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CASE REPORT

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Evaluation of the Efficacy of Pars Plana Ahmed Glaucoma Valve Implantation with Vitrectomy in Uncontrolled Neovascular Glaucoma Secondary to Proliferative Diabetic Retinopathy: A Retrospective Analysis

Proliferatif Diyabetik Retinopatiye Sekonder Kontrolsüz Neovasküler Glokomda Vitrektomi ile Birlikte Pars Plana Ahmed Glokom Valfi İmplantasyonunun Etkinliğinin Değerlendirilmesi: Retrospektif Bir Analiz

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ABSTRACT

Background: Today, debate continues regarding the effective management of neovascular glaucoma (NVG) associated with proliferative diabetic retinopathy (PDR) and the success of the combination approach of pars plana (PP) Ahmed glaucoma valve (AGV) implantation and PP vitrectomy (PPV) in this patient. To evaluate the effect and tolerability of PP AGV implantation and PPV combined approach on intraocular pressure (IOP), visual acuity, and tolerability in patients with PDR and secondary uncontrolled NVG.

Materials and Methods: Thirty-seven patients with severe NVG secondary to PDR who were resistant to conventional medical therapies underwent surgery between May 2020 and January 2023. The surgical procedure involved 23-gauge PPV along with PP AGV implantation. Demographic information, surgical details, and complications were recorded. Statistical analyses were performed using the IBM SPSS statistics software.

Results: The mean age of the patients was 52.8 years. Preoperatively, the mean IOP was 36.9±12.3 mmHg, decreasing significantly to 19.1±4.0 mmHg at the 12 month follow-up. The mean number of glaucoma medications reduced from 3.9±0.2 to 1.9±1.5 postoperatively. Best-corrected visual acuity improved in 17 patients, remained unchanged in 11, and deteriorated in 9. The complications included fibrinoid reaction, hyphema, transient hypotony, choroidal effusion, and one case requiring fibrotic band excision. No retinal complications or corneal insufficiency were reported.

Conclusion: The study concludes that the combined surgical approach of PP AGV implantation and 23-gauge PPV is a promising and effective strategy for managing uncontrolled NVG secondary to PDR. The method demonstrated positive outcomes in terms of IOP control, medication reduction, and visual improvement, with manageable complication rates.

Keywords: Ahmed glaucoma valve, neovascular glaucoma, pars plana vitrectomy, proliferative diabetic retinopathy

ÖZ

Amaç: Günümüzde proliferatif diyabetik retinopatiye (PDR) ile ilişkili neovasküler glokomun (NVG) etkili bir şekilde yönetilmesi ve bu hastalarda uygulanan pars plana (PP) Ahmed glokom valfi (AGV) implantasyonu ve PP vitrektomi (PPV) kombinasyonu yaklaşımının başarısı konusunda tartışmalar devam etmektedir. Sekonder kontrol edilemeyen NVG'si olan PDR'li hastalarda, PP AGV implantasyonu ve PPV kombine yaklaşımın göz içi basıncı (GİB), görme keskinliği üzerine etkisini ve tolere edilebilirliğini değerlendirmek amaçlanmıştır.

Gereç ve Yöntemler: Medikal tedavilere dirençli, PDR'ye ikincil şiddetli NVG'si olan 37 hastaya Mayıs 2020 ile Ocak 2023 tarihleri arasında ameliyat yapıldı. Cerrahi prosedür, PP AGV implantasyonu ile birlikte 23-gauge PPV'yi içeriyordu. Demografik bilgiler, cerrahi ayrıntılar ve komplikasyonlar kaydedildi.

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ÖZ

Bulgular: Hastaların ortalama yaşı 52,8 idi. Ameliyat öncesi ortalama GİB 36,9±12,3 mmHg iken, 12 aylık takipte 19,1±4,0 mmHg'ye düşmüştür. Ortalama glokom ilacı sayısı ameliyat sonrasında 3,9±0,2'den 1,9±1,5'e düşmüştür. En iyi düzeltilmiş görme keskinliği 17 hastada iyileşti, 11'inde değişmedi ve 9'unda kötüleşti. Komplikasyonlar arasında fibrinoid reaksiyon, hifema, geçici hipotoni, koroidal efüzyon ve fibrotik bant eksizyonu gerektiren bir olgu yer aldı. Retinal komplikasyon veya kornea yetmezliği bildirilmedi.

Sonuç: Bu çalışma, PP AGV implantasyonu ve 23-gauge PPV kombine cerrahi yaklaşımının PDR'ye ikincil kontrolsüz NVG'yi yönetmek için umut verici ve etkili bir strateji olduğu sonucuna varmaktadır. Yöntem, yönetilebilir komplikasyon oranları ile GİB kontrolü, ilaçların azaltılması ve görsel iyileşme açısından olumlu sonuçlar ortaya koymaktadır.

Anahtar Kelimeler: Ahmed glokom valfi, neovasküler glokom, pars plana vitrektomi, proliferatif diyabetik retinopati

Introduction

Neovascular glaucoma (NVG), a challenging and potentially devastating consequence of proliferative diabetic retinopathy (PDR), is characterized by the growth of new, abnormal blood vessels on the iris and the anterior chamber angle, resulting in increased intraocular pressure (IOP) and optic nerve damage (1). Conventional medical therapies frequently fail to effectively manage NVG associated with PDR, necessitating more invasive interventions. Among these, the use of glaucoma drainage implants has emerged as a viable option for refractory glaucoma in the context of PDR. These devices typically involve the placement of a tube in the anterior chamber, which functions to divert aqueous humor to an extracorporeal reservoir, thereby alleviating elevated IOP (2). However, the clinical management of NVG in PDR is complicated by secondary complications such as vitreous hemorrhage or vitreous opacity. In such scenarios, vitrectomy might be necessary to clear the visual axis and allow for adequate laser treatment. Furthermore, anatomical and pathological considerations in advanced stages of the disease often render the anterior chamber an unsuitable site for tube placement (3,4).

In specific cases involving patients with uncontrolled glaucoma and concurrent posterior segment disease, the application of combined pars plana vitrectomy (PPV) alongside the placement of a glaucoma valve in the PP region may yield optimal outcomes. The anterior chamber may not be the optimal site for tube implantation in certain clinical scenarios, such as advanced glaucoma accompanied by secondary angle closure or angle neovascularization, as well as in cases involving corneal diseases and other anterior chamber abnormalities. In such instances, a more suitable alternative is the placement of the implant through the PP, concomitant with vitrectomy. This approach proves particularly beneficial when anterior segment disease poses a safety concern, making the conventional placement of the glaucoma tube in the anterior chamber impractical. This procedure not only addresses the challenges posed by anterior segment abnormalities but also provides a comprehensive solution for conditions necessitating both glaucoma management and posterior segment intervention. The combined implementation of a drainage device, such as Ahmed glaucoma valve (AGV), and PPV presents a viable and judicious option for patients experiencing ocular hypertension despite undergoing maximum IOP-lowering treatments, along with complications such as vitreous hemorrhage (5,6). Furthermore, when challenges such as compromised retinal fundus visualization arise due to factors like dense cataract, corneal edema, hyphema, or vitreous hemorrhage, the inclusion of PPV becomes imperative for the comprehensive performance of panretinal photocoagulation. This integrated surgical strategy offers the advantage of addressing both pathologies in a single procedure, potentially streamlining the overall management and enhancing patient outcomes, as opposed to undertaking these surgeries at different time points.

Effective management of NVG associated with PDR has sparked controversy in current discussions. This study aimed to assess the outcomes of a combined approach involving PP AGV implantation and PPV in patients with PDR experiencing secondary uncontrolled NVG. The evaluation focuses on key parameters such as IOP, visual acuity, and tolerability. By investigating the impact of this combined intervention, we contribute valuable insights to the ongoing discourse surrounding the optimal treatment strategy for NVG associated with PDR.

Materials and Methods

The present study, which was conducted with the approval of the Ethics Committee of Başakşehir Çam and Sakura City Hospital (KAEK/17.01.2024.01, date: 18.01.2024) and in adherence to the principles of the Declaration of Helsinki, aimed to retrospectively analyze the clinical outcomes of a combined surgical approach in patients with PDR complicated by uncontrolled NVG. This study focused on cases where NVG was resistant to conventional medical therapies and necessitated the implementation of a 23-gauge vitrectomy in conjunction with AGV implantation. Patients who underwent surgery between May 1, 2020 and January 31, 2023 were included in the study.

The patient inclusion criteria for this study were defined to encompass individuals experiencing severe NVG, as evidenced by an IOP of 30 mmHg. In addition, vitreous hemorrhage or dense vitreous opacity with underlying pathology of PDR was observed in eligible patients. In total, 37 patients were identified who met these criteria and were thus included in the study. Phakic patients were not included in the study. Demographic information of the patients was recorded, and complications arising from surgery were tracked.

