BEHÇET HASTALIĞI AMİLOİDOZ VE RENAL TUTULUM

Dr.Atalay DOĞRU
Süleyman Demirel üniversitesi Tıp Fakültesi
İç Hastalıkları AD, Romatoloji BD

BEHÇET HASTALIĞI RENAL TUTULUM

- Vaskülit ile karakterize multisistemik bir hastalık
- 1937 Hulusi Behçet
- 1963 Oshima ve ark BH ilişkili proteinüri ve hematüri
- Nadir bir tutulum tipi
- Asemptomatik hematüri/proteinüri→SDBY
- Anormal idrar bulguları %10,8

Review > Semin Arthritis Rheum. 2008 Dec;38(3):241-8. doi: 10.1016/j.semarthrit.2007.11.001.
Epub 2008 Jan 25.

Renal Behçet's disease: an update

Tekin Akpolat [1], Melda Dilek, Kenan Aksu, Gökhan Keser, Omer Toprak, Mustafa Cirit, Yusuf Oğuz, Hülya Taşkapan, Zelal Adibelli, Harun Akar, Bülent Tokgöz, Mustafa Arici, Hüseyin Celiker, Banu Diri, Ilkser Akpolat

Table 3 The Frequency of Renal Manifestations in BD

Author (reference no.)	Country	No. of Patients with BD	Frequency Renal Involvement (%)	Parameter Evaluated (if specified)
Kiraz (50)	Turkey	122	10	Hematuria
			1	Mild proteinuria
Ergin (19)	Turkey	211	16	Proteinuria
				Microalbuminuria
Altiparmak (23)	Turkey	674	11	Hematuria/proteinuria
		4212	<1	Glomerulonephritis
Shahram (11)	Iran	5059	10	Hematuria/proteinuria
				Leukocyturia/casts
		5059	<1	Glomerulonephritis
Wang (51)	Taiwan	67	5	
Papoutsis (52)	Germany	590	2	Renal vasculitis
Karci (53)	Turkey	500	1	Chronic renal failure, glomerular disease
Hamdan (54)	Lebanon	90	2	
Sahin (55)	Turkey	28	29	Microalbuminuria
Tursen (14)	Turkey	2353	<1	Amyloidosis

TUTULUM TIPLERI

- Amiloidoz
- Glomerulonefrit
- Renal ven trombozu
- Mikroskopik vasküler hastalık
- İlaçlar (Siklosporin) nedenli nefrotoksisitesi
- Nörojenik mesane
- Diğer

AMILOIDOZ

- En sık görülen renal hastalık
- Erkek cinsiyet risk faktörü
- Vasküler tutulum ile ilişkili
- 5 yıllık survi %46, 1/3 hasta tanı sonrası 6 ayda ex
- Hilar, mesanjiokapiller, mesanjial noduler tip
- MEFV mutasyonu ve SAA gen polimorfizmi
- Cerrahpaşa kohortu 27 /9410 hasta, 2000 yılı sonrası 3/5590 (%0.054)

- Hastaların 22 si erkek cinsiyette (22/27) (%81,5)
- BH tanısı ile AA arası ortanca süre 9 yıl
- Major organ tutulumu 22/27 vasküler 15/27, göz 12/27
- Hastaların büyük çoğunluğu AA tanısı öncesi tedavi alıyor
- Tanı renal ve rektal biyopsi

RHEUMATOLOGY

Rheumatology 2023;62:9–18
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Systematic review and meta analysis

Frequency of AA amyloidosis has decreased in Behçet's syndrome: a retrospective study with long-term follow-up and a systematic review

Amyloidosis in Behçet's syndrome

Guzin Karatemiz[1], Sinem Nihal Esatoglu[1], Mert Gurcan[1], Yesim Ozguler[1], Sebahattin Yurdakul[1], Vedat Hamuryudan [1], Izzet Fresko[1], Melike Melikoglu[1], Emire Seyahi[1], Serdal Ugurlu [1], Huri Ozdogan[1], Hasan Yazici[1] and Gulen Hatemi [1]

