical and genetic aspects of Takayasu arteritis can be counted as achievements of Hacettepe [10-19].

Pediatric Vasculitis patients were initially followed in the Department of Pediatric Nephrology where we used to care for both nephrology and rheumatology patients. Based on a large international registry of over 1500 children with vasculitis we have developed the Ankara 2008 Criteria for the Classification of Childhood Vasculitidis, endorsed by EULAR, PRoS and PRINTO(20). Since their publication all pediatric literature has used these criteria. In 2014 the two departments split. Subsequently the Pediatric Rheumatology department became a main reference center for vasculitis in the country.

Our group had more PAN cases, which partly might have been due to the cases of DADA2(21). DADA2 was defined in 2014 with also inclusion of our adult and pediatric patients 21 and some cases were probably misdiagnosed before that date. Pediatrics team took part in developing the recommendations for the management and treatment for pediatric vasculitides with the international "SHARE" initiative, supported by an European grant. We also took part in developing criteria for pediatric Behçet disease.

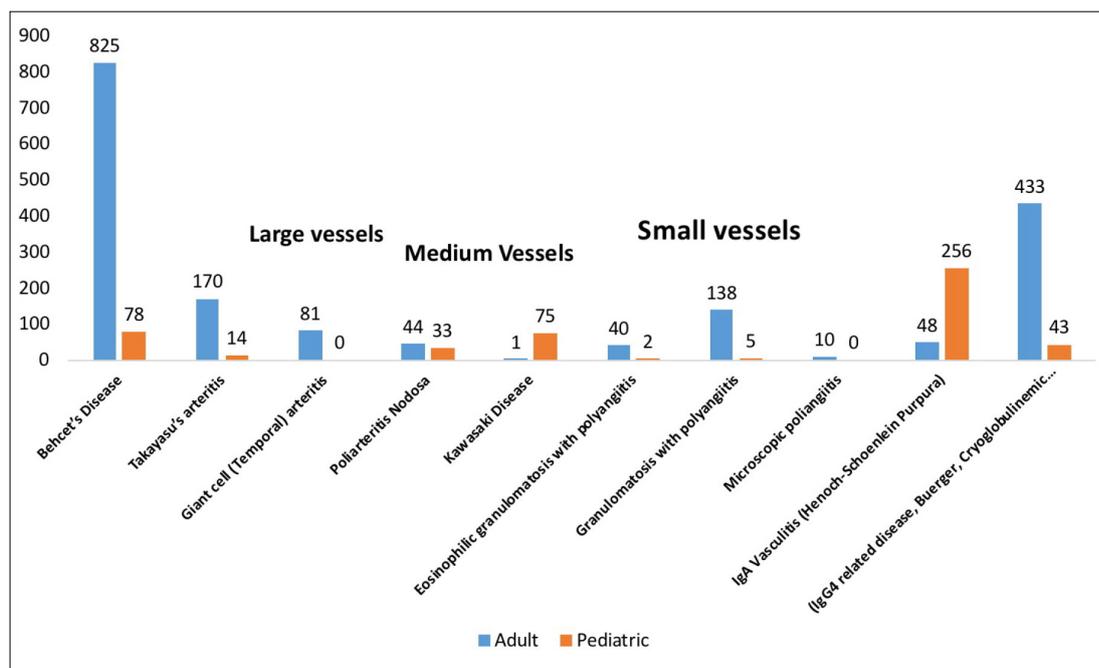


Figure: Distribution of adult and pediatric patients with vasculitis registered to HUVAC by the middle of 2020.

In 2014, with the collaboration of 14 different Departments and Division, Hacettepe University Vasculitis Research Centre (HUVAC) was established officially [22]. The aims of this center are to strengthen interdisciplinary collaboration, to establish a national/international database, to produce and present our experience on international platforms and to raise the awareness of public community about vasculitis. In the figure, the distribution of adult and pediatric patients with vasculitis registered to HUVAC by June 2020.

Several studies have already been published under the umbrella of HUVAC in the topics such as Behcet's syndrome, polyarteritis nodosa and IgG4-related disease [23-28]. One of the fruitful advantages of this collaboration is comparisons of adult patients with pediatric patients in terms of PAN, IgA vasculitis and Takayasu arteritis [28,29].

With the first one was done in 2017, every year we have organized workshops on the topic of vasculitis activity and damage scores. With the experiences from these workshops, we have published our book named 'Disease Activity and Damage Indexes in Primary Vasculitides & Exercise with Sample Cases'. Due to pandemic, we have done our first workshop on ANCA-Associated vasculitis, online. Last year, we have decided to move our prospective database to a web-based system. As a part of the RedCAP online system, we will continue to gather data and collaborate online with the aid of this system [30].