Surgical Procedure

The surgical procedure, conducted under general anesthesia, began with a fornix-based periotomy complemented by superotemporal and superonasal relaxing incisions. The extraocular rectus muscles were carefully isolated using a muscle hook. The functionality and patency of the AGV were verified using balanced saline solution. Subsequently, the AGV was anchored to the sclera using an ethibond suture approximately 9-10 mm from the limbus in the superotemporal quadrant. Vitrectomy was performed using a 23-gauge vitreous cutter driven by a vitrectomy unit. A sclerotomy was placed 3.5 mm posterior to the limbus in all eyes. Panretinal endolaser photocoagulation was executed. To place the AGV tubes in the PP, a 23-gauge sclerotomy was performed at a distance of 3.5 mm from the limbus. Notably, this was performed without creating a scleral flap. The tubes were then sutured to the sclera. Postoperative care included a regimen of topical antibiotics (moxifloxacin administered four times daily), corticosteroids (dexamethasone four times daily), and cycloplegic agents (cyclopentolate three times daily) for 1 month.

Statistical Analysis

Statistical analyses for this study were conducted using IBM SPSS Statistics software, version 28. Descriptive statistics were employed to summarize continuous variables, with mean values presented along with standard deviations and medians accompanied by minimum and maximum range values. Categorical variables are reported using numbers and percentages. For the analysis of more than two repeated measurements, Friedman test (Non-parametric repeated measures ANOVA) with post-test (Dunn's multiple comparisons test) and repeated measures ANOVA with post-test (Tukey-Kramer multiple comparisons test) were applied. Pairwise comparisons before and after surgery were conducted using the Wilcoxon matched-pairs signed-ranks test. The chosen significance level for all analyses was set at 95%, deeming results as statistically significant when the p-value was 0.05.

Results

The study comprised 37 patients who developed NVG as a complication of PDR and subsequently underwent AGV implantation. Table 1 presents the demographic and clinical characteristics of the patients. The mean age at the time of surgery was 52.8±15.8 years, with 51.3% of the patients being male and 48.7% female. The mean axial length was 21.9±1.4 mm. When the preoperative and postoperative data of the patients were compared (Table 2), it was determined that the preoperative IOP values of the patients were significantly higher than the postoperative 1st, 3rd, and 12th IOP values (36.9±12.3, 19.4±6.5, 18.9±3.6 and 19.1±4.0; p<0.001, respectively) (Figure 1). However, there was no statistically significant difference between the postoperative 1st, 3rd, and 12th IOP values (p>0.05). Table 2 elucidates the alterations in the mean anti-glaucoma medication number (AGM-N) used by the patients in the pre- and postoperative periods. When the patients' preoperative and postoperative AGM-Ns were compared (Table 2), preoperative AGM-N values were higher than the numbers of postoperative 1st, 3rd, and 12th month AGM-N (3.9±0.2, 1.4±1.4, 1.8±1.5 and 1.9±1.5; p<0.001, respectively). However, there was no statistical difference between the AGM-Ns at postoperative 1st, 3rd, and 12th month (p>0.05).

While 11 patients experienced no change in visual acuity, 9 patients exhibited a decrease, and 17 patients demonstrated an improvement. The mean best-corrected visual acuity (BCVA-logMAR) values were 1.06±0.64 preoperatively and 0.91±0.45 postoperatively. The postoperative 12th month visual acuity levels of the patients were found to be lower than the preoperative month visual acuity levels (p=0.0039) (Figure 2). Fibrinoid reaction in three patients and hyphema in four patients occurred and

Table 1. Demographics and clinical characteristics of the participants

		Avg. ± SD	Median (min.-max.)
Surgical age (years)		52.8±15.8	53.0 (41-68)
Sex	**Male**	19 (51.3%)	
	Female	18 (48.7%)	
Axial length (mm)		21.9±1.4	21.8 (20.3-25.4)
Preoperative BCVA (logMAR)		0.91±0.46	1.00 (0.7-1.3)
IOP (preoperative)		37.6±8.1	39.0 (29.0-55.0)
Number of anti-glaucoma medications (preoperative)		3.8±0.5	4.0 (3.0-4.0)

Continuous variables are presented as the mean ± standard deviation/median (min.-max.). Categorical variables are presented as numbers (%)
Avg.: Average, BCVA: Best corrected visual acuity, IOP: Intraocular pressure, SD: Standard deviation, min.-max.: Minimum, maximum

Table 2. Comparison of the preoperative and postoperative results of the study groups

	Preoperative (A)	Postoperative 1st month (B)	Postoperative 3rd month (C)	Postoperative 12th month (D)	p-value
n	37	37	37	37	-
IOP, mmHg	36.9±12.3 36.0 (15.0-60.0)	19.4±6.5 19 (10-35)	18.9±3.6 19 (14-29)	19.1±4.0 19 (13-29)	[b] <0.0001
Comparison p	<0.001, <0.001, <0.01, >0.05, >0.05, >0.05				
AGM-N, n	3.9±0.2 4 (3-4)	1.4±1.4 1 (0-3)	1.8±1.5 2 (0-4)	1.9±1.5 2 (0-4)	[a] <0.0001
Comparison p	<0.001, <0.001, <0.001, >0.05, >0.05, >0.05				
Visual acuity (logMAR)	1.06±0.64 1.00 (0.00-2.00)			0.91±0.45 1.00 (0.00-1.30)	[c] 0.0039

[a]: Friedman test (Non-parametric repeated measures ANOVA) with post-test (Dunn's multiple comparisons test)
[b]: Repeated measures ANOVA with post-test (Tukey-Kramer multiple comparisons test)
[c]: Wilcoxon matched-pairs signed-ranks test
Statistical significance level =p<0.05. When p values obtained by ANOVA tests are <0.05, comparison p values between groups are determined (group A-B, group A-C, group A-D, group B-C, group B-D, group C-D, respectively). Non-parametric data are given as mean ± SD and median (min.-max.)
SD: Standard deviation, IOP: Intraocular pressure, AGM-N: Number of anti-glaucoma medications, min.-max.: Minimum, maximum

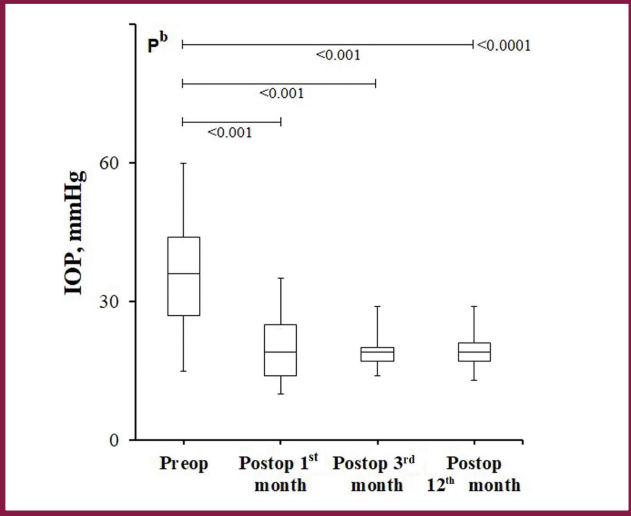

Figure 1. Comparison of preop and postop IOP values. It is seen that the IOP values of the postoperative 1st, 3rd, and 12th months are lower than the preoperative IOP values
b: Repeated measures ANOVA with post-test
IOP: Intraocular pressure

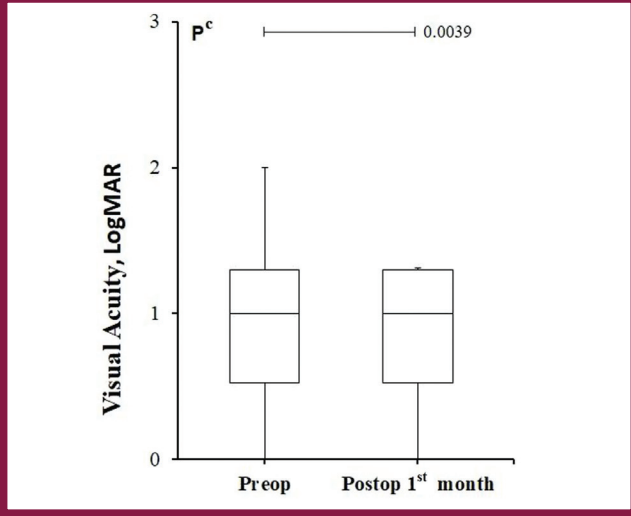

Figure 2. Comparison of preop and postop visual acuity values. It can be seen that the visual acuity values of the postoperative 12th month are lower than the preoperative visual acuity values
c: Wilcoxon matched-pairs signed-ranks test

resolved with topical treatment. Transient hypotony and choroidal effusion were observed in seven patients, with one patient requiring fibrotic band excision from the tube tip 2 months postoperatively. Ten patients had elevated IOP above 21 at the 12-month examination. Notably, no retinal complications or corneal insufficiency were reported in any patient.