TABLE 1 Demographic and clinical characteristics of our 27 BS patients and those identified through the systematic review

	Our cases ($n = 27$)	Systematic review[a] ($n = 82$)	*P* value
Male, *n*, (%)	22/27, (81.5)	69/81, (85)	0.65
Patients who fulfilled ISG criteria, *n/N*, (%)	24/27, (89)	62/66, (94)	0.40
Juvenile-onset BS, *n/N*, (%)	3/27, (11)	8/35, (23)	0.23
Median (IQR) age at BS onset, years	25 (5)	25 (16)	0.81
Median (IQR) age at BS diagnosis, years	30 (8)	30 (11)	0.99
Median (IQR) age at AA amyloidosis diagnosis, years	37 (10)	35 (14)	0.38
Median (IQR) duration since BS diagnosis to AA amyloidosis diagnosis, years	9 (11)	5 (8.25)	0.03
BS manifestations, *n/N*, (%)			
Major organ involvement	22/27 (81.5)	52/66, (79)	0.77
Joint involvement	14/27 (52)	23/57, (40)	0.32
Eye involvement	12/27 (44)	40/63, (64)	0.09
Vascular involvement	15/27 (55.5)	41/66, (62)	0.56
Neurologic involvement	2/27 (7)	10/57 (17.5)	0.03
Gastrointestinal involvement	0	3/58	0.11
Comorbidities related to AA amyloidosis, *n/N*, (%)	4/27 (15)	7/82, (8.5)	0.35
Previous medications before AA amyloidosis diagnosis, *n/N*, (%)			
Colchicine	19/27 (70)	10/40, (25)	<0.0001
Immunosuppressives	15/27 (55.5)	17/40, (42.5)	0.29
Diagnostic tool, *n/N*, (%)			
Renal biopsy	14/27 (52)	62/82, (76)	0.02
Rectal biopsy	13/27 (48)	9/82, (11)	<0.0001
Nephrotic proteinuria at AA amyloidosis, *n/N*, (%)	19/27 (70)	48/67, (72)	0.82

- Literatürde 24 BH+amiloidoz vakası mevcut
- Erkek cinsiyet, uzun hastalık süresi, çoklu organ tutulumu, pozitif paterji testi

Review › Ann Rheum Dis. 1988 Feb;47(2):157-63. doi: 10.1136/ard.47.2.157.

Behçet's disease associated with amyloidosis in Turkey and in the world

N Dilşen [1], M Koniçe, O Aral, T Erbengi, V Uysal, N Koçak, E Ozdogan

Table 1 *Demographic and clinical characteristics of our eight patients with Behçet's disease with amyloidosis*

	Patient No							
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Sex	M	M	M	M	M	M	M	M
Present age (years)	33	46	31	44	43	40	31	42
Behçet's disease								
Age of onset (years)	7	39	16	32	16	23	21	28
Duration of BD (years)	26	7	15	12	27	17	10	14
First symptom	OA	EN	EN	Acne	OA,GU, TP,PA	OA	OA,GU, AG	OA
Type	C	IC	C	C	C	C	C	C
Manifestations								
Oral	+	+	+	+	+	+	+	+
Genital	+	+	+	+	+	+	+	+
Eye	+	–	+	+	+	+	+	+
Arthritis	+	–	+	+	+	+	AG	+
Skin	+	+	+	+	+	–	–	–
Thrombophlebitis	+	+	+	+	+	+	+	–
Pleuropulmonary	+	+	–	–	–	+	–	–
Neuropsychiatric	+	+	–	–	+	–	–	–
Skin pathergy test	+	+	–	+	+	+	+	–
Oedema	–	–	3+	2+	–	1+	3+	3+
Blood pressure	N	N	H	N	H	H	N	N

