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Phenotypes of Patients with Atypical Hemolytic Uremic Syndrome

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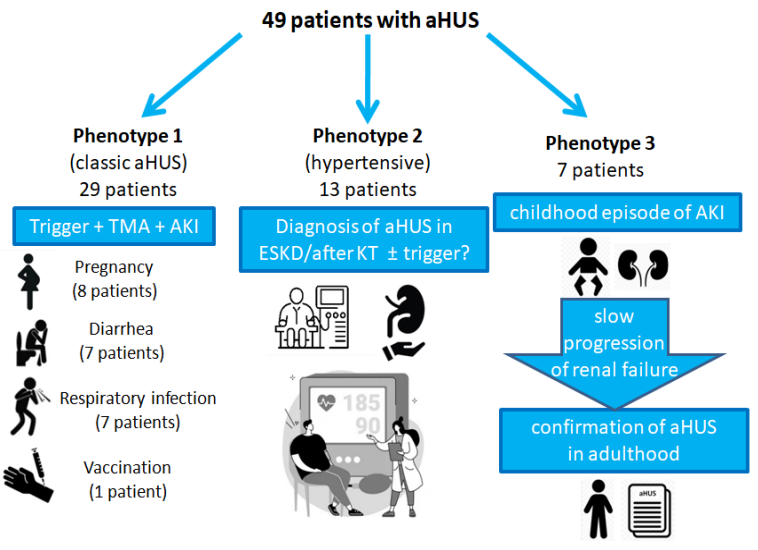
Introduction

The clinical presentation of atypical hemolytic uremic syndrome (aHUS) can vary from patient to patient. Not all patients show the complete triad of thrombotic microangiopathy (TMA), a known triggering factor, genetic mutations of the complement system, malignant arterial hypertension (MAH), and extrarenal manifestations with other organ involvement. We have differentiated and compared the phenotypes of patients with aHUS based on their clinical presentation.

Methods

Forty-nine patients with aHUS were included in the study. All patients were diagnosed in adulthood. They were divided into 3 groups according to the phenotype of the disease course. Phenotype 1 (29 patients) represented the classic aHUS progression, occurring after exposure to a triggering factor and manifesting a vivid picture of TMA with acute kidney injury (AKI). The triggering factor was pregnancy in 8 patients, diarrhea in 7 patients, upper respiratory tract infection in 7 patients and vaccination in 1 patient. In 6 patients, no clear triggering factor could be identified. Phenotype 2 (13 patients) was identified in end-stage chronic kidney disease (ESKD) or after renal allotransplantation; there was no evidence of a triggering factor in the history with the developed clinical picture of aHUS, but there was a long-term severe unstudied arterial hypertension. Phenotype 3 (7 patients) was related to an early childhood episode of AKI with recovery of renal function, slow progression of renal failure, and confirmation of aHUS in adulthood. We evaluated the presence of aHUS-associated genetic mutations, the development of the full triad of TMA at disease onset, MAH, and extrarenal manifestations of aHUS.



Results

Most patients with phenotype 2 were male (12 of 13). The age of patients with phenotypes 1 and 2 at the time of diagnosis verification was slightly higher than that of patients with phenotypes 3 and 4 (see Table 1), but these differences did not reach statistical significance ($p > 0.05$). All patients with phenotype 3 had aHUS genetic mutations, whereas only 38.5% of patients with phenotype 2 had aHUS genetic mutations ($p < 0.05$). The complete TMA triad was present in 83% of patients with phenotype 1. The TMA triad was observed much less frequently in patients with phenotype 3 and phenotype 2, accounting for 29% ($p < 0.05$) and 46% ($p < 0.05$), respectively. MAH was present in almost all patients with phenotype 2 (92%), was absent in patients with phenotype 3 ($p < 0.001$) and was statistically less frequent in patients with phenotype 1 (14% ($p < 0.001$). Extrarenal manifestations of aHUS were less frequent in patients with phenotype 3 (29%), but the differences did not reach statistical significance ($p > 0.05$). Most patients with phenotype 1 were treated with eculizumab (83%), of whom only 29% progressed to ESCKD. Of the 69% of patients with phenotype 2 treated with eculizumab, 67% developed ESCKD. However, the difference between the incidence of ESCKD in phenotype 1 and 2 patients treated with eculizumab did not reach statistical significance ($p = 0.12$). Eculizumab was administered to 57% of phenotype 3 patients, half of whom lost renal function and required dialysis.

	Phenotype 1 (n=29)	Phenotype 2 (n=13)	Phenotype 3 (n=7)
Sex (M/F)	12/17	12/1	3/4
Age	34 [28.5; 41.0]	39.0 [34.0; 45.5]	28 [25.0; 46.0]
Genetic mutations	58%	38,5%	100%
TMA triad	83%	46%	29%
MAH	14%	92%	0%
Extrarenal manifestations	76%	69%	29%
Eculizumab therapy	83%	69%	57%
ESKD with eculizumab	29%	67%	50%

Conclusion

Patients with the selected phenotypes showed significant differences in the presence of genetic mutations, MAH and the complete triad of TMA at disease onset. In addition, a trend toward better renal outcomes with eculizumab treatment was observed in patients with the classic phenotype 1, although this difference did not reach statistical significance. Despite the absence of typical symptoms in some patients, recognizing the differences in the progression of aHUS and certain phenotypic variants allows for early detection of the disease and timely initiation of therapy.