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Uremic pruritus and associated factors in chronic hemodialysis patients: past and current experience

Prurito urémico y factores asociados en pacientes en hemodiálisis crónica: experiencia pasada y actual

Enes Cömert[1], Aylia Yesilova[1], Gülay Koçak[2], Ahmet Vedat Çelik[3], Hakan Yavuz[4], Nermin Erdoğan[4]

RESUMEN

Introducción: El prurito urémico (PU) es un problema prevalente pero subestimado en la enfermedad renal crónica (ERC). Este estudio tuvo como objetivo investigar la prevalencia de PU en pacientes en hemodiálisis crónica y su correlación con parámetros demográficos, clínicos y bioquímicos. **Métodos**: El estudio incluyó a todos los pacientes mayores de 18 años que habían sido sometidos a hemodiálisis 3 días a la semana durante al menos 6 meses y aceptaron participar en el estudio. Se excluyeron del estudio a las mujeres embarazadas y los pacientes con antecedentes de uso de esteroides, malignidad, enfermedad hepática o de las vías biliares y enfermedades dermatológicas. La severidad del prurito fue evaluada usando la Escala Visual Análoga (EVA) y la Escala de Prurito 5-D. **Resultados**: De 1093 pacientes, 582 (53,25%) eran hombres y 511 (46,75%) eran mujeres, con una edad media de 62,39±14,27 años. Los resultados mostraron que 224 (20,5%) de los pacientes tenían PU, con una fuerte correlación positiva entre la EVA y la Escala de Prurito 5-D en el grupo con prurito (r=0,883, p=0,0001). Se observó que los niveles de proteína C reactiva (PCR) estaban significativamente aumentados y que los niveles de Kt/V y de la tasa de reducción de urea (TRU) estaban significativamente disminuidos en los pacientes con PU. Además, se demostró que la presencia de hipertensión, niveles altos de PCR y baja TRU eran factores de riesgo para PU (p: 0,037, p: 0,048 y p: 0,011, respectivamente). La agrupación de los pacientes según la severidad del prurito como leve, moderado y severo no mostró diferencias significativas entre los grupos, excepto por una edad media significativamente menor en el grupo de prurito severo (p=0,003). **Conclusiones**: La correlación entre el PU y la PCR apoya la hipótesis inmunológica en la patogénesis del PU. Además, aumentar la dosis de diálisis podría ser beneficioso para mitigar los síntomas del PU, incluso en pacientes con niveles normales de Kt/V y TRU.

Palabras Clave: Prurito urémico, pacientes en hemodiálisis, hipótesis inmune.

ABSTRACT

Introduction: Uremic pruritus (UP) is a prevalent but overlooked problem in chronic kidney disease (CKD). This study aimed to investigate the prevalence of UP in chronic dialysis patients and its correlation

Correspondencia:
Gülay Koçak
ORCID:
0000-0002-3633-9546
gulaykad@hotmail.com

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1) MD Department of Internal Medicine, University of Health Sciences, Prof. Dr. Cemil Taşçıoğlu City Hospital.
2) Prof. Department of Internal Medicine, Division of Nephrology, University of Health Sciences, Prof. Dr. Cemil Taşçıoğlu City Hospital.
3) MD Department of Nephrology, School of Health Sciences, İstanbul Beykent University.
4) Nephrology Nurse Practitioner, Koç Dialysis Centers.

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with demographic, clinical, and biochemical parameters. **Methods**: The study included all patients >18 years of age who had undergone hemodialysis three days a week for at least six months and agreed to participate. Pregnant women and patients with a history of steroid use, malignancy, chronic liver or biliary tract disease, and dermatological disease were excluded from the study. Pruritus severity was evaluated using the Visual Analog Scale (VAS) and the 5-D Itch Scale. **Results**: Of 1093 patients, 582 (53.25%) were male, and 511 (46.75%) were female, with a mean age of 62.39±14.27 years. The results showed that 224 (20.5%) patients had UP, with a strong positive correlation between VAS and the 5-D Itch Scale in the pruritus group (r=0.883, p=0.0001). C-reactive protein (CRP) levels were significantly increased, and Kt/V and urea reduction rate (URR) levels significantly decreased in UP patients. In addition, we showed that hypertension, high CRP, and low URR were risk factors affecting UP (p: 0.037, p: 0.048, and p: 0.011, respectively). Grouping patients by pruritus severity as mild, moderate, and severe revealed no significant difference between the groups, except for the significantly lower mean age in the severe pruritus group (p=0.003). **Conclusions**: The correlation between UP and CRP supported the immune hypothesis in the pathogenesis of UP. Moreover, increasing the dialysis dose may be beneficial in mitigating UP symptoms, even in patients with normal Kt/V and URR levels.

