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Single-center Experience of Therapeutic Plasma Exchange in Children with Neuroimmunological Disorders: Indications, Efficacy, and Safety

Nöroimmünolojik Hastalıkları Olan Çocuklarda Terapötik Plazma Değişiminde Tek-merkez Deneyimi: Endikasyonlar, Etkinlik ve Güvenilirlik

Çağatay Günay[1], Gazi Arslan[2], Özlem Özsoy[1], Gamze Sarıkaya Uzan[1], Duygu Aykol[1], Tolga Besci[2], Semra Hız Kurul[1], Adem Aydın[1], Uluç Yiş[1]

[1]Dokuz Eylül University Faculty of Medicine, Department of Pediatric Neurology, İzmir, Turkey
[2]Dokuz Eylül University Faculty of Medicine, Department of Pediatric Intensive Care, İzmir, Turkey

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Abstract

Objective: Therapeutic plasma exchange (TPE) is frequently employed to treat neurological conditions with known or presumed immune pathogenesis in adults, however knowledge and experience in children remains insufficient. The purpose of this study is to perform a retrospective assessment of the indications, long-term efficacy, safety, and complications of TPE in children with various neuroimmunological conditions.

Methods: This investigation was a single-center, retrospective cohort study conducted at a tertiary hospital, analyzing pediatric patients with neuroimmunological diseases who were subjected to TPE.

Results: The median age of the patients was 74.5 (22-180) months, and 60% (n=6) of the patients were female. The indications for TPE included acute disseminated encephalomyelitis, Guillain-Barré syndrome, autoimmune encephalitis, acute necrotizing encephalopathy of childhood, transverse myelitis, acute flaccid myelitis, thrombotic thrombocytopenic purpura, and febrile infection-related epilepsy syndrome. The median number of TPE sessions per patient was five, with a median duration of 8.5 (5-14) days. The study found that two (20%) patients exhibited a complete response to TPE, while partial response was observed in remaining eight (80%) patients. There was neither mortality nor serious adverse events associated with the TPE procedure. At the most recent follow-up, 80% of the patients exhibited neurological sequelae.

Conclusion: TPE was observed to be an effective and well-tolerated treatment modality for children with various neuroimmunological disorders, resulting in a partial response in the majority of cases without any life-threatening complications. The rate of neurological sequelae was high despite positive clinical response, albeit in varying degrees.

Keywords: Therapeutic plasma exchange, Guillain-Barré syndrome, acute disseminated encephalomyelitis, efficacy, safety

Address for Correspondence/Yazışma Adresi: Çağatay Günay MD, Dokuz Eylül University Faculty of Medicine, Department of Pediatric Neurology, İzmir, Turkey
Phone: +90 554 430 82 46 **E-mail:** cagataygunaymd@gmail.com
ORCID ID: orcid.org/0000-0001-7860-6297

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Öz

Amaç: Terapötik plazma değişimi (TPD), yetişkinlerde bilinen veya varsayılan immün patogenezi olan nörolojik durumları tedavi etmek için sıklıkla kullanılmasına rağmen çocuklarda bilgi ve deneyim yetersizdir. Bu çalışmanın amacı, çeşitli nöroimmünolojik hastalıkları olan çocuklarda TPD'nin endikasyonları, uzun süreli etkinliği, güvenliği ve komplikasyonlarının retrospektif bir değerlendirmesini yapmaktır.

Yöntem: Bu araştırma, üçüncü basamak bir hastanede nöroimmünolojik hastalıklara yönelik TPD yapılan pediyatrik hastaları inceleyen, tek merkezli, retrospektif bir kohort çalışmasıydı.

Bulgular: İlk TPD işleminde ortanca yaş 74,5 (22-180) ay olup, hastaların %60'ı (n=6) kızdı. TPD endikasyonları arasında akut dissemine ensefalomiyelit, Guillain-Barré sendromu, otoimmün ensefalit, çocukluk çağı akut nekrotizan ensefalopatisi, transvers miyelit, akut flask miyelit, trombotik trombositopenik purpura ve febril enfeksiyonla ilişkili epilepsi sendromu vardı. Hasta başına ortanca TPD seansı sayısı beşti ve ortanca süre 8,5 (5-14) gündü. Çalışmada iki (%20) hastanın TPD'ye tam bir yanıt gösterdiği, geri kalan sekiz (%80) hastada ise kısmi yanıtın gözlendiği bulundu. TPD prosedürüyle ilişkili mortalite ya da ciddi yan etki yoktu. En son takipte, hastaların %80'inde nörolojik sekel izlendi.