Discussion

This retrospective study focused on evaluating the efficacy of PP AGV implantation in patients with NVG. The primary findings of this study revealed a significant improvement in both IOP control and a reduction in the need for glaucoma medications postoperatively. At the end of the 12-month follow-up period, IOP <21 was observed in

26 (70.2%) patients. The mean AGM-Ns used decreased from 3.9±0.2 to 1.9±1.5. The study by Yalvac et al. (7) provided valuable insights into the 1-year surgical success rate of AGV implantation for NVG. In their investigation involving 38 eyes with NVG, the reported 1-year surgical success rate was 63.3%. In comparison, Netland (8) reported a slightly higher 1-year surgical success rate of 73.1% in a study involving 38 eyes with NVG.

In the management of complex glaucoma cases, particularly those involving concurrent PDR, the integration of PPV with PP placement of a glaucoma drainage device has emerged as a promising therapeutic strategy. The literature reflects a growing interest in this technique, with studies examining the efficacy and safety profiles of various glaucoma valves, including Baerveldt (5,6) Molteno (5,7) and AGV (8,9), each presenting unique characteristics and challenges. The Baerveldt and Molteno tubes are noted for their unregulated flow feature, which, while effective in reducing IOP, carries the risk of postoperative complications such as hypotony and choroidal detachment. On the other hand, the AGV, distinguished by its built-in flow regulation mechanism, offers a significant advantage in preventing hypotony (10). This feature is particularly advantageous in complex glaucoma cases where the regulation of IOP is crucial. Additionally, the AGV is often considered technically easier to insert, a factor that can influence surgical outcomes and postoperative recovery.

The success of PP placement of glaucoma drainage devices, such as Baerveldt or Molteno tubes, in lowering IOP in patients with NVG has been well documented in previous studies. A seminal study by Luttrull and Avery (9) in 1995 demonstrated compelling results, showcasing IOP control below 22 mmHg in all 2 patients with NVG following PP placement of Baerveldt or Molteno tubes. The mean IOP exhibited a remarkable decrease from 46 mmHg to 16 mmHg, accompanied by a reduction in AGM-Ns from 2.9 to 0.7. Subsequent investigations, such as the study by Faghihi et al. (5), focused on the PP placement of an AGV combined with vitrectomy in 18 eyes with NVG. The mean preoperative IOP was notably high at 53.3 mmHg, with 2.7 drugs, and IOP improved to 16.3 managed by 0.94 drugs postoperatively. Similarly, Jeong et al. (6) demonstrated favorable outcomes with PP AGV in 11 eyes, achieving IOP levels between 8 mmHg and 18 mmHg. In our current study involving the PP placement of the AGV for NVG, we observed outcomes consistent with those reported for Baerveldt and Molteno tubes. Specifically, 70.2% of the NVG eyes in our study achieved IOP levels below 21 mmHg at the final examination. Collective evidence from these studies suggests that PP placement of various glaucoma drainage devices, including AGV, yields favorable outcomes in terms of IOP control and reduction in AGM dependence for patients with NVG. These findings contribute to the growing body of knowledge supporting the efficacy of this surgical approach in managing the complex challenges posed by NVG.

The combined approach of AGV with vitrectomy offers several advantages in patients with PDR suffering from uncontrolled IOP. This methodology not only addresses elevated IOP but also directly combats the underlying issues associated with PDR and NVG. The combined surgery facilitates the removal of vitreous hemorrhages and opacities. This clearance is crucial because it allows for an improved evaluation of the fundus during the early postoperative period, which is essential for monitoring the patient's progress and detecting any potential complications. By combining these procedures, both NVG and PDR can be addressed in a single operation. This approach is not only efficient but also reduces the patient's exposure to multiple surgical risks and recovery periods. In addition, intraoperative endolaser photocoagulation, often performed during vitrectomy, can induce regression of iris neovascularization, a significant factor in NVG. Placing the drainage implant in the PP region minimizes the risk of endothelial touch and hyphema (10). This placement is especially beneficial in patients with compromised anterior segments. However, this combined surgical approach is not without potential complications. Posterior segment issues such as incorrect placement of the tube and retinal detachment are risks that need to be considered (5,11). Furthermore, when the tube is placed in the anterior chamber, it allows for easier visualization and diagnosis of tube obstruction. Preference is based on the belief that the final visual outcome in these patients is influenced not only by the management of IOP but also by the progression and control of the underlying diabetic retinopathy.

The comparison of complications associated with the use of PP drainage implants in various studies highlights the general safety and manageability of this approach, although it is not without risks. In a previous study involving PP Baerveldt or Molteno tubes, the reported complications included one instance each of vitreous hemorrhage, hyphema, and choroidal hemorrhage along with eight cases of choroidal effusion (12). These complications, while serious, appear to be relatively rare. Faghihi et al. (5) reported a slightly broader range of complications, with one patient each developing vitreous hemorrhage, hypotony, and choroidal effusion, and two patients experiencing phthisis bulbi. This indicates a risk of more severe outcomes, albeit in a minority of cases. This suggests that while complications can occur, they can often be managed effectively without long-term detriment to the patient. In your study, the most common complication was hyphema formation, occurring in

4 eyes (10.8%). There were no cases requiring the removal of the AGV because of persistent hypotony, and issues like transient hypotony and choroidal effusion were resolved with topical treatment. These findings suggest that while there is a risk of complications with PP drainage implants in patients with NVG, these complications are generally limited and manageable. This supports the use of these implants as a viable option for treating NVG, particularly in complex cases where other treatments have failed.

Study Limitations

This study has several limitations that must be acknowledged. As a retrospective study, it inherently lacks the control and randomization of a prospective trial. There was a potential loss of follow-up data. The follow-up schedule was not standardized but was based on clinical necessity. The non-randomized nature of the study and the variable follow-up periods could lead to selection biases. Our findings, while promising, underscore the need for more rigorous prospective and comparative clinical trials.

Conclusion

In conclusion, while this study contributes valuable data to the existing body of knowledge on NVG treatment, these limitations highlight the need for continued research. Future studies, particularly those that are prospective and comparative, are essential to further validate and refine the treatment strategies for NVG.

Ethics

Ethics Committee Approval: The present study, which was conducted with the approval of the Ethics Committee of Başakşehir Çam and Sakura City Hospital (KAEK/17.01.2024.01, date: 18.01.2024) and in adherence to the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: M.K., D.Ö., Concept: M.K., D.Ö., D.Ç.Y., Design: M.K., D.Ç.Y., Data Collection or Processing: M.K., C.G., Analysis or Interpretation: M.K., D.Ö., Literature Search: C.G., D.Ç.Y., Writing: M.K., C.G., D.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

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Behavior Comparison and Social Evaluation Study of Parents of Twins with Autism Spectrum Disorder

Otizm Spektrum Bozukluğu olan İkizlerin Ebeveynleri Üzerinde Yapılan Davranış Karşılaştırması ve Sosyal Değerlendirme Çalışması

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ABSTRACT

Background: Autism spectrum disorder (ASD) is the most well-known neurodevelopmental disorder. Because there is no definitive biomarker for ASD, diagnosis is made based on the assessment of the patient's behavior. The aim of this study was to reveal the effect of psychological evaluation of parents on the behavioral and social situations of individuals with autism.

Materials and Methods: A total of 94 individuals aged 3-18, consisting of 15 pairs of monozygotic (MZ) (ASD: 29, healthy: 1), 32 pairs of dizygotic (DZ) twins (ASD: 41, healthy: 23) and their parents, were included in the study. In addition to comparing autistic and healthy twins in terms of clinical and developmental data, social inadequacies, communicative limitations, repetitive interests, and limitations were evaluated in patients with MZ and DZ. While the Autism Spectrum Questionnaire (AQ) and Toronto Alexithymia Scale (TAS-20) tests were administered to the parents, Beck Depression Inventory (BDI) and World Health Organization Quality of Life (WHOQOL-BREF) tests were also administered to the mothers.

Results: According to the developmental data of the individuals, significant differences were found between ASD and healthy individuals in terms of talking (p=0.00002) and toilet training (p=0.0003). In patients, it was determined that there was a relationship between the severity of the disease, repetitive interests and limitations (p=0.046) and speech (p=0.012). While there was a relationship between the WHOQOL-BREF subcategories applied to mothers and both AQ and BDI tests, statistical significance was also determined between the TAS-20 and BDI tests (p=0.016).

Conclusion: The effect of parents' psychological states on individuals with autism has been revealed. We believe that the clinical examinations of the twins, the psychological evaluations of their families, and the psychological state of the parents in the ASD clinic are effective. Thus, it has been clearly shown that the family factor is also important in improving the clinic of individuals with autism.

Keywords: Autism spectrum disorder, social and behavioral assessment, twins

ÖZ

Amaç: Otizm spektrum bozukluğu (OSB), en iyi bilinen nörogelişimsel bozukluk türüdür. OSB için kesin bir biyobelirteç olmadığından, hastanın davranışının değerlendirilmesine dayanarak tanı konur. Araştırma ile, ebeveynlerin psikolojik açıdan değerlendirilmesinin otizmli bireylerin davranışsal ve sosyal durumlarına etkisinin ortaya konması hedeflenmiştir.