Keywords: Uremic pruritus, hemodialysis patients, immune hypothesis

INTRODUCTION

Uremic pruritus (UP) remains a significant medical problem for dialysis patients despite its decreased prevalence in recent years [1,2]. The pathophysiology still needs to be fully elucidated. Studies have dwelled on the relationship of UP with inflammation and changes in opioid receptors in the skin. Other factors considered to contribute to pruritus include xerosis, increased release of histamine from mast cells, dialysis inadequacy, hyperparathyroidism, elevated serum concentrations of phosphorus, magnesium, and aluminum, and increased levels of vitamin A and beta-2 microglobulin [3,4]. The symptoms are alleviated with treatment but not completely eliminated.

This study aimed to determine the prevalence of UP in patients on a chronic hemodialysis program, establish the factors associated with pruritus, and thereby emphasize changes in its characteristics over the years.

MATERIALS AND METHODS

The study was approved by the Ethics Committee of Prof. Dr. Cemil Tascioğlu City Hospital at a meeting held on April 05, 2021 (decision number 140). Patients on chronic hemodialysis who were admitted to the University of Health Sciences Prof. Dr. Cemil Tascioğlu City Hospital, the dialysis unit of the Nephrology Department, and seven private dialysis centers between June 01, 2021, and December 31, 2021, were prospectively evaluated.

The study included all patients >18 years of age who had undergone hemodialysis three days a week for 4 hours for at least six months and agreed to participate. High-flux dialysis membranes were used in all patients during dialysis. Pregnant women and patients with a history of steroid use, malignancy, chronic liver or biliary tract disease, and dermatological disease were excluded from the study.

All patients' characteristics such demographics, comorbidities such as diabetes mellitus (DM) and hypertension (HT), last 6-month mean values of laboratory parameters (including urea, creatinine, albumin, total protein, corrected calcium, phosphorus, intact parathyroid hormone (iPTH), hemoglobin, hematocrit, ferritin, serum iron, total iron binding capacity, and C-reactive protein (CRP)), duration of dialysis (months), and dialysis adequacy parameters (including the last 6-month mean values of urea clearance (single pool Kt/V: K= dialyzer clearance of urea, t=time, V= volume of distribution of urea) and urea reduction ratio (URR) were recorded.

In all patients, the frequency and severity of pruritus were determined separately with both the Visual Analog Scale (VAS) and the 5-D Itch Scale, which have been frequently used in UP studies [5,6,7]. Patients assessed the severity of pruritus by rating their itch intensity on a 10-point VAS, with a score of 0 points representing "no itch,"≥1-<4 points "mild itch,"≥4-<7 points "moderate itch," and ≥7-10 points "severe itch" [5,6].

The 5-D Itch Scale assesses the five dimensions of itch separately: duration (rated from 1 to 5 points), degree (rated from 1 to 5 points), direction (rated from 1 to 5 points), disability (4 items rated from 1 to 5 points and then averaged) and distribution (16 different body parts assessed according to the number of the affected area; 0-2 areas: 1 point, 3-5 areas: 2 points, 6-10 areas: 3 points, 11-13 areas: 4 points and 14-16 areas: 5 points) [7]. The total score of this scale, which assesses not only the current severity of pruritus but also its course in the last two weeks and its impact on the individual's daily functioning, ranges from 5 points (no itch) to 25 points (very severe itch).

Statistical Analysis: Number Cruncher Statistical System (NCSS) Software (Utah, USA) was used for statistical analysis. We assessed the normality of the continuous parameters using the Kolmogorov-Smirnov test and box plot graphics. Numerical parameters are revealed as median, mean, standard deviation, and ratio. We analyzed the non-parametric variables by the Mann-Whitney U test. A T-test was used to compare independent groups with normal distribution. The Wilcoxon sign-ranked test compared the relation between the two dependent tests. The chi-square test with Yates's correction and Fisher's exact test were used when appropriate for non-numeric data. Spearman's correlation coefficient was used to assess the relationship between variables. $p < 0.05$ was accepted as statistically significant.