Sonuç: TPD'nin, çeşitli nöroimmünolojik bozuklukları olan çocuklar için etkili ve iyi tolere edilen bir tedavi yöntemi olduğu ve hastaların çoğunda yaşamı tehdit eden herhangi bir komplikasyon olmaksızın kısmi yanıtla sonuçlandığı gözlendi. Değişen derecelerde pozitif klinik yanıta rağmen nörolojik sekel oranı yüksekti.

Anahtar Kelimeler: Terapötik plazma değişimi, Guillain-Barré sendromu, akut dissemine ensefalomiyelit, etkinlik, güvenlik

Introduction

Therapeutic plasma exchange (TPE) is a procedure that lowers the levels of circulating autoantibodies, alloantibodies, monoclonal proteins, and immune complexes by centrifugation and replacement of the plasma with albumin solution or fresh frozen plasma[1-3]. In recent decades, TPE has emerged as a widely recognized therapeutic modality for various pediatric immune-mediated disorders. Among which, neurological disorders are the most common indications[4,5]. However, there still exists only a restricted set of case series and a dearth of randomized controlled trials examining the efficacy and safety of TPE in pediatric patients with neurological disorders, probably due to relative scarcity of these disorders and the technical challenges associated with implementing TPE in pediatric patients[6-8]. Consequently, knowledge pertaining to the acute and long-term outcomes of TPE in the pediatric population remains insufficient and further reports are warranted to establish the effectiveness of TPE in the context of neurological disorders among pediatric patients. Progress in this area of inquiry may pave the way for improved management of neurological disorders and may, in turn, help mitigate the occurrence of chronic neurological sequelae. We therefore conducted a retrospective study of the medical records of pediatric patients with neurological disorders who underwent TPE, with the aim of evaluating the indications, safety, complications, and outcomes of TPE in children.

Materials and Methods

The present study is a retrospective cohort analysis conducted in a single-center on pediatric patients who had undergone TPE due to neurological disorders events between 2015 and 2023. The medical records were perused to gather demographic and clinical data, types of neurological disorders, immunotherapies, length of stay in intensive care units and hospitals, and procedure details including replacement fluid, vascular access, intubation status, number of procedures and courses, duration of the courses, complications, efficacy, and overall outcome.

Determining the Indication of TPE

The criteria for indicating TPE encompassed an inadequate response to first line or standard treatments and the abrupt progression of clinical symptoms, such as marked muscular impairment or respiratory failure. According to the American Society for Apheresis (ASFA) 2019 guidelines, which provide a list of evidence-based indications for TPE in pediatric neurological diseases, all patients were reclassified into four categories based on the quality of published evidence and the strength of recommendations[9]. For patients without a recommendation level in ASFA, the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence were used to categorize[10].

TPE Procedures

A double-lumen venous catheter was inserted into the internal jugular (preferred) or femoral veins for TPE procedures, which were performed every other day at a rate of 1.5 times the predicted plasma volume using Teruma BCT Spectra Optia® Apheresis Sysytem (Tokya, Japan). The plasma volume for each patient was calculated using body surface area, gender, and hematocrit. Fresh frozen plasma

was used as the volume replacement fluid, and acid citrate dextrose-A (dilution 1:10-1:20) was used for anticoagulation during TPE as previously decribed[11]. Vital signs were closely monitored for adverse events during the procedure. Procedure time, whole blood flow rate, processed and removed plasma volumes were recorded. Ionized calcium levels were measured before and after TPE to prevent severe hypocalcemia. All procedures were performed by experienced physicians specialized in apheresis and written informed consent was obtained from all patients after detailed explanation of the procedural risks.

Ethical Approval

The present study was conducted in accordance with the 1964 Declaration of Helsinki and approved by the Local Ethics Committee of Dokuz Eylül University (number of approval: 2021/30-12).