As for future plans, we have plenty of current and future collaborations and projects ongoing with several national/international research groups such as TRVaS, DCVAS, EUVAS, VCRC, V-Preg. Further information is available on our web-site [31]. Active translational research is carried out in our newly established "pediatric rheumatology lab" and with collaborations with our colleagues. We (including our fellows) are currently members for the working groups on vasculitis nationally and internationally.

References

1. <https://hacettepe.edu.tr/english/hakkinda/tarihce> (Access Date 17.01.2021)
2. Usbutun A, Gedikoglu G. Turk J Pathology 2007;23(2):68-73
3. Koksall M. Extraction of a heparin-like substance from mast cell granules in mouse connective tissue Nature 1953;172(4381):733-4.
4. Koksall M. Aneurysm of the lower branch of the left pulmonary artery, case report with, post-mortem control Minerva Med 1956;47(53):24-6.
5. Ruacan Ş. Türk tıbbında Hacettepe'nin yeri. Sağlık ve Toplum 1990; (3):36-37.
6. Ozsoylu S, Hicsonmez G, Berkel I, Say B, Tinaztepe B. Goodpasture's syndrome (pulmonary hemosiderosis with nephritis). Clin Pediatr (Phila). 1976;15(4):358-60.

7. Koc Y, Gullu I, Akpek G; et al. Vascular Involvement In Behcet's Disease. *Journal of Rheumatology*, 19 (3): 4 02-410
8. The effect of prophylactic penicillin treatment on the course of arthritis episodes in patients with Behçet's disease. A randomized clinical trial. Calgüneri M, Kiraz S, Ertenli I, Benekli M, Karaarslan Y, Celik I. *Arthritis Rheum*. 1996;39(12):2062-5.
9. Budd-Chiari syndrome: a common complication of Behçet's disease. Bayraktar Y, Balkanci F, Bayraktar M, Calguneri M. *Am J Gastroenterol*. 1997;92(5):858-62.
10. Polyarteritis nodosa in patients with Familial Mediterranean Fever (FMF): a concomitant disease or a feature of FMF? Ozen S, Ben-Chetrit E, Bakkaloglu A, Gur H, Tinaztepe K, Calguneri M, Turgan C, Turkmen A, Akpolat I, Danaci M, Besbas N, Akpolat T. *Semin Arthritis Rheum*. 2001;30(4):281-7.
11. Pathological haemostasis and "prothrombotic state" in Behçet's disease. Kiraz S, Ertenli I, Oztürk MA, Haznedaroğlu IC, Celik I, Calgüneri M. *Thromb Res*. 2002;105(2):125-33.
12. Effects of interferon alpha treatment on the clinical course of refractory Behçet's disease: an open study. Calgüneri M, Oztürk MA, Ertenli I, Kiraz S, Apraş S, Ozbalkan Z. *Ann Rheum Dis*. 2003;62(5):492-3.
13. Decreased protein Z concentrations complicating the hypercoagulable state of Behçet's disease. Oztürk MA, Ozbalkan Z, Onat AM, Ertenli I, Kiraz S, Aytemir K, Ureten K, Abali G, Calgüneri M, Kirazli S, Haznedaroğlu IC. *Clin Appl Thromb Hemost*. 2003;9(3):259-63.
14. Takayasu's arteritis: results of a university hospital of 45 patients in Turkey. Ureten K, Oztürk MA, Onat AM, Oztürk MH, Ozbalkan Z, Güvener M, Kiraz S, Ertenli I, Calgüneri M. *Int J Cardiol*. 2004;96(2):259-64.
15. The efficacy of interferon-alpha in a patient with resistant familial Mediterranean fever complicated by polyarteritis nodosa. Calguneri M, Apras S, Ozbalkan Z, Ozturk MA. *Intern Med*. 2004;43(7):612-4.
16. Transverse myelitis in a patient with Behcet's disease: favorable outcome with a combination of interferon-alpha. Calguneri M, Onat AM, Oztürk MA, Ozçakar L, Ureten K, Akdogan A, Ertenli I, Kiraz S. *Clin Rheumatol*. 2005;24(1):64-6.