RESULTS

This study evaluated 1320 patients on a chronic hemodialysis program. A total of 227 patients with a history of known chronic liver and biliary tract disease (n=86), dermatological disease (n=35), malignancy (n=48), steroid use (n=12), pregnancy (n=1), hemodialysis duration of less than six months (n=42), and age <18 years (n=2) were excluded from the study. Of the remaining 1093 patients, 582 (53.25%) were male, and 511 (46.75%) were female, with a mean age of 62.39±14.27 years.

The evaluation of the patients by etiology of CKD revealed that DM (36%), HT (35%), glomerulonephritis (8%), polycystic kidney disease (5%), amyloidosis (2%), obstructive nephropathy (2%), vesicourethral reflux (1%) and chronic pyelonephritis (1%) accounted for CKD. In 10% of the patients, no etiology of CKD was found.

UP was noted in 224 (20.49%) patients on a chronic hemodialysis program. There was no significant difference between patients with and without UP regarding age, gender distribution, and DM frequency, while the frequency of HT was significantly higher in the UP group (p: 0.038).

The comparison of patients with and without UP in terms of the mean values of the last 6-month hemoglobin (gr/dL), hematocrit (%), CRP (mg/L), serum iron (mcg/dL), total iron binding capacity (mcg/dL), ferritin (ng/ ml), total protein (gr/dL), albumin (gr/dL), calcium (mg/dL), phosphorus (mg/dL), and iPTH (pg/ml) showed that only CRP value was significantly higher in the UP group (p: 0.025) (**Table 1**).

Given the last 6-month mean values of Kt/V and URR to evaluate dialysis adequacy, these parameters were significantly lower in the UP group compared to the group without UP (p: 0.018 and p: 0.008, respectively)
(**Table 1**).

The analysis of the itch severity of patients with UP by VAS score revealed mild itch in 79 patients, moderate in 95 patients, and severe in 50 patients. The categorization of patients with UP into three groups by itch severity showed no difference in gender distribution, comorbidities (DM and HT frequency), and duration of dialysis. The severe itch group was significantly younger than the mild and moderate itch group (p: 0.003). The classification of dialysis patients by itch severity revealed no significant difference between the groups in terms of the last 6-month mean values of biochemical and dialysis adequacy parameters ($p>0.05$)
(**Table 2**).

All hemodialysis patients were also evaluated for itch severity using the 5-D Itch Scale simultaneously with the VAS score. As the itch severity on VAS increased, the 5-D Itch Scale score increased, and the difference in the 5-D Itch Scale was significant between the three groups (**Table 2**). In addition, the VAS score used to assess UP in hemodialysis patients was strongly correlated with the 5-D Itch Scale (r: 0.883, p: 0.0001)
(**Figure 1**).

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Table 1: Evaluation of dialysis patients with uremic pruritus in terms of demographic, biochemical, and dialysis adequacy parameters