Statistical Analysis

All statistical analyses were conducted using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL). The variables were investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether they were normally distributed. Continuous variables were expressed as mean ± standard deviation, median (minimum-maximum) and interquartile range (IQR), as appropriate.

Results

Demographic and Clinical Data

A total of 92 children received TPE treatment in the specified time period. In 10 of whom, an acute neurological condition was certified as an indication for TPE. Majority of the patients (n=6, 60%) were female and the median age at first procedure of TPE was 74.5 (range: 22-180, 93.8±53.6, IQR: 72-139) months. The indications of TPE encompassed acute disseminated encephalomyelitis (ADEM; n=2, %20), Guillain-Barré syndrome (GBS; n=2, %20), and autoimmune encephalitis (AE), acute necrotizing encephalopathy of childhood, transverse myelitis, acute flaccid myelitis, thrombotic thrombocytopenic purpura (TTP), and febrile infection-related epilepsy syndrome in one patient each (10%). The decision of TPE was based on an inadequate response to first-line or standard treatments in majority of the cohort (n=8, 80%). In contrast, two (20%) patients underwent TPE due to sudden progression of clinical findings, such as severe muscle weakness or respiratory failure. Based on the 2019 guidelines set forth by the ASFA, four individuals, constituting 40% of the cohort, were categorized under group I, whereas two participants, comprising 20% of the sample, were categorized under group II. The roles of TPE in the remaining four (40%) patients were not covered by the ASFA recommendations, but had Oxford level 4 evidence which represents case-series and poor cohort studies. Demographic and clinical features, treatment modalities and outcomes of the study population are summarized in Table 1.

Procedures and Other Treatment Modalities

The number and frequency of TPE procedures were determined based on the clinical scenario. A total of 58 procedures were administered to ten patients. The median number of TPE sessions per patient was five and ranged between five and seven (mean: 5.8±1.03, IQR: 5-7). The median duration of procedures was 8.5 days (range: 5-14, mean: 8.5±2.79, IQR: 7-10). The time interval from the onset of the acute condition to the first TPE intervention varied between 1-10 days (with a median value of 4.5 days, mean value of 4.4±2.75 days, and an IQR of 2.5-5 days).

TPE was first-line therapy in only one (10%) patient with TTP, in whom steroid treatment was given adjunctively. In one of the GBS patients, TPE and intravenous immunoglobulin (IVIg) were applied in combination and sequentially (zipper method) due to rapidly progressive muscle weakness and respiratory failure. A total of seven (70%) patients received IVIg, of which four (40%) were administered prior to TPE. The duration of IVIg treatments ranged from two to five days, with a total dose of 2 g/kg. Out of the total number of patients, 80% (n=8) received corticosteroids, with 70% of whom (n=7) having taken it before undergoing TPE. Corticosteroid regimens consisted of pulse methylprednisolone 30 mg/kg/dose, maximum 1 g) given for 5-10 days followed by a gradual reduction in dosage over a period ranging from 7 to 30 days using oral maintenance taper. While five (50%) patients were administered both IVIg and corticosteroid therapy, none of the patients were subjected to second-line immunotherapy.

Adverse Events and Complications

There was no mortality associated with TPE procedure. The procedures were not terminated due to adverse events in any of the patients. A slight and easily rectifiable electrolyte imbalance was detected in a combined group of four (40%) patients, with three of them (30%) experiencing hyponatremia.

Table 1. Demographic and clinical features, treatment modalities and outcomes of the study population