Gereç ve Yöntemler: Çalışmaya yaşları 3-18 arası 15 çift monozigotik (MZ) (OSB: 29, sağlıklı: 1), 32 çift dizigotik (DZ) ikiz (OSB: 41, sağlıklı: 23) ve bunların ebeveynlerinden oluşan toplam 94 birey dahil edildi. İkizlerde otistik ve sağlıklı bireylerin klinik ve gelişimsel veriler açısından karşılaştırılmasının yanında, MZ ve DZ hastalarda sosyal yetersizlik, iletişimsel kısıtlılık, tekrarlayan ilgi ve kısıtlılıklar değerlendirildi. Ebeveynlere Otizm Spektrum Anketi (AQ) ve Toronto Aleksitimi Ölçeği (TAS-20) testleri uygulanırken, ayrıca annelere Beck Depresyon Envanteri (BDI) ve Dünya Sağlık Örgütü Yaşam Kalitesi (WHOQOL-BREF) testleri de uygulandı.

Bulgular: Bireylerin gelişimsel verilerine göre OSB ve sağlıklı bireyler arasında konuşma (p=0,00002) ve tuvalet eğitimi (p=0,0003) açısından anlamlı fark bulundu. Hasta bireylerde ise hastalığın şiddetinin, tekrarlayan ilgi ve kısıtlılıklar (p=0,046) ve konuşma (p=0,012) arasında ilişki olduğu belirlendi. Annelere uygulanan WHOQOL-BREF alt kategorilerinin ise hem AQ hem de BDI testleri arasında ilişki bulunurken, TAS-20 ve BDI testleri arasında da istatistiksel anlamlılık belirlendi (p=0,016).

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ÖZ

Sonuç: Çalışmamız neticesinde, otizmde ebeveynlerin psikolojik durumlarının otizmli bireyler üzerinde etkisi ortaya konmuştur. İkizlerin klinik muayeneleri ve ailelerinin psikolojik değerlendirmeleri ile OSB kliniğinde ebeveynlerin psikolojik durumunun etkili olduğunu düşünmekteyiz. Böylece, otizmli bireylerin kliniğinin iyileştirilmesinde aile faktörünün de önemli olduğu net bir şekilde görülmüştür.

Anahtar Kelimeler: Otizm spektrum bozukluğu, sosyal ve davranışsal değerlendirme, ikizler

Introduction

Autism spectrum disorder (ASD) refers to common neurodevelopmental disorders such as autism, Asperger's syndrome, and pervasive developmental disorder-not otherwise specified. ASD is characterized by deficits in social communication and behavioral disturbances. Repetitive interests and limitations, pragmatic communicative disorder, and different interests are symptoms associated with the disease (1). While the prevalence of the disease is approximately 5.2/1000, it is more common in boys (7.4/1000 boy births) than girls (2.8/1000) (2).

Emotional and behavioral disorders such as depression, anxiety, attention deficit and hyperactivity, tantrums, aggression, and sleep and eating disorders can be observed in individuals with ASD. Language and speech disorders, differences in cognitive functions, and aggressive behaviors are important in measuring the severity of ASD.

In the evaluation of autism-related symptoms, tools such as the Autism Diagnostic Interview-Revised, which is conducted through interviews with the families of the patients, and the Autism Diagnostic Observation Schedule, which is applied directly to individuals with autism, are used (3).

In individuals with autism, conditions such as attention deficit/hyperactivity disorder, epilepsy, depression, anxiety, and oppositional defiant disorder, as well as gastrointestinal symptoms, sleep problems, feeding problems, and toilet problems are among the comorbidities encountered in ASD (4).

Studies conducted with twin individuals on the etiology of the disease have reported that genetic and environmental factors play a crucial role in the emergence of neurological and psychiatric conditions such as ASD. Although ASD is known as a heterogenic disease with over 1000 genes, it has been reported that these genetic factors are effective in approximately 25-35% of patients (5).

As pharmaceutical therapy, risperidone and aripiprazole are US food and drug administration-approved drugs used for the treatment of ASD-related symptoms. When current treatment options are examined, it reveals the importance of personalized therapy and early treatment in individuals with autism in increasing the quality of life of patients (6).

In the literature, various tests are applied to individuals with ASD and their parents, such as Autism Spectrum Quotient (AQ), Social Communication Questionnaire (SCQ), Childhood Autism Rating Scale (CARS), Autism Behavior Checklist (ABC), Beck Depression Inventory (BDI), Toronto Alexithymia Scale (TAS-20), and World Health Organization Quality of Life (WHOQOL-BREF). While tests such as AQ, SCQ, CARS, and ABC are used to evaluate autism characteristics, BDI is used to evaluate depression status, TAS-20 is used to describe and express moods, and WHOQOL-BREF is used to evaluate quality of life (7,8,9,10,11,12).

Although there are some studies in which the psychological state of individuals is evaluated using various tests, there is no comprehensive study in the literature that specifically evaluates the emotional state and psychological condition of the parents of twin patients and their contribution to the disease. In this study, we evaluated monozygotic (MZ) and dizygotic twins (DZ) individuals with ASD in terms of clinical features such as social disability, communicative limitations, repetitive interests, and limitations, compared characteristic features and developmental aspects, and investigated the differences in clinical features between ASD and healthy individuals. In addition, we tested the parents of the twins by applying tests such as BDI, TAS-20, WHOQOL-BREF, and AQ and making psychological, social, and behavioral evaluations to examine whether the parents could influence the behavior of individuals with autism. Concordantly, we aimed to clarify whether the parents of twins with autism are psychologically healthy or not may affect the behavioral characteristics of the patients.

Numerous studies on MZ and DZ twins have investigated the genetic and clinical background of ASD. These studies are very useful in examining the influence of familial factors on the etiology of the disease (13). Based on this, we decided to conduct a study on MZ and DZ twins to investigate whether familial factors influence ASD patients. Because of this research, we bring individuals with more favorable living standards into society by adding the family factor to their treatment.

Materials and Methods

Study Design

Our study was conducted with concordant and discordant twins diagnosed with ASD at the Child and Adolescent Psychiatry Clinic. The number of volunteers required for the study was calculated using the G*Power program (V.3.1.9.4, Heinrich-Heine-University) (Effect size DZ: 0.343, α err prob: 0.05, Power (1-β err prob): 0.95, Total sample size: 94). Ethical approval of the project was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, İstanbul Ümraniye Training and Research Hospital (decision number: 218, date: 19/12/2018). Data of the volunteers were collected after obtaining informed consent from their parents. The study included 30 monozygotes (29 affected, 1 healthy), 64 dizygotes (41 affected, 23 healthy), and their mothers and/or fathers. The age of the individuals ranged from 3 to 18 years. The diagnosis was made by a specialist pediatric psychiatrist in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (1). In addition, the Turkish version of the SCQ (current version) CARS and ABC tests were used. Following clinical evaluations and autism-related tests by a specialist psychiatrist, either one or both twin pairs were diagnosed with ASD. Twin siblings who did not show any disease symptoms were included in the control group. Individuals who were not twins and whose ages were not between 3 and 18 years, as well as patients with psychotic disorders and bipolar mood disorders, were not included in the study. Care was taken to ensure that the healthy twins with ASD did not have autism symptoms or any neurodevelopmental disease.

After the diagnosis, a clinical data form including demographic data (Table 1, 2 and 3), social disability, communicative limitation, and repetitive interests and limitations (Table 4) was filled with the families of twins. Then, a set of tests was applied to examine the psychological status of their parents and to investigate the effect of this on individuals with autism. AQ and TAS-20 tests were applied to the mothers and fathers of the individuals. Additionally, BDI and WHOQOL-BREF tests were administered to mothers. The Turkish version of all the tests administered to individuals was used.

Autism Spectrum Quotient (AQ)

The AQ test, which is used to measure the autistic characteristics of individuals, consists of 50 questions divided into five categories. These categories are social skill (items 1, 11, 13, 15, 22, 36, 44, 45, 47, 48); attention switching (items 2, 4, 10, 16, 25, 32, 34, 37, 43, 46); attention to detail (items 5, 6, 9, 12, 19, 23, 28, 29, 30, 49); communication (items 7, 17, 18, 26, 27, 31, 33, 35, 38, 39); and imagination (items 3, 8, 14, 20, 21, 24, 40, 41, 42, 50). Evaluated candidates give an answer "strongly agree", "frequently agree", "sometimes agree" or "strongly disagree" for each item. Scoring system 2, 4, 5, 6, 7, 9, 12, 13, 16, 18, 19, 20, 21, 22, 23, 26, 33, 35, 39, 41, 42, 43, 45, 46. One point, 1, 3, 8, 10, 11, 14, 15, 17, 24, 25, 27, 28, 29, 30, 31, 32, 34 for each "strongly agree" or "frequently agree" answers to the items 36, 37, 38, 40, 44, 47, 48, 49 and 50 items were calculated as 1 point for "strongly disagree" or "sometimes agree" answers. The minimum score that can be obtained from the OA test is 0, and the maximum score is 50. The minimum score that can be taken from the AQ test is 0 and the maximum score is 50. The cut-off value for the test was determined as AQ≥32 (11,14).