		All Patients (n:1093)	Patients without itching (n:869)	Patients with itching (n:224)	p
Age	Mean±SD	62,39±14,27	62,18±14,44	63,21±13,57	0.334
Gender	Male (n,%)	582 (53.25%)	466 (80.06%)	116(19.94%)	0.623
	Female (n,%)	511(46.75%)	403(78.86%)	108(21.14%)	
HT (n, %)		737 (67.43%)	573 (65.94%)	164 (73.21%)	**0,038**
DM (n, %)		423 (38.7%)	335 (38.55%)	88 (38.29%)	0,840
Duration of Dialysis (months)	Mean±SD	65,6±58,53	66,99±59,21	60,21±55,62	0,080
Hemoglobin (gr/dl)	Mean±SD	11,22±3,39	11,28±3,74	11,01±1,38	0,293
Hematocrit (%)	Mean±SD	34,91±3,98	35±3,9	34,53±4,24	0,112
Serum Iron (mcg/dL)	Mean±SD	59,82±24,61	59,83±23,57	59,81±28,32	0,994
TIBC(mcg/dL)	Mean±SD	237,64±67,14	236,16±64,33	243,41±76,96	0,149
Ferritin (ng/ml)	Mean±SD	534,02±493,86	521,75±468,55	581,61±580,49	0,405
Albumin (gr/dL)	Mean±SD	37,94±3,52	38,05±3,37	37,53±4,03	0,055
Total protein(gr/dL)	Mean±SD	67±17,4	67,1±19,21	66,62±6,84	0,713
CRP (mg/L)	Mean±SD	13,31±21,41	12,69±20,31	15,73±25,15	**0,025***
Calcium (mg/dL)	Mean±SD	9,2±0,76	9,2±0,71	9,2±0,9	0,965
Phosphorus (mg/dL)	Mean±SD	4,49±1,18	4,49±1,15	4,48±1,32	0,931
iPTH (pg/ml)	Mean±SD	373,7±305	374,82±295,08	369,37±341,41	0,069
Kt/V	Mean±SD	1,73±0,3	1,74±0,29	1,69±0,31	**0,018***
URR	Mean±SD	76±5,91	76,24±5,74	75,06±6,45	**0,008***

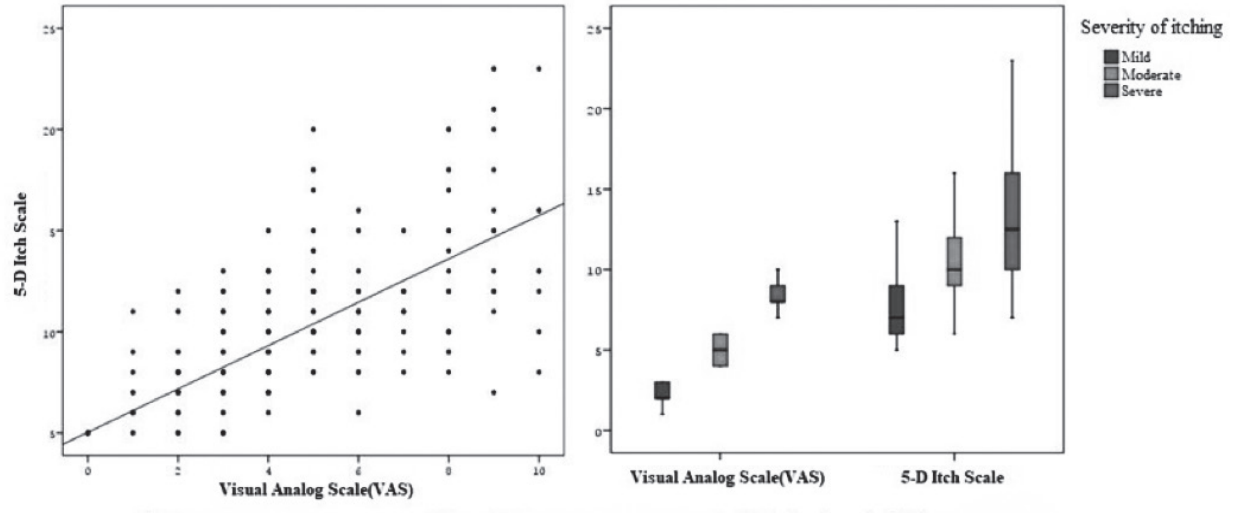
***DM**: Diabetes Mellitus, **HT**: Hypertension, **TIBC**: Total Iron Binding Capacity, **CRP**: C-reactive protein, **iPTH**: Intact Parathyroid Hormone, **Kt/V**: K(Dialyzer clearance of urea) t(Time) V(Volume of distribution of urea), **URR**: Urea Reduction Ratio, *p<0,05 was accepted statistically significant.*

Table 2: Comparison of patients with uremic pruritus according to the severity of itching