17. Wegener's granulomatosis: clinical and laboratory results of a university hospital study of 20 patients from Turkey. Ozbalkan Z, Kiraz S, Ozturk MA, Ertenli AI, Apras S, Calguneri M. *Clin Rheumatol*. 2006;25(3):358-63.
18. Takayasu arteritis in Turkey. Bicakcigil M, Aksu K, Kamali S, Ozbalkan Z, Ates A, Karadag O, Ozer HT, Seyahi E, Akar S, Onen F, Cefle A, Aydin SZ, Yilmaz N, Onat AM, Cobankara V, Tunc E, Ozturk MA, Fresko I, Karaaslan Y, Akkoc N, Yücel AE, Kiraz S, Keser G, Inanc M, Direskeneli H. *Clin Exp Rheumatol*. 2009;27(1 Suppl 52):S59-64.
19. Polyarteritis nodosa revisited: a review of historical approaches, subphenotypes and a research agenda. Karadag O, Jayne DJ. *Clin Exp Rheumatol*. 2018;36 Suppl 111(2):135-142.
20. Vasculitis: do we know more to classify better? Batu ED, Ozen S. *Pediatric Nephrology* 2015 (30): 1425-32
21. Early-onset stroke and vasculopathy associated with mutations in ADA2. Zhou Q, Yang D, Ombrello AK, Zavialov AV, Toro C, Zavialov AV, Stone DL, Chae JJ, Rosenzweig SD, Bishop K, Barron KS, Kuehn HS, Hoffmann P, Negro A, Tsai WL, Cowen EW, Pei W, Milner JD, Silvin C, Heller T, Chin DT, Patronas NJ, Barber JS, Lee CC, Wood GM, Ling A, Kelly SJ, Kleiner DE, Mullikin JC, Ganson NJ, Kong HH, Hambleton S, Candotti F, Quezado MM, Calvo KR, Alao H, Barham BK, Jones A, Meschia JF, Worrall BB, Kasner SE, Rich SS, Goldbach-Mansky R, Abinun M, Chalom E, Gotte AC, Punaro M, Pascual V, Verbsky JW, Torgerson TR, Singer NG, Gershon TR, Ozen S, Karadag O, Fleisher TA, Remmers EF, Burgess SM, Moir SL, Gadina M, Sood R, Hershfield MS, Boehm M, Kastner DL, Aksentijevich I. *N Engl J Med*. 2014;370(10):911-20.
22. <http://www.vaskulit.hacettepe.edu.tr/yonetmelik.pdf> (Access Date 22.01.2021)
23. A retrospective study comparing the phenotype and outcomes of patients with polyarteritis nodosa between UK and Turkish cohorts. Karadag O, Erden A, Bilginer Y, Gopaluni S, Sari A, Armagan B, Ertenli I, Ozen S, Jayne D. *Rheumatol Int*. 2018;38(10):1833-1840.
24. Clinical features and disease course of neurological involvement in Behçet's disease: HUVAC experience. Bolek EC, Sari A, Kilic L, Kalyoncu U, Kurne A, Oguz KK, Topcuoglu MA, Ertenli I, Karadag O. *Mult Scler Relat Disord*. 2020;38:101512.
25. Histopathological subgrouping versus renal risk score for the prediction of end-stage renal disease in ANCA-associated vasculitis. Gercik O, Bilgin E, Solmaz D, Cakalagaoglu F, Saglam A, Aybi O, Kardas RC, Soypacaci Z, Kabadayi G, Yildirim T, Kurut Aysin I, Karadag O, Akar S. *Ann Rheum Dis*. 2020;79(5):675-676.
26. Management of Behçet's syndrome. Karadag O, Bolek EC. *Rheumatology (Oxford)*. 2020;59(Suppl 3):iii108-iii117.
27. Cryoglobulinemic vasculitis: having giant steps; but there are still unanswered questions. Karadag O, Duran E. *Intern Emerg Med*. 2021;16(1):33-35.
28. Is Takayasu's arteritis more severe in children? Bolek EC, Kaya Akca U, Sari A, Sag E, Demir S, Kilic L, Sener YZ, Aykan HH, Kaya EB, Bilginer Y, Akdogan A, Kiraz S, Karadag O, Ozen S. *Clin Exp Rheumatol*. 2020 Sep 16.
29. Comparing immunoglobulin A vasculitis (Henoch-Schönlein purpura) in children and adults: a single-centre study from Turkey. Batu ED, Sari A, Erden A, Sönmez HE, Armağan B, Kalyoncu U, Karadağ Ö, Bilginer Y, Akdoğan A, Kiraz S, Özen S. *Scand J Rheumatol*. 2018;47(6):481-486.
30. <http://redcap.huvac.hacettepe.edu.tr/index.php?action=myprojects> (Access Date 22.01.2021)
31. <http://www.vaskulit.hacettepe.edu.tr> (Access Date 20.01.2021)