Toronto Alexithymia Scale-20 (TAS-20)

TAS-20 consists of 20 questions divided into three categories. These categories are "difficulty identifying feelings" (items 1, 3, 6, 9, 13, 14), "difficulty describing feelings" (items 2, 4, 11, 12, 17) and "externally-oriented thinking" (5, 8, 10, 15, 16, 18, 20). Respondents were given a score of 1-5 for their answers, "never", "rarely", "sometimes", "often" and "always". According to the total score obtained, a score of ⩽51 was evaluated as "no alexithymia", 52-62 points as "probable alexithymia" and ⩾61 points as "have alexithymia" (12).

Beck Depression Inventory (BDI)

The BDI, which we use to measure the level of depression in mothers, consists of 21 items. Scores between 0 and 3 are given for the answer given to each item. The total score that can be obtained from the test is between 0 and 63. Depression grade according to the total score was evaluated as "minimal depression" between 0 and 9, "mild depression" between 10 and 16, "moderate depression" approximately 17-29 and "severe depression" between 30 and 63 (7,15,16).

WHOQOL-BREF

This test, which is used to evaluate the quality of life of mothers, consists of 27 items. Individuals' answers to each question were evaluated on a score of 1-5. The questions were evaluated by dividing into 5 sub-parameters as "general health status" (items 1, 2), "physical health" (items 3, 4, 10, 15, 16, 17, 18), "psychological" (items 5, 6, 7, 11, 19, 26), "Social relations" (items 20, 21, 22) and "Environment" (items 8, 9, 12, 13, 14, 23, 24, 25). The formula for converting the obtained scores from the "raw" score to the percentage system is as follows (8,17).

$$\frac{\text{The raw score of the patient} - \text{The lowest possible score for that sub parameter}}{\text{The score range of that sub parameter}} \times 100$$

Table 1. Characteristics of twins

	ASD		Healthy				
	Mean (min.-max.)	SD	Mean (min.-max.)	SD	p-value	CI	
						Lower	Upper
Age	7.24 (3-18)	2.961	8.04 (3-18)	4.144	0.308	-2.348	0.750
	n	%	n	%	p-value		
Gender	70		24				
Male	44	62.86	14	58.33	0.809		
Female	26	37.14	10	41.66			
Twins	70		24				
MZ	29	41.43	1	4.17	0.001		
DZ	41	58.57	23	95.83			
Diagnosis-severity	70		24				
Mild	44	62.86	-	-	0.903*		
Moderate	20	28.57	-	-			
Severe	6	8.57	-	-			
Birth time	70		24				
Pre-term (<37th week)	40	57.14	14	58.33	0.149		
Term (37-41th week)	30	42.86	10	41.67			
Post-term (≥42th week)	-	-	-	-			
Birth weight	70		24				
Very low (<1500 g)	6	8.57	2	8.33	0.817		
Low (<2500 g)	33	47.14	13	54.17			
Normal (2500-3999 g)	29	41.43	9	37.50			
High (>4000 g)	2	2.86	-	-			
Epilepsy	70		24				
Yes	4	5.71	0	0.00	0.301		
No	66	94.29	24	100.0			
History of the incubator	70		24				
Yes	37	52.86	16	66.67	0.239		
No	33	47.14	8	33.33			

*: p-value was calculated between the MZ and DZ groups for this category
ASD: Autism spectrum disorder, n: Number of volunteers, SD: Standard deviation, CI: Confidence interval, MZ: Monozygotic twins, DZ: Dizygotic twins, min.-max.: Minimum-maximum

Statistical Analysis

The SPSS (V 25.0) statistical analysis program for Windows was used to evaluate the obtained data (IBM SPSS Statistics, SPSS Inc., Chicago, IL, USA). Pearson's chi-square and Fisher's Exact tests were used to compare the characteristics and developmental information of ASD and healthy twins, diagnostic features in twins with ASD, characteristics of the families of the twins, and other parental information. Pearson correlation and One-Way ANOVA tests were used in the analysis of the TAS-20, AQ, WHOQOL-BREF, and BDI tests applied to mothers and fathers. In addition, logistic regression analysis was performed to determine the relationship between the AQ score and alexithymia in the parents. The statistical significance value found because of the comparison between variables was accepted as $p \leq 0.05$.

Table 2. Developmental information of twins

	ASD		Healthy		
	n	%	n	%	p-value
Unsupported sitting	70		24		
Early (<7 months)	9	12.86	1	4.17	0.067
In time (7-9 month)	52	74.3	23	95.83	
Late (>7-9 month)	9	12.86	-	-	
Babbling	70		24		
Early (<3 month)	-	-	1	4.17	0.075
In time (3 month)	54	77.14	22	91.67	
Late (>3 months)	13	18.57	1	4.17	
No babbling	3	4.26	-	-	
Teething	70		24		
Early (<6 months)	6	8.57	-	-	0.199
In time (6-8 month)	50	71.43	21	87.50	
Late (>6-8 month)	14	20.00	3	12.50	
Walking	70		24		
Early (<11 months)	5	7.14	-	-	0.236
In time (11-15 month)	47	67.14	21	87.50	
Late (>11-15 month)	17	24.38	3	12.50	
No walking	1	1.43	-	-	
Talking	70		24		
Yes	33	47.14	24	100.0	0.00002
No	11	15.71	-	-	
Regression	26	37.14	-	-	
Toilet training	70		24		
Early (<2-3 years)	1	1.43	-	-	0.0003
Normal (2-3 years)	22	31.43	19	79.17	
Late (≥4 years)	23	32.86	-	-	
No toilet training	24	34.28	5	20.83	

ASD: Autism spectrum disorder, n: Number of volunteers

Results

When the clinical characteristics of twin individuals were examined, it was observed that most of the individuals with ASD consisted of males (62.86%). While the age range of the individuals ranged from 3 to 18, the average age of individuals with ASD were 7.4 (±2.961) and that of healthy individuals were 8.4 (±4.144). When the ratio of patients and healthy individuals in MZ and DZ included in the study was examined, it was observed that the number of couples in which both siblings were sick was higher in MZ individuals (p=0.001). According to the evaluation of MZ and DZ individuals in terms of the severity of the disease, there was no significant difference between the two groups (p=0.903). Moreover, it was observed that the diagnosis of the disease was mild (62.86%) in most of the individuals and a very small portion (8.57%) was severe. In addition, epilepsy was detected in one MZ couple and two separated DZ individuals with ASD disease, and the disease was not observed in any of the healthy individuals (p=0.301) (Table 1).

According to the developmental data of the individuals, significant differences were found between ASD and healthy individuals in terms of talking (p=0.00002) and toilet training (p=0.0003). It was observed that 37.14% of individuals with ASD had regression in terms of talking in certain periods of their lives (Table 2). In addition, there was a correlation between the severity of the disease and speech (p=0.012).

When the demographic data of the mothers and fathers of twin individuals were examined, there was statistical significance in terms of age (p=0.012), education level (p=0.0001), and childbearing age (p=0.001). The research revealed that more than half of the mothers (51.06%) and fathers (55.32%) used alcohol, cigarettes, or drugs (p=0.029). While the age at which mothers had twins was between 20 and 43, the age at which fathers had twins was between 25 and 44 (Table 3).

In the study, the diagnostic characteristics of the patients were examined by dividing them into social disability, communicative limitation, and repetitive interests and limitations (Table 4), and then these data were compared between MZ and DZ patients.

In the social disability category, a significant difference was found in terms of "not looking when his/her name is called" (p=0.009) and "play with certain repetitive objects" (p=0.011). Additionally, regression was found in two individuals in terms of "not looking when his/her name is called", and "play with certain repetitive objects" features (Table 4).

When the category of communicative limitations was examined, statistical significance was determined in the "no speaking" feature between the two groups (p=0.007) (Table 4). It was also observed that most patients had "communicative limitation" (78.0%), "speech delay" (91.43%), "limitations in non-verbal communication" (75.6%), and "atypical speech and prosody" (72.0%).

Because of the examination of repetitive interests and limitations in patients with MZ and DZ, a statistical significance was found in "an area of interest with abnormal intensity or focus, which has become highly restricted and unchanged" characteristic (p=0.030) (Table 4). In individuals with ASD, there was a correlation between the severity of the disease and repetitive interests and limitations (p=0.046).