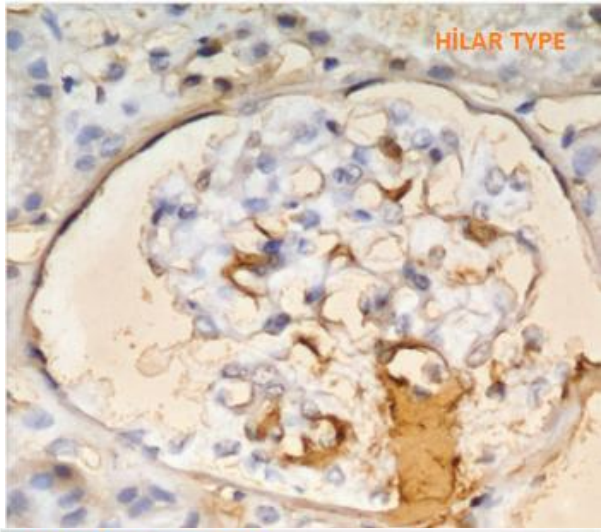
OA=oral aphthae; EN=erythema nodosum; GU=genital ulceration; TP=thrombophlebitis; PA=peripheral arthritis; AG=arthralgia; C=complete; IC=incomplete; N=normal, H=high.

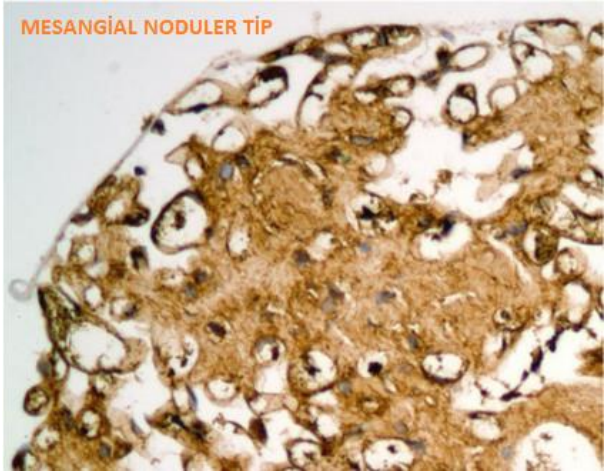
- 26 yılda 220 AA vakasının 8 BH
- Hilar (3), mesangial noduler(2), mesangiokapillar tip depolanma(3)
- MC form en ağır seyirli
- H vasküler dominant form

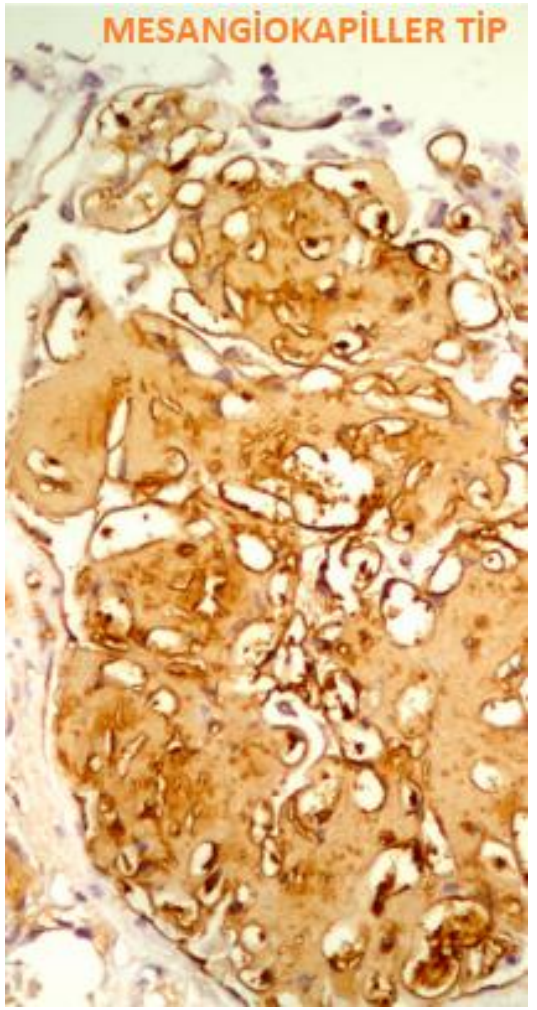
Comparative Study > Int Urol Nephrol. 2013 Jun;45(3):785-94. doi: 10.1007/s11255-012-0268-z. Epub 2012 Sep 9.