		Itching severity-VAS						P
		Mild (n:79)		Moderate (n:95)		Severe (n:50)		
5-D Itch Scale	Mean±SD	7,66±1,98		10,59±2,64		13,66±4,21		**0,0001***
Age	Mean±SD	64,97±12,78		64,72±11,44		57,56±16,89		**0,003***
Gender	Male	36	45,57%	52	54,74%	28	56,00%	0,385
	Female	43	54,43%	43	45,26%	22	44,00%	
DM (n,%)		25	31,65%	38	40,00%	25	50,00%	0,113
HT (n, %)		55	69,62%	73	76,84%	36	72,00%	0,550
Duration of Dialysis (months)	Mean±SD	67,32±66,23		56,03±47,49		56,9±51,41		0,551
Hemoglobin (gr/dL)	Mean±SD	11,05±1,38		10,94±1,46		11,09±1,25		0,800
Hematocrit (%)	Mean±SD	34,75±4,26		34,28±4,58		34,67±3,56		0,739
Serum Iron (mcg/dL)	Mean±SD	58,68±32,69		60,02±26,21		61,22±25,03		0,882
TIBC (mcg/dL)	Mean±SD	255,63±84,22		236,63±73,09		236,98±71		0,215
Ferritin (ng/ml)	Mean±SD	591,19±570,24		592,25±608,64		546,23±551,06		0,928
Albumin (gr/dL)	Mean±SD	37,79±4,63		37,01±3,87		38,11±3,16		0,232
Total protein(gr/dL)	Mean±SD	66,46±8,18		66,58±6,27		66,97±5,56		0,916
CRP (mg/L)	Mean±SD	13,12±19,34		19,34±32,06		12,98±16,34		0,712
Calcium (mg/dL)	Mean±SD	9,25±0,86		9,25±0,86		9,01±1,02		0,262
Phosphorus (mg/dL)	Mean±SD	4,46±1,23		4,29±1,18		4,86±1,62		0,056
iPTH (pg/ml)	Mean±SD	376,98±364,96		352,45±326,32		389,5±336,33		0,647
Kt/V	Mean±SD	1,73±0,32		1,67±0,29		1,65±0,31		0,253
URR	Mean±SD	75,87±6,32		74,84±6,33		74,19±6,84		0,325

***VAS**: Visual Analog Scale, **DM**: Diabetes Mellitus, **HT**: Hypertension, **TIBC**: Total Iron Binding Capacity, **CRP**: C-reactive protein, **iPTH**: Intact Parathyroid Hormone, **Kt/V**: K(Dialyzer clearance of urea) t(Time) V(Volume of distribution of urea), **URR**: Urea Reduction Ratio, *p<0,05 was accepted statistically significant.*

Figure 1: Relationship between VAS and 5-D itch scale scores in patients on hemodialysis



The analysis of factors correlated with VAS and 5-D Itch Scale in the hemodialysis patient group revealed a weak negative correlation with the Kt/V and URR values but no significant correlation with the CRP value (**Table 3**).

Table 3: Evaluation of factors correlated with VAS and 5-D Itch Scale

		VAS	5-D Itch Scale
VAS	**r**	1	**0,883**
	p		**0,0001**
5-D Itch Scale	**r**	**0,883**	1
	p	**0,0001**	
Kt/V	**r**	**-0,196**	**-0,187**
	p	**0,002**	**0,004**
URR	**r**	**-0,103**	**-0,197**
	p	**0,001**	**0,001**
CRP	**r**	0,051	0,052
	p	0,094	0,085

***VAS**: Visual Analog Scale, **Kt/V**: K(Dialyzer clearance of urea) t(Time) V(Volume of distribution of urea), **URR**: Urea Reduction Ratio, **CRP**: C-reactive protein*

The present study used multivariate logistic regression analysis with HT, CRP, KtV, and URR variables to determine the contributing factors to pruritus. Accordingly, the presence of HT, high CRP, and low URR were found to be the factors statistically affecting pruritus (p: 0.037, p: 0.048, and p: 0.011, respectively) (**Table 4**).