Table 3. Characteristics of parents of twins

	Mother		Father		
	Mean (min.-max.)	**SD**	**Mean (min.-max.)**	**SD**	**p-value**
Age	37.94 (25-54)	6.34	41.40 (30-57)	5.34	0.012
Childbearing age	30.45 (20-43)	5.28	33.91 (25-44)	4.40	0.001
	n	**%**	**n**	**%**	**p-value**
Educational level	47		47		
Elementary school	12	25.53	10	21.28	0.0001
Middle school	3	6.38	2	4.26	
High school	16	34.04	13	27.66	
Bachelor's degree	12	25.53	17	36.17	
Associate degree	4	8.51	5	10.64	
Alcohol, smoking, or drug use	47		47		
Yes	24	51.06	26	55.32	0.029
No	23	48.94	21	44.68	

n: Number of volunteers, SD: Standard deviation, min.-max.: Minimum-maximum

Table 4. Diagnostic features in twins with ASD

	No		Few		Yes		Yes, Then No/		Getting better with special education		Regression		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	***p-value**
Not looking when his/her name is called	15	21.43	12	17.14	14	20.00	24	34.29	4	5.71	1	1.43	0.009
Play with certain repetitive objects	33	47.14	4	5.71	23	32.86	8	11.43	1	1.43	1	1.43	0.011
No speaking	60	85.71	-	-	10	14.29	-	-	-	-	-	-	0.007
Speech delay	6	8.57	-	-	64	91.43	-	-	-	-	-	-	0.069
Inability to understand what is being said	42	60.00	12	17.14	14	20.00	1	1.43	1	1.43	-	-	0.603
An area of interest with abnormal intensity or focus that has become highly restricted and unchanged	40	57.14	-	-	30	42.86	-	-	-	-	-	-	0.030

*: P-values were calculated between the MZ and DZ groups
ASD: Autism spectrum disorder, n: Number of volunteers

Table 5. TAS-20 and AQ evaluations in the mother and father of twins

MOTHER				**FATHER**			
	Mean (min.-max.)	**SD**	**p-value**		**Mean (min.-max.)**	**SD**	**p-value**
AQ	18.42 (7-31)	5.521	0.168	AQ	20.64 (7-33)	5.645	0.083
	n	**%**			**n**	**%**	
TAS-20	**45**			TAS-20	**34**		
No alexitimia	16	35.56		No alexitimia	13	33.33	
Possible alexitimia	22	48.89		Possible alexitimia	10	25.64	
Have alexitimia	7	15.56		Have alexitimia	16	41.03	

Comparison between TAS-20 and AQ
AQ: Autism spectrum questionnaire, TAS-20: Toronto alexithymia scale-20, n: Number of volunteers, SD: Standard deviation, min.-max.: Minimum-maximum

The statistical significance between the TAS-20 and AQ tests applied to mothers and fathers was examined consequently; as a result, no significance was found in the tests of both mothers (p=0.168) and fathers (p=0.083) (Table 5). When the relationship between the parents' AQ score and the results of alexithymia were examined by logistic regression analysis, no significance was observed for any category (p>0.05). However, in the TAS-20 test performed on mothers, it was observed that most of the individuals had "possible alexithymia" (48.89%), while fathers had "have alexithymia" (41.03%). In addition, with the AQ test score applied to the fathers, it was determined that two individuals exceeded the cut-off value. When the results of the WHOQOL-BREF and BDI tests applied to the mothers were evaluated, it was determined that there was statistical significance in all WHOQOL-BREF raw scores and percentage system results when compared with the BDI test (Table 6). However, the results were not significant in terms of the BDI subgroups (p=0.058).

When examining whether there is a relationship between the results of the AQ and WHOQOL-BREF test applied to mothers, a correlation was found between Physical health (p=0.002), Psychological (p=0.001), Social relations (p=0.006) and Environment (p=0.001) scores, and AQ, respectively. According to the comparison between the TAS-20 and BDI test results, statistical significance was determined between the groups (p=0.016).

Discussion

Table 6. WHOQOL-BREF and BDI evaluations in mothers of twins

	Mean (min.-max.)	SD	p-value
WHOQOL-BREF raw score			
General health status	6.49 (3-9)	1.520	0.0003
Physical health	26.00 (12-35)	5.011	0.001
Psychological	21.26 (7-29)	4.541	0.0008
Social relations	9.28 (4-13)	2.438	0.016
Environment	25.95 (14-36)	5.256	0.052
WHOQOL-BREF percentage system			
General health status (%)	56.09 (12.5-87.5)	18.99	0.0003
Physical health (%)	67.85 (17.9-100.0)	17.89	0.0008
Psychological (%)	63.57 (4.2-95.8)	18.91	0.0000002
Social relations (%)	52.35 (8.3-83.3)	20.32	0.015
Environment (%)	56.11 (18.8-87.5)	16.42	0.052

Comparison between WHOQOL-BREF and BDI
BDI: Beck depression inventory, WHOQOL-BREF: World Health Organization Quality of Life, SD: Standard deviation, min.-max.: Minimum-maximum

Various neuroanatomical changes in the human brain are crucial for developing behaviors during the first years of life. Along with the enlargement of the brain volume of individuals with autism, it was observed that white matter increased in the frontotemporal regions related to social cognition and language and decreased in the frontal region when viewed regionally (18).

It has been detected that non-verbal, cognitive, and social skills are also important for language development in individuals, besides speech-related disorders that frequently occur in individuals with ASD (19). Although speech delay is seen in most patients, situations such as not being able to speak have been detected in some individuals. In addition, situations such as meaningless words and echolalia are also known as encountered speech disorders in individuals with autism (20). When the ABC scores were compared in individuals with autism who speak and do not speak, it was reported that dumb individuals in terms of autistic behavior come into prominence more according to speakers. In addition, when expressive language skills were excluded from scoring, dumb individuals had a higher degree of autism severity (21). While speech delay was detected in most of our patients in our study too (91.43%), inability to speak situation (14.29%) was also observed in some individuals. repetitive behaviors are common in phenomena associated with developmental disorders and ASD. When this situation was compared according to age in individuals with autism, it was seen that it occurs less frequently and in severity in elderly individuals. Therefore, it is thought that the severity of autism symptoms in the phenotype is related to age (22). In a study comparing children with ASD with individuals who have developmental disorders and typical development in terms of repetitive behaviors and limitations, it has been revealed that situations such as sensorimotor and insistence on sameness are more common in children with ASD, but there is no relationship in terms of the severity of disease (23). In this study, it was understood that this kind of behaviors were seen more clearly in the phenotype with the severity of disease by detecting the correlation between repetitive interest and limitations. In light of this information, a statistically significant difference was detected among the severity of disease and inability to speak (p=0.007) and repetitive interests and limitations (p=0.046).

When the risk factors that cause ASD were evaluated, while considering mother's smoking in her gestation period, it was reported that grandmother's smoking may also be effective in the emergence of ASD in her grandchild via mother (23). However, there are studies in which smoking is not related to autism (24). In addition, there is no sufficient evidence that alcohol use can cause autism (25). Although

there are studies in the literature about how smoking and alcohol use during pregnancy can cause common neurodevelopmental disorders such as autism, there is no study in which mothers and fathers evaluated these risk factors except gestation. In addition, exact information could not be obtained in terms of smoking and alcohol use during pregnancy causing ASD. In our study, in consequence of the evaluation of parents in terms of smoking, alcohol, and drug use, it was determined that approximately half of both mothers (51.06%) and fathers (55.32%) used at least one of these potential risk factors (p=0.029).

In the social deficiency category, a statistically significant difference was detected in our patients in terms of symptoms such as "not looking when his/her name is called" (p=0.009), "being passive, reaching the desired toy with the help of the caregiver" (p=0.042), and just "playing specific objects continually" (p=0.011). Although autism is a disease characterized by mood disorders, symptoms of which are seen in the early period of an individual's life, and especially social deficiency is prominent, the mechanisms causing these situations are still being investigated. When social behaviors in two-year-old individuals with ASD were examined, it was observed that the lack of eye contact was correlated with an excess level of social deficiency, and it was suggested that this behavior could be a clinical marker for the early detection of the disease (26).

Brain volume overgrowth is associated with the emergence of autistic social disorders. This situation demonstrates that early brain changes occur during the period in which autistic behaviors first emerge (27). In this study, which we conducted with twin individuals, consistent results with the literature were obtained in the wake of the evaluation of individuals regarding social disability, especially in terms of eye contact deficiency. In addition, it has been determined that there is a decrease in social disability with special education given to individuals from an early age.

Tests such as AQ, BDI, TAS-20, and WHOQOL-BREF are applied in the investigation of the relationship between the conditions observed in individuals and the occurrence of the disease by measuring the mental and physical health of parents of children with ASD. In a study that evaluated individuals' life quality, it was detected that the life quality of parents with individuals with autism is lower than those who have healthy and physically disabled children (p<0.01) in all categories, with WHOQOL-BREF scale evaluation (28). In a similar study in which quality of life and depression levels were measured with WHOQOL-BREF and BDI tests, it was reported that while there was a negative correlation between depression level and quality of life scores in Turkish mothers with children with Down syndrome, cerebral palsy, and ASD, it has also been revealed that age, education, and income level are also effective on depression and life expectancy on the quality of life because of the evaluation of these tests with demographic data (29). When depression and anxiety situations are examined in parents of autism patients, while depression situations are not detected in fathers, it has been seen that mothers' anxiety and depression levels are higher than those of fathers. Therefore, it is determined that psychologic problems are mostly seen in individuals' mothers (30). In our study, while mild and moderate depression was determined in mothers, it was found that quality of life had a negative correlation with depression level, in line with the literature (p=0.001). As it has been thought that parents with children with autism may have autistic characteristics, in some studies, the AQ survey was applied to mothers and fathers apart from children to examine this situation. Because of the comparison of mothers and fathers with and without children with ASD, it has been reported that parents with diseased children have a higher AQ score. Although there are studies supporting this result in the literature (14), a similar study reported that there was no significant difference between individuals in terms of AQ scores (31). While there was no significant result supporting this study in our study's results, it was found that the AQ score exceeded the cut-off value in only two fathers. With these evaluations, it has not been conclusively demonstrated that the AQ score of the parents is effective in determining a relationship in terms of having a child with autism.

Because of the examination of TAS-20 and BDI scores in individuals with children with autism, the subcategories of "complexity in identifying emotions" and "difficulty in identifying emotions" in mothers were associated with depression measurement results (32). In our study, with the comparison of these two tests administered to the mothers of autism patients, it was determined that there was a relationship between the results of the two tests. When we evaluated the alexithymia situation among mothers and fathers, we found that most of the mothers were in the "possible alexithymia" category, and most of the fathers were in the "have alexithymia" category. In another study, it was determined that while the TAS-20 scores of the parents of individuals with ASD were higher than those of the control group, it was reported that the children of fathers with high alexithymia scores had higher repetitive behavioral symptoms scores (33). In another study evaluating the relationship between depression, anxiety, and alexithymia in the parents of individuals with neurodevelopmental disorders and the severity of the disease in children, it was reported that alexithymia symptoms were higher in the parents of individuals with autism, whereas depression and anxiety situations in mothers were higher than those in fathers. It was also revealed a correlation among alexithymia,

anxiety, and depression in parents as a consequence of research (34). When we evaluated the relationship between alexithymia and depression, we found a relationship between alexithymia and depression in accordance with the literature, according to the comparison between TAS-20 and BDI test results (p=0.016).

Study Limitations

Studies on the importance of familial factors in autism clinics are very limited. Because ASD is a disease characterized by limitations in social communication, the attitudes and behaviors of the individual, especially the close people, are considered to be a factor in the development of the disease.

Conclusion

In addition to the evaluation of social and behavioral abnormalities in autism, considering the psychological status and quality of life of the parents of the patients sheds light on the etiology of the disease. This research is important in revealing the role of parents' psychological states in neurodevelopmental diseases such as ASD. Such studies are especially important for determining the emergence and prognosis of diseases related to behavioral disorders like autism.

Ethics

Ethics Committee Approval: Ethical approval of the project was obtained from the Clinical Research Ethics Committee of the University of Health Sciences Türkiye, İstanbul Ümraniye Training and Research Hospital (decision number: 218, date: 19/12/2018).

Informed Consent: Data of the volunteers were collected after obtaining informed consent from their parents.

Authorship Contributions

Concept: E.C., Design: E.C., H.Y., Data Collection or Processing: H.Y., P.A.D., Analysis or Interpretation: E.C., H.Y., Literature Search: E.C., H.Y., Writing: E.C., H.Y., P.A.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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ORIGINAL ARTICLE

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Visualization Analysis of Transversus Abdominis Plane Block in Abdominal Surgery Based on Bibliometrics

Transversus Abdominis Plan Bloğunun Abdominal Cerrahide Bibliyometrik Temelli Görselleştirme Analizi

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ABSTRACT

Background: Acute pain following surgery is common and constitutes a significant healthcare priority because of its potential impact on quality of life. The use of transversus abdominal plane block (TAP-B) has emerged as a current approach to alleviate postoperative pain. This study was designed to (a) assess the scientific trends in the use of TAP-B and (b) determine the trend toward the decision to use TAP-B, especially when central neuraxial blocks are technically difficult or contraindicated.

Materials and Methods: This study examines TAP-B research from a bibliometric perspective. As of June 12, 2023, the literature related to TAP-B published in the last two decades (2003-2023) was retrieved from the Web of Science Core Collection database. The keywords "transversus abdominis plane" and "abdominal" were used for the search strategy. Data analysis and visualizations were conducted using VOSviewer 1.6.0.

Results: A total of 546 studies were examined, with the year 2021 (n=1491) receiving the highest number of citations and 2022 (n=56) being the most productive year in terms of publications. The first publication in 2007, authored by McDonnell JG. from Ireland, had the highest publication frequency (n=9) and citations (n=498).

Conclusion: Studies in the literature indicate an increasing trend in the use of TAP-B for postoperative pain management after lower abdominal surgery, which emphasizes its efficacy. The TAP block is emerging as a cornerstone in postoperative multimodal analgesia in cases where central nerve blocks are contraindicated or technically difficult, especially where central neuraxial blocks are contraindicated or technically difficult.

Keywords: Postoperative pain, transversus abdominis plane block, anesthesia, abdominal surgery, bibliometrics

ÖZ

Amaç: Alt karın cerrahisini takiben akut postoperatif ağrı yaygın bir endişe kaynağıdır. Transversus abdominis plan bloğunun (TAP-B) kullanımı, postoperatif ağrıyı hafifletmek için güncel bir yaklaşım olarak ortaya çıkmıştır. Bu çalışma (a) TAP-B'nin kullanımı konusunda bilimsel eğilimleri değerlendirmek ve (b) özellikle santral nöroaksiyel blokların teknik olarak zor veya kontrendike olduğu durumlarda, TAP-B'nin kullanım kararına yönelik eğilimi belirlemek amacıyla planlandı.

Gereç ve Yöntemler: Bu çalışma, TAP-B araştırma çıktılarının genel bir bakışını sunmak amacıyla bibliyometrik bir perspektiften incelenmiştir. 12 Haziran 2023 itibariyle, son yirmi yılda (2003-2023) yayınlanan TAP-B ile ilgili literatür Web of Science Core Collection veri tabanından alınmıştır. Arama strateji olarak "transversus abdominis plane" ve "abdominal" anahtar kelimeleri kullanıldı. Veri analizi ve görsellikler VOSviewer 1.6.0 kullanılarak gerçekleştirilmiştir.

Bulgular: Toplam 546 çalışma incelenmiş olup, 2021 yılı (n=1491) en çok atıf alan ve 2022 yılı (n=56) yayın açısından en üretken yıl olmuştur. İlk yayın 2007 yılında, en yüksek yayın sıklığı (n=9) ve atıf (n=498) ile İrlanda'dan McDonnell JG tarafından yapılmıştır.

Sonuç: Bu konuda literatürde yer alan araştırmalar, TAP-B'nin alt karın cerrahisi sonrası postoperatif ağrı yönetiminde etkinliğini vurgulayarak kullanımında artan bir eğilimi işaret etmektedir. Santral sinir bloklarının kontrendike olduğu veya teknik olarak zor olduğu durumlarda, TAP bloğu postoperatif multimodal analjezide, özellikle santral nöroaksiyel blokların kontrendike olduğu veya teknik olarak zor olduğu durumlarda, postoperatif multimodal analjezide bir köşe taşı olarak ortaya çıkmaktadır.

Anahtar Kelimeler: Postoperatif ağrı, transversus abdominis plan blok, anestezi, abdominal cerrahi, bibliyometri

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Introduction

Acute postoperative pain following abdominal surgery, a prevalent medical procedure, has become a recurrent concern in recent times. It can adversely affect various organs and tissues, impede postoperative recovery, and lead to significant morbidity and mortality. Effective postoperative pain management coupled with early postoperative mobilization enhances quality of life and reduces the incidence of morbidity and mortality. Consequently, the control of postoperative pain is of paramount importance (1,2,3). Postoperative pain management encompasses a spectrum of techniques, including the administration of pharmacological agents, patient-controlled analgesia using morphine, epidural pain relief, intravenous pain relief, intrathecal pain relief administration, local anesthetic infiltration, and the application of regional nerve blocks (4).

Transversus abdominis plane block (TAP-B), a peripheral nerve block, is extensively used for postoperative analgesia. A local anesthetic is introduced into the space between the internal oblique and transversus abdominis muscles, effectively blocking the nerves within the abdominal wall. TAP-B demonstrates efficacy in providing analgesia, which diminishes the postoperative stress response and expedites postoperative recovery (4,5,6).

This study explored TAP-B research from a bibliometric perspective to provide an overview of the research outputs in this field. Bibliometric analysis serves as a compass for navigating the literature and pinpointing precise research directions. From the inception of the first publication on the TAP-B technique in abdominal surgery in 2007 to 2023, our study conducted a comprehensive statistical and visual analysis. This study was designed to (a) assess the scientific trends in the use of TAP-B and (b) determine the trend toward the decision to use TAP-B, especially when central neuraxial blocks are technically difficult or contraindicated. We aim to provide insights that not only reflect the current state but also anticipate future developments by scrutinizing influential research papers, contemporary topics, and emerging trends during this period.

Materials and Methods

Study Design and Participants

Data were extracted from an online dataset for this descriptive bibliography study. Participants were not directly involved in the study.

Database and Search Strategy

On June 12, 2023, researchers extracted TAP-B literature from the Web of Science Core Collection (WoSCC) database published during the past two decades (between 2003 and 2023). The search strategy was based on Boolean operators and the potential keywords "transversus abdominis plane" (all fields) AND "abdominal" (all fields). The 546 studies found at the end of the search strategy were analyzed according to publication trends, numerical values, citation frequencies, countries, institutions, authors, keywords, and average number of citations (Figure 1).

Ethics committee approval was not required because this was a bibliometric study. Not required as this was a bibliometric study.

Research Methods

Fundamental data from the literature, gathered through WoSCC, were exported and systematically documented to enhance comprehension of the prospective applications of TAP-B technology in abdominal surgery.

Statistical Analysis

In this study, academic papers were analyzed using statistical techniques such as frequency count, percentage, average, and mode. This analysis unveiled the current status and trends in research within this domain and to pinpoint priorities and orientations for future studies. The data underwent thorough analysis and visualization using VOSviewer 1.6.0, Microsoft Excel, and WoSCC report.

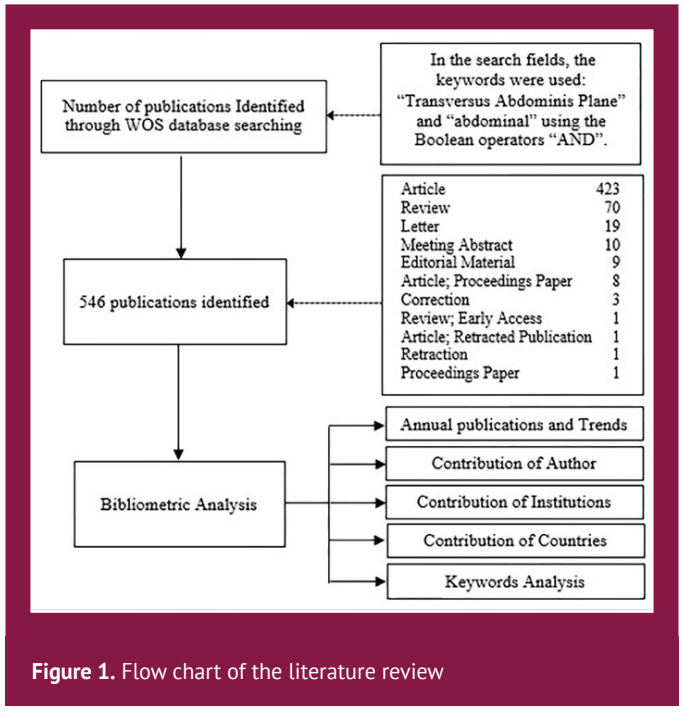

Figure 1. Flow chart of the literature review

Results

There are 546 studies on the use of TAP-B technology in abdominal surgery published between 2003 and 2023. The first study on this topic was published in 2007. The cumulative times cited amount to 11.887, with an average of 21.77 per item and an h-index of 52. The primary focus of these studies was on parameters such as total opioid dose, acetaminophen use, duration of pain relief, and patient satisfaction within the initial 24 hours post-surgery. Secondary objectives included determining the opioid quantity administered over 24 h, pain intensity, occurrences of nausea and vomiting, clinical ileus rate, time to flatulence, and duration of hospitalization.

The peak number of citations occurred in 2021 (citations: 1491, publications: 45), whereas the highest number of publications was observed in 2022 (citations: 1371, publications: 56). The most cited publication (n=498) was published in 2007 in Anesthesia and Analgesia (Journal Citation Indicator 1.95 and Q1). The frequency of published studies exhibited a fluctuating pattern and gradually increased over time. The h-index reached its zenith in 2012. TAP-B in abdominal surgery has garnered increasing attention recently (Figure 2).

Bibliometric Analysis of the Authors of the Studies

The research on TAP-B studies in abdominal surgery involved the ranking of author collaboration networks, identifying key authors, and major collaboration networks in the field using visualization software. McDonnell JG emerged as the first-named author of the most cited paper and holds the record for the highest number of publications, with a total of nine papers, three of which list him as the primary author. Furthermore, the study, which involved a maximum of 16 authors, was published in 2019 and received 19 citations (7).

A total of 2367 different authors contributed to the subject. By grouping them, 92 authors were identified, forming five main author groups. While there are connections between the groups, most connections are observed between the main groups (Figure 3).

TAP-B has been a focal point of academic research in the field of abdominal surgery, leading to the emergence of numerous certified professionals and researchers during the past 16 years. The inaugural study on the subject was published in 2007 and investigated the effectiveness of painkillers in patients undergoing abdominal surgery within the first 24 h. This randomized, controlled, double-blind study reported a reduction in visual analog scale measurement at postoperative time points, decreased morphine requirements in the first 24 hours postoperatively, absence of complications attributable to TAP-B, and provision of highly effective postoperative analgesia in the initial 24 hours after major abdominal surgery. This study laid the foundation for subsequent research with 498 citations (7). According to a network analysis of authors' collaboration status, studies on TAP-B applications in abdominal surgery generally involve "relatively concentrated investigators with strong academic affiliations and recognition".

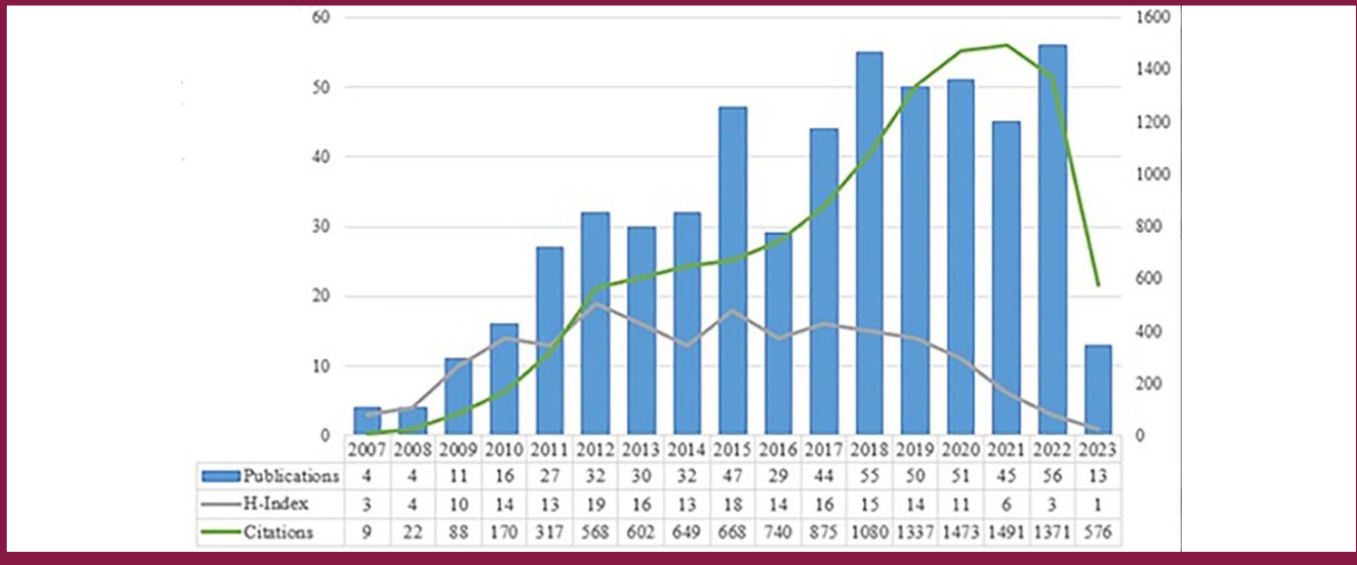

Figure 2. Publications h-index, citations, distribution by years

Bibliometric Analysis of Research Institutions and Countries

Research institutions are considered to play a significant role in scientific research. There are currently 15 research institutes divided into three main clusters according to the data provided by the author's institution (Figure 4a). The scientific knowledge map of institutional collaboration demonstrates a high degree of inter-institutional collaboration.

Our analysis revealed that 23 countries contributed to the three main topics with ⩾5 publications (Figure 4b). The USA (n=122) is the global leader in this field, followed by India (n=59), and China (n=53) follows. Other notable contributors include the United Kingdom, Egypt, Türkiye, and Canada. The connection among clusters is strong, suggesting international collaboration in TAP-B implementation in abdominal surgery. Interestingly, the most cited article originated from Ireland, highlighting the potential for geographically diverse contributions to impactful research in this domain. Moreover, our analysis revealed specific differences in the research focus and contributions of the world's leading countries within TAP-B research for abdominal surgery.

Centrality analysis suggests that the United States plays a pivotal role in research collaboration, having the most common co-publications with other countries exceeding five publications. India leads with 31% of collaborations during studies examining the combined use of adjuvants