Renal amyloidosis in Behçet's disease: clinicopathologic features of 8 cases

Kemal Kosemehmetoglu [1], Dilek Ertoy Baydar







- BD ve FMF'nin tarihsel geçmişi, coğrafi kökenleri ve etnik dağılımı temelinde pek çok benzerliği vardır. Ortak çeşitli inflamatuar özellikler
- %0.5 BH (FMF kohortu 14/2716)
- 15 MEFV mutasyonu/57 BH, 11 hasta vasküler tutulum
- Cerrahpaşa kohortu 1 FMF/27 BH+AA
- 3 hastaya MEFV mut bakılmış, 1 hastada M680I homozigot, M694V heterozigot

Case Reports > Clin Rheumatol. 1998;17(5):397-9. doi: 10.1007/BF01450901.

Coexistence of familial Mediterranean fever with sacroiliitis and Behçet's disease: a rare occurrence

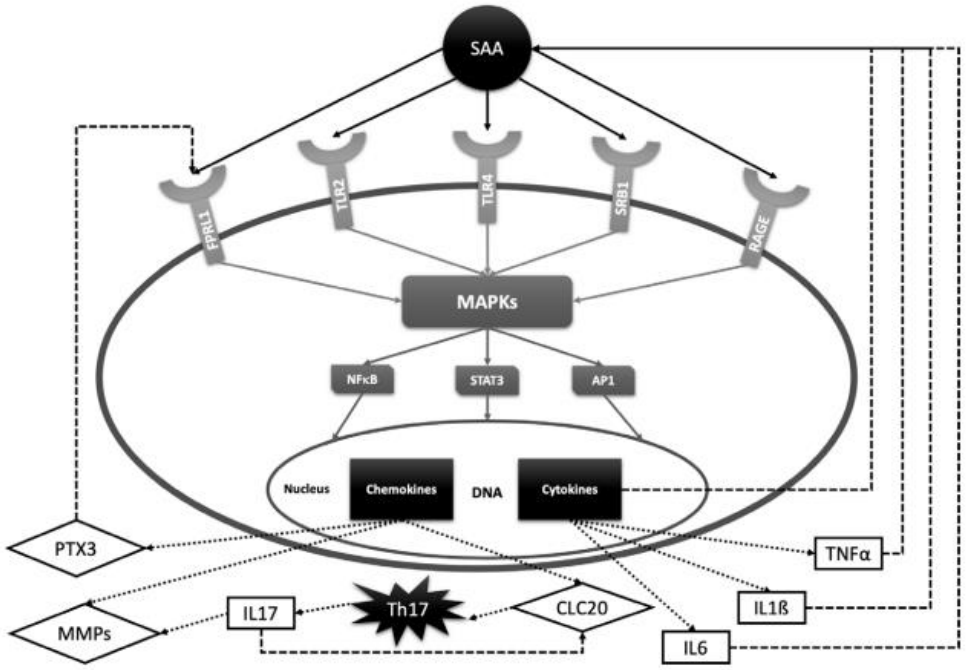
M Birlik [1], M Tunca, N Hizli, M Soytürk, Y Yeniçerioğlu, M A Ozcan, O El

Review > Clin Immunol. 2023 Jun:251:109630. doi: 10.1016/j.clim.2023.109630. Epub 2023 Apr 30.

Behçet disease, familial Mediterranean fever and MEFV variations: More than just an association

Emire Seyahi [1], Serdal Ugurlu [2], Shirkhan Amikishiyev [3], Ahmet Gul [4]

1. Tunca M, Akar S, Onen F, Ozdogan H, Kasapcopur O, Yalcinkaya F, Tutar E, Ozen S, Topaloglu R, Yilmaz E, Arici M, Bakkaloglu A, Besbas N, Akpolat T, Dinc A, E E (2005) Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore) 84:1–11
2. Atagunduz P, Ergun T, Direskeneli H (2003) MEFV mutations are increased in Behcet's disease (BD) and are associated with vascular involvement. Clin Exp Rheum 21:S35–S37



- SAA1 α/α genotype BH+AA için bir risk faktörüdür.

› Clin Rheumatol. 2007 Jun;26(6):927-9. doi: 10.1007/s10067-006-0435-7. Epub 2006 Oct 13.

SAA1 alpha/alpha alleles in Behçet's disease related amyloidosis

Umut Utku [1], Melda Dilek, Ilkser Akpolat, Abdülkerim Bedir, Tekin Akpolat

Table 1 The number of homozygous α/α and other genotypes in Behçet's disease (BD) related amyloidosis, BD without amyloidosis, and healthy controls

Groups	α/α genotype	Other genotypes
BD related amyloidosis (n=9)	7	2
BD without amyloidosis (n=39)	6*	33
Healthy controls (n=63)	18*	45

*p<0.01 compared to patients with BD related amyloidosis

Soric Hosman I, Kos I, Lamot L. Serum amyloid A in inflammatory rheumatic diseases: a compendious review of a renowned biomarker. Front Immunol 2020;11:631299

GLOMERULONEFRIT

- Birçok GN tanımlanmış fakat BH spesifik bir tip yok
- Diğer vaskülitlere göre daha az etkilenme
- BH görülen 2. en sık renal hastalık
- Sıklığı <%1 (7/4212, 13/5059)
- Hematüri/proteinüri (%10), hafif glomerular hastalık?

Table 4 New Cases (published and ours) with BD-Related GN Based on the Pathologic Diagnoses of the Authors

Type of Glomerular Disease	n	Reference No.
Diffuse proliferative GN	7	(13,23, our case)
Focal and segmental glomerulosclerosis	7	(12,19,24, our case)
Focal proliferative GN	5	(13)
Mesangial proliferative GN	4	(13, our case)
IgA nephritis	4	(23,26,27)
Membranoproliferative GN	3	(23, our case)
Crescentic GN	2	(21,25)
Minor glomerular lesion	2	Our cases
Membranous GN	1	(19)
Proliferative GN	1	(22)
Focal and segmental GN	1	(23)
Total	37	

Shahram F, Nadji A, Jamshidi A, Chams H, Chams C, Shafaie N, et al. Behcet's disease in Iran. Analysis of 5,059 cases. Arch Iranian Med 2004;7:9-14
Altiparmak MR, Tanverdi M, Pamuk N, Tunç R, Hamuryudan V. Glomerulonephritis in Behcet's disease: report of seven cases and review of the literature. Clin Rheumatol 2002;21:14-8

- 7 hasta/674/4212 (%0,16)
- Hematüri/proteinüri ile tanımlanmış
- 2 IgA, 2 DPGN, 2 MPGN, 1 FSGS
- 4 Kadın/3 Erkek

Review > Clin Rheumatol. 2002 Feb;21(1):14-8. doi: 10.1007/s100670200004.

Glomerulonephritis in Behçet's disease: report of seven cases and review of the literature

M R Altiparmak [1], M Tanverdi, O N Pamuk, R Tunç, V Hamuryudan

Table 2. Pathologic findings in renal biopsies performed on seven patients

No	Light microscopy	Immunofluorescence microscopy	Electron microscopy	Pathological diagnosis
1	Increase in mesangial matrix, diffuse cell proliferation	3+ granular staining for IgM 1+ granular staining for IgA and IgG on the mesangial area	Not done	DPGN
2	Focal, segmental sclerotic segments, focal tubular atrophy	Not done	Not done	FSGN
3	Diffuse expansion due to increased cellularity in mesangium	3+ granular staining for IgG 2+ for C3 on the mesangial area	Not done	DPGN
4	Increased cellularity and matrix in mesangial area	2+ staining for IgA in mesangial area 1+ staining for IgA in GBM	Not done	IgA-N
5	Mildly increased cellularity in mesangium, thickening of the GBM	2+ staining for IgM in GBM 1+ staining for IgA in GBM	Subendothelial electron-dense deposits	MPGN
6	Slight focal mesangial and interstitial expansion, increased cellularity in mesangium	3+ granular staining for IgA 2+ granular staining for C3 in mesangium	Nodular electron-dense deposits in the mesangial area	IgA-N
7	Moderate increased cellularity, thickening of GBM, mild tubular loss	2+ liner staining for IgG in GBM 2+ granular staining for IgM in GBM 3+ C3 and 2+ fibrinogen in GBM	Abundant subendothelial electron-dense deposits	MPGN

GBM: Glomerular basement membrane, DPGN:diffuse proliferative GN, IgA-N:IgA nephritis, FSGN:focal segmental GN, MPGN:membranoproliferative GN.

- Immünfloresan inceleme 16/37, IgA, IgM ve C3 depolanması
- Elektron mikroskopu 4 hastada bakılmış, non spesifik bulgular
- Steroid, AZA, Siklofosfamid tedavileri kullanılmış
- Prognoz iyi, birkaç hastada SDBY gelişmiş

Review > Semin Arthritis Rheum. 2008 Dec;38(3):241-8. doi: 10.1016/j.semarthrit.2007.11.001. Epub 2008 Jan 25.

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Total	37	

RENAL VASKÜLER HASTALIK

- Vasküler tutulum, Renal BH 3. en sık nedeni
- Makrovasküler/mikrovasküler
- Makrovasküler BH 3 formu mevcut; venöz oklüzyon-arteriyel anevrizma-arteriyel oklüzyon
- Vasküler tutulum %30 a kadar olmasına rağmen renal damarlar nadir etkileniyor
- Hipertansiyon ana bulgu

- 4 renal ven trombozu, 2 mikroskobik vasküler hastalık (33 hasta)
- BH+intrarenal mikroanevrizma isimlendirme ? PAN?
- Makroskopik böbrek damar hastalığı:Lezyonun lokalizasyonu, boyutu ve ciddiyetine bağlı olarak kısa vadeli prognoz olumlu görünüyor
- Mikroskopik: renal mikroinfark ve hafif renal yetmezlik

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Table 2 Cumulative Analysis of Patients with BD and Renal Involvement (including our cases)

Type of Renal Involvement	No. of Cases	References for Newly Published Cases*
Amyloidosis	108	(9-20)
Glomerulonephritis	88	(11-12,19,21-27)
Renal vascular disease		
Macroscopic vascular disease		
Renal artery aneurysm	18	(28-34)
Renal artery stenosis/ occlusion	16	(9,35-37)
Renal vein thrombosis	14	(38-40)
Microscopic vascular disease	7	(41)
Interstitial nephritis	5	(42)
Total	253†	

*References for cases which were not included in the cumulative analysis (8).
†Three patients in the literature had more than 1 renal disease (amyloidosis + glomerulonephritis, amyloidosis + renal vein thrombosis, renal vein thrombosis + microscopic vascular disease).

Int J Rheum Dis. 2015 Nov;18(8):892-7. doi: 10.1111/1756-185X.12529. Epub 2015 Jan 3.

Renal involvement in Chinese patients with Behcet's disease: a report of 16 cases

Wenjie Zheng [1], Guohua Li [2], Mengyu Zhou [3], Limeng Chen [3], Xinping Tian [1], Fengchun Zhang [1]

Table 1 Clinical characteristics of BD with renal damage

No.	Gender	Age	Manifestations of BD	Manifestations of Renal damage	24 h/P†	Microscopic hematuria	Stage of CKD	Hypertention	Pathology	Treatment
1	M	45	O, G, U, S, A	CGN	+	+	1	+	GML,IgAN (stageIII)	GCs/CTX/ACEI
2	M	23	O, G, I	CGN	+	+	1	–	–	GCs/AZA
3	M	20	O, G, U, S, P, A	CGN	+	+	1	–	MsPGN(mild)	GCs/TW/MTX/MMF/AZA
4	M	21	O, G, I	NS	+++	+	1	–	IgAN (stage II) to IgAN (stage IV)	GCs/CTX/ACEI
5	F	26	O, G, P	RTA	++	+	3a	–	CTIL	GCs/CTX
6	F	43	O, G, S, P, A	CGN	++	+	1	–	GML	Thalidomide/TW/ARB
7	M	19	O, G, P, U, V	RVT	–	–	1	–	–	GCs/CTX/AZA/warfarin
8	M	15	O, U, S, P	CGN	+	+	1	–	–	HCQ
9	M	36	O, G, S, I, V	RAS	+	+	3b	+	–	GCs/Thalidomide/ACEI
10	F	44	O, G, P	RAS	+	–	2	+	–	Surgery/GCs/CTX/TW
11	F	61	O, S, V	RAS	–	–	2	+	Thrombosis	Surgery/GCs/CTX
12	F	43	O, G, S, P, V	RAS	+	–	2	–	–	GCs/CTX/LMWH/warfarin
13	F	24	O, G, S, P, V	RAS	–	–	1	+	–	GCs, CTX, warfarin
14	F	31	O, G, U, P, V	RAS	–	–	1	+	–	GCs, CTX
15	M	48	O, G, S, P, V, A	RAS	–	–	1	–	–	GCs/CTX/aspirin
16	M	31	O, G, S, H, V	RAS	–	–	1	–	–	GCs/CTX/warfarin

- 16/618 hasta, 8 RAS, 1 RVT

İNTERSTİSYEL NEFRİT

- Tubulointerstisyel nefrit+üveit (TINU) ayrıcı tanısında BH
- TINU, kadınlarda ve anterior üveit
- Literatüre az sayıda vaka mevcut

Table 2 Cumulative Analysis of Patients with BD and Renal Involvement (including our cases)

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Akpolat T, Dilek M, Aksu K, et al. (2008) Renal Behcet's disease: an update. Semin Arthritis Rheum 38, 241–8

RENAL YETMEZLIK/RENAL REPLASMAN TEDAVISI

- BH ilişkili böbrek yetmeliğinin en sık sebebi amiloidoz ve GN
- Diyaliz başlandığında BH aktivasyonu azalıyor
- Hemodiyaliz en sık kullanılan yöntem fakat damar yolu ile ilgili problemler

- 350 diyaliz merkezi (20596 hasta)
- 14 BH tespit edilmiş
- 9/17 BH+amiloidoz
- 1 hasta transplant, 1 yıl sonra HD
- %59 hasta BH+vasküler tutulum
- BH aktivitesi diyaliz sonrası azalmış
- 15/17 hasta arterivenöz fistül, 6 sı ilk denemede
- 2 hasta tekrarlayan fistül trombozu
- 14 hasta geçici katater, 7 si tromboz ve enfeksiyon

Review > Nephrol Dial Transplant. 2003 May;18(5):888-91. doi: 10.1093/ndt/gfg084.

Behçet's disease and renal failure

Tekin Akpolat [1], Banu Diri, Yusuf Oğuz, Emin Yilmaz, Mahmut Yavuz, Melda Dilek

Table 1. Causes of ESRD among our patients with BD and literature review of causes of BD-related renal failure based on the diagnosis of the authors

Cause	Our patients (*n*)	Literature review (*n*)
Amyloidosis	9	29
Glomerulonephritis	–	21
Cyclosporin nephrotoxicity	1[a]	5[b]
Amyloidosis + cyclosporin nephrotoxicity	1[a]	–
Cyclosporin-related TTP/HUS	–	4
Renal artery aneurysm	–	2
Renal vein thrombosis	–	2[c]
Interstitial nephritis	–	2
Multiple aortic aneurysms	–	1
Renal artery stenosis (left) + small kidney (right)	1	–
Hydronephrosis (left) + aortic aneurysm	1	–
Diabetes mellitus	1[d]	–
Uncertain	3[e]	4
Total	17	67

SONUÇ OLARAK;

- BH seyrinde renal tutulum nadir olarak görülmektedir
- Asemptomatik hematüri/proteinüri %10 a varan oranlarda görülebilir
- Amiloidoz ve glomerulonefrit en sık görülen tutulumlardır
- Amiloidoz genellikle majör organ(vasküler) tutulumlarda daha sık
- BH ‘na özel bir GN yok
- İlaç toksisitesine bağlı böbrek yetmezliği unutulmamalı

- **Katılımınız için teşekkür ederim.**