Table 4: Multivariate Logistic Regression Analysis

	OR	OR (%95 GA)	P
HT(+)	1,70	0,83-1,75	**0,037***
CRP (mg/L)	1,01	0,99-1,03	**0,045***
Kt/V	1,68	0,30-3,53	0,557
URR	0,97	0,87-1,03	**0,042***

***HT**: Hypertension, **CRP**: C-reactive protein, **Kt/V**: K = Clearance - Dialyzer clearance of urea (liters/minute) t = Time - The duration of treatment (minutes) V = Volume - The amount of body fluid (liters), **URR**: Urea Reduction Ratio, * p<0.05 was considered statistically significant.*

DISCUSSION

Our study revealed a UP prevalence of 20.5% in chronic hemodialysis patients. The analysis of the laboratory characteristics of hemodialysis patients showed significantly higher CRP but lower Kt/V and URR levels in patients with UP. Studies have reported a strong positive correlation between the 5-D itch scale and VAS, and both scales have helped evaluate UP in chronic hemodialysis patients. Classifying patients with UP by pruritus severity using the 5-D Itch Scale and VAS revealed no significant difference between the groups regarding demographic and laboratory characteristics, except for age. It was observed that the patients with severe itching were significantly younger than the other patients.

The prevalence of UP in hemodialysis patients has decreased over the years due to the more effective use of dialysis, as seen in previous

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literature, with prevalence rates ranging from 50-90% to 20-30%. A UP prevalence of 20.5% in hemodialysis patients included in our study aligns with the current literature.

Because dry skin is a risk factor for UP, patients with UP are expected to be older than those without pruritus because of age-related changes in sweat glands, such as atrophy. Nonetheless, our study found no significant difference in age between hemodialysis patients with and without UP. Patients experiencing severe pruritus were significantly younger than the others. A similar retrospective analysis of approximately 100,000 dialysis patients in the literature also found that patients with severe itching were younger and had a higher prevalence of specific comorbidities such as DM, cardiovascular disease, and liver disease. However, our study showed no significant difference in comorbidity prevalence between the groups classified by pruritus severity. Patients with severe itching may have more sensitive skin to UP, which occurs in a complex metabolic environment of CKD for psychosocial reasons. However, no questionnaire was simultaneously used for the psychosocial assessment of our hemodialysis patients.

Recent clinical and experimental studies investigating the pathogenesis of UP have suggested a relationship between pruritus and inflammation, also known as the immune hypothesis [11-13]. In line with our study, it has been shown that patients with UP have elevated levels of CRP and that immunomodulatory therapies such as thalidomide, calcineurin inhibitors, and ultraviolet phototherapy may alleviate UP symptoms [13-16].

Given the literature, inadequate dialysis has been reported to be another risk factor associated with UP. Studies have found a decrease or improvement in the severity of itching of uremic patients not undergoing dialysis with the initiation of dialysis, highlighting the importance of dialysis adequacy in managing UP [1,15]. Moreover, it has been suggested that hemodialysis patients with UP should have their dialysis adjusted to increase Kt/V, as dialysis adequacy is inversely associated with the severity of pruritus. However, previous studies have reported contradictory results regarding the association between Kt/V and UP. While Ko et al. suggested that hemodialysis patients with Kt/V >1.5 are less likely to have pruritus [16], another study including 105 hemodialysis patients found no significant difference in Kt/V values between patients with and without pruritus, reporting mean Kt/V values of 1.7 and 1.82, respectively [17]. Although Kt/V values were above 1.5 in both groups in our study, patients with UP had significantly lower Kt/V and URR values than those without UP.

Regarding hyperparathyroidism and high calcium x phosphorus, other known risk factors for UP, there was no discernible difference between hemodialysis patients with and without UP. Studies in the literature suggest that calcium and phosphorus may accumulate in the skin, causing uremic pruritus by releasing histamine and serotonin from mast cells [18]. On the other hand, some studies have shown no correlation between calcium, phosphate, calcium-phosphate product, and UP levels, similar to our study [19-20]. A study by Chou et al. evaluating pruritus by VAS found a decrease from 5.5 to 1.8 in hemodialysis patients who underwent parathyroidectomy. However, parathyroidectomy has not proven beneficial in patients with UP who do not have significantly higher PTH concentrations [21].

The medications used by the patients during our study were not recorded, which is a limitation of our study. In our study, hypertension was shown to be one of the most critical determinants of UP. This fact may be due to antihypertensive medications, especially ACE inhibitors. However, we cannot conclude this issue with our existing data.

CONCLUSION

Despite its decreased prevalence in recent years, UP remains a significant problem among hemodialysis patients. Increasing the dialysis dose may be beneficial in mitigating UP symptoms, even in patients with normal Kt/V and URR levels.

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