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age (months)	156	37	72	76	73	22	72	161	180	89
Gender	F	F	M	M	M	F	F	F	F	M
Diagnosis	GBS	GBS	ADEM	ADEM	AE	ANEC	TM	AFM	TTP	FIRES
Evidence level of indication	ASFA I, 1A	ASFA I, 1A	ASFA II, 2C	ASFA II, 2C	ASFA I, 1C	Oxford level 4, grade D	Oxford level 4, grade D	Oxford level 4, grade D	ASFA I, 1A	Oxford level 4, grade D
Disease duration before TPE (days)	1	4	5	4	10	5	7	5	1	2
Treatments	IVIg (zipper method)	IVIg (after TPE)	IVIg (before TPE) MP (before IVIg)	IVIg (before TPE) MP (before IVIg)	IVIg (before TPE) MP (before IVIg)	IVIg (before TPE) MP (before IVIg)	MP (before TPE)	IVIg (before TPE) MP (before IVIg)	MP (adjucvant)	MP (before TPE)
PIM3 score	3.90%	4.05%	10.10%	10.05%	3.5%	5.01%	3.09%	4.08%	1.50%	2.60%
PRISM3 score	4	11	12	12	5	5	6	5	2	5
Vascular access	Jugular vein	Jugular vein	Jugular vein	Jugular vein	Subclavian vein	Jugular vein	Jugular vein	Jugular vein	Jugular vein	Subclavian vein
Intubation time with/ without TPE (days)	10/26	10/36	7/2	5/6	0/0	1/7	10/10	14/4	0/0	0/0
Number of TPE procedures/courses	1/5	1/5	1/7	1/5	1/7	1/5	1/5	1/7	1/5	1/7
Length of TPE course (days)	10	10	7	5	7	5	10	14	10	7
Complications related to TPE	Hyponatremia	Hyponatremia	None	None	None	None	None	Hyponatremia	Hypocalcemia	None
Improvement with TPE	Partial response	Partial response	Partial response	Partial response	Complete response	Partial response	Partial response	Partial response	Complete response	Partial response
Length of stay in the intensive care unit/ hospital (days)	36/65	46/56	12/37	15/32	11/21	14/34	20/23	18/26	9/14	9/12
Follow-up duration (months)	8	60	5	156	12	60	24	36	12	48
Outcome										
Motor impairment	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Cognitive impairment	No	No	Yes	Yes	No	Yes	No	No	No	Yes
Epilepsy	No	No	No	No	No	Yes	No	No	No	Yes

TPE: Therapeutic plasma exchange, PIM3: Pediatric index of mortality, PRISM3: Pediatric risk of mortality 3, F: Female, M: Male, GBS: Guillain-Barré syndrome, ADEM: Acute disseminated encephalomyelitis, AE: Autoimmune encephalitis, ANEC: Acute necrotizing encephalopathy of childhood, TM: Transverse myelitis, AFM: Acute flaccid myelitis, TTP: Thrombotic thrombocytopenic purpura, FIRES: Febrile infection-related epilepsy syndrome, ASFA: American Society for Apheresis, IVIg: Intravenous immunoglobulin, MP: Methylprednisolone

Efficacy and Outcome

After undergoing TPE, two patients (20%) exhibited a complete response in signs and symptoms. Patients with a complete response to TPE had underlying etiologies of AE and TTP. Although partial response was observed in eight (80%) patients, no patient demonstrated a complete lack of response.

The study findings indicate that patients spent a median of 14.5 days in the intensive care unit (range: 9-46, mean: 19±12.35, IQR: 11.25-19.5). Furthermore, the median hospital stay duration was 29 days, with a range of 12 to 65 days and an IQR of 21.5-36.25 (mean: 32±17.7). The overall clinical follow-up duration varied from 6 to 156 months, with a mean of 42.1±36.17 months and a median of 30 months (IQR: 12-57). At the most recent follow-up examination, eight out of ten patients (80%) exhibited neurological sequelae, including motor impairment (n=4, 40%), cognitive and motor impairment (n=2, 20%), and cognitive-motor impairment and epilepsy (n=2, 20%). Regarding the two patients who achieved full recovery, one had AE and the other had TTP.

Discussion

Rapid clearance of pathogenic molecules in immune-mediated or autoimmune disorders is anticipated to accelerate the recovery process or provide sufficient time for alternative therapies to take effect. TPE is most frequently used for neurological disorders in adults, whereas its application in children poses greater challenges due to a lack of consensus regarding the indications, more frequent technical issues concerning vascular access, reduced blood volume, higher incidence of adverse events, and relatively poor cooperation[12-14]. Nonetheless, recent technical advancements and the availability of different types of central venous catheters and ports have improved safety and encouraged the use of TPE in in pediatric patients[15,16]. This modality is now utilized as a primary intervention or as an ancillary or substitute therapy for neurological disorders based on the ASFA 2019 guidelines which regularly revise evidence-based suggestions[9]. Due to the paucity of randomized controlled trials investigating the efficacy and safety of TPE in pediatric populations, the literature has largely relied on the retrospective analysis of small cohorts of patients from various centers, with each center contributing its own experiences to the body of knowledge[6,7,17]. Therefore, the objective of this study is to provide a comprehensive description of the experience of a tertiary pediatric center regarding the use of TPE. Our investigation identified GBS and ADEM as the predominant indications for TPE in our cohort. These findings are in line with those reported in previous studies that have specifically evaluated the use of TPE in pediatric neurology[6,18]. Moreover, it is noteworthy that GBS was initially reported as the most frequent indication for TPE in a study that encompassed a broader range of diseases beyond neurological conditions in the pediatric population[19].

After the diagnosis of ADEM, the therapeutic goal is to promptly mitigate the inflammatory response in the central nervous system to facilitate clinical recovery. Although there have been no randomized controlled trials for the treatment of ADEM, the available therapies are derived from anecdotal evidence presented in case reports and case series. Given the presumed immune-mediated mechanism of ADEM, immunomodulatory agents remain the primary treatment form. The use of high-dose steroids may benefit ADEM patients with early intervention of inflammatory response, but this has not been validated by randomized controlled trials. Intravenous immunoglobulin is advocated for children who are unresponsive to steroids or in whom a contraindication is identified. TPE is recommended for patients with refractory fulminant disease. There is no established standard for determining the optimal TPE regimen in ADEM. In most studies, clinical improvement was observed within days, usually after 2-3 TPE sessions. Most published experiences describe 5-7 TPE treatments. Overall, according to the ASFA 2019 guidelines, ADEM is classified as a category II indication[9]. Our patients diagnosed with ADEM received pulse methylprednisolone and IVIG as the initial treatment regimen. However, due to the lack of clinical improvement with these therapies, we proceeded with TPE. Although our patients exhibited some partial response after undergoing 5-7 TPE sessions, they continued to experience residual deficits, such as motor and cognitive impairments. In contrast, other studies have reported moderate to marked improvements in 50-75% of ADEM patients with a similar history of prior steroid and IVIG treatments[6,7,20]. Hence, there is abundant room for further progress in determining the role of TPE in ADEM.

Published data presents conflicting findings regarding the efficacy, response to treatment, and neurological sequelae of treatment options in GBS. Both TPE and IVIg have demonstrated superiority over conservative treatment for disability recovery, making them the most efficacious treatments for both pediatric and adult populations[9,21,22]. Aside from studies indicating no substantial difference

between TPE and IVIg in treating GBS, there is also evidence suggesting that TPE may be somewhat more effective in children with GBS who require mechanical ventilation[9,23-25]. Lower incidence of adverse effects and readily availability of IVIG makes it commonly employed first-line therapy in GBS[6,7,9,21]. In GBS, the standard TPE protocol involves exchanging 1-1.5 plasma volumes 5-6 times during a 10-14 day period, with some patients requiring further treatment sessions[9]. According to the ASFA 2019 guidelines, TPE in GBS belongs to ASFA category I as primary treatment. In our study population, we treated our two GBS cases in accordance with the ASFA-recommended number and timing of TPE procedures. We administered IVIg treatment sequentially (via the zipper method) in one patient, while in the other patient, we provided IVIg treatment after observing only a partial response to TPE. Although GBS typically carries a favorable prognosis, the presence of motor sequelae in our patients could be attributed to the administration of TPE in individuals with pre-existing severe clinical manifestations.

In the present study, two patients underwent TPE in accordance with the ASFA recommendations under category I for AE and TTP, and both were associated with complete recovery. The number of published pediatric patients of AE treated with TPE has been increasing steadily, but due to a lack of consistent data, it is difficult to estimate the proportion of TPE usage compared to other immune interventions[26]. Once diagnosed, immunotherapy should be initiated promptly. High-dose corticosteroids, IVIG, or TPE are considered first-line therapies, and a search for underlying tumors should be conducted. However, there is no consensus on the exact order in which to apply these treatments or when to initiate a combined multimodal approach. There are no systematic comparisons available between the modalities. TPE removes pathophysiologically relevant antibodies and is an adjunct to immunotherapy for suppressing active inflammation and antibody production[9,26]. The rate of full recovery demonstrated a steady increase over time, from immediately after TPE (21.1%) to the last follow-up (64.2%). In children with a similar median length of follow-up, a trend towards a higher rate of full recovery was observed with a first-line immune therapy strategy consisting of TPE, steroids, and IVIG (67.1%), or TPE and steroids (65.2%), compared to TPE and IVIG (50%) or TPE alone (42.8%)[26]. For AE, 5-12 TPE treatments over 1-3 weeks with individually adjusted intervals between treatments are recommended[9]. The strategy of using all three first-line immune therapies associated with the best prognosis in the literature was applied in our patient with AE (seven procedures of TPE over seven days), who had full recovery in line with the literature[26].

Acquired TTP is a rare and potentially life-threatening hematological disorder in pediatric patients, characterized by the formation of microthrombi throughout the body[27]. The current routine initial treatment involves a combination of TPE, corticosteroids, and rituximab. The rationale for TPE is based on its ability to remove the patient's deficient plasma and replace it with donor plasma containing normal levels of ADAMTS13, thereby preventing further thrombus formation and promoting resolution of the disease[9,27]. Corticosteroids are commonly used as an adjunctive therapy, either as daily prednisone or pulsed methylprednisolone for a few days, or a combination; however, the comparative efficacy of these approaches has not been definitively established by clinical trials. Rituximab is frequently used to treat refractory or relapsing cases[9]. The prompt initiation of treatment is crucial in pediatric patients with acquired TTP, as even in the absence of neurological symptoms at presentation, there is a significant risk of subsequent major stroke[28]. As per the recommended guidelines, TPE was initiated expeditiously along with adjuvant pulse methylprednisolone in our pediatric, leading to an excellent clinical outcome. Although TPE has been shown to increase the survival rate of pediatric patients with acquired TTP from 10-20% to 80-90%, as evidenced by our case, further randomized controlled trials are warranted to establish standard therapeutic modalities for pediatric TTP.

Study Limitations

Among the remaining four patients in our study, diagnosed with acute necrotizing encephalopathy of childhood, transverse myelitis, acute flaccid myelitis, and febrile infection-related epilepsy syndrome, the level of evidence for TPE was supported by case series and low-quality cohort studies, rather than by established guidelines from the ASFA[29-33]. While our study found partial benefit of TPE in these patients, the simultaneous use of immunomodulatory agents, antibiotic-antiviral treatments, anti-seizure medications, and other supportive treatments may have contributed to the recovery. Even though our findings suggest that TPE may be a viable treatment option for these conditions in children, given the diverse etiologies and clinical presentations of these diseases, more research is needed to clarify the exact role, efficacy, and safety of TPE in pediatric patients.

Conclusion

The current study provides evidence that TPE is a safe and effective treatment option for immune-mediated neurological diseases, leading to substantial neurological recovery in a significant proportion of the pediatric patients with severe manifestations. The limited availability of established guidelines and experience derived from a large number of cases in the adult population, coupled with the prolonged neurological sequelae experienced by pediatric patients, underscores the need for further research in this topic.

Ethics

Ethics Committee Approval: The present study was conducted in accordance with the 1964 Declaration of Helsinki and approved by the Local Ethics Committee of Dokuz Eylül University (number of approval: 2021/30-12).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ç.G., G.A., Ö.Ö., G.S.U., D.A., T.B., S.H.K., A.A., U.Y., Concept: Ç.G., G.A., G.S.U., T.B., A.A., Design: Ç.G., Ö.Ö., D.A., S.H.K., U.Y., Data Collection or Processing: Ç.G., G.A., Ö.Ö., G.S.U., D.A., T.B., Analysis or Interpretation: Ç.G., G.A., S.H.K., A.A., U.Y., Literature Search: Ç.G., Ö.Ö., G.S.U., D.A., T.B., Writing: Ç.G., G.A., Ö.Ö., G.S.U., D.A., T.B., S.H.K., A.A., U.Y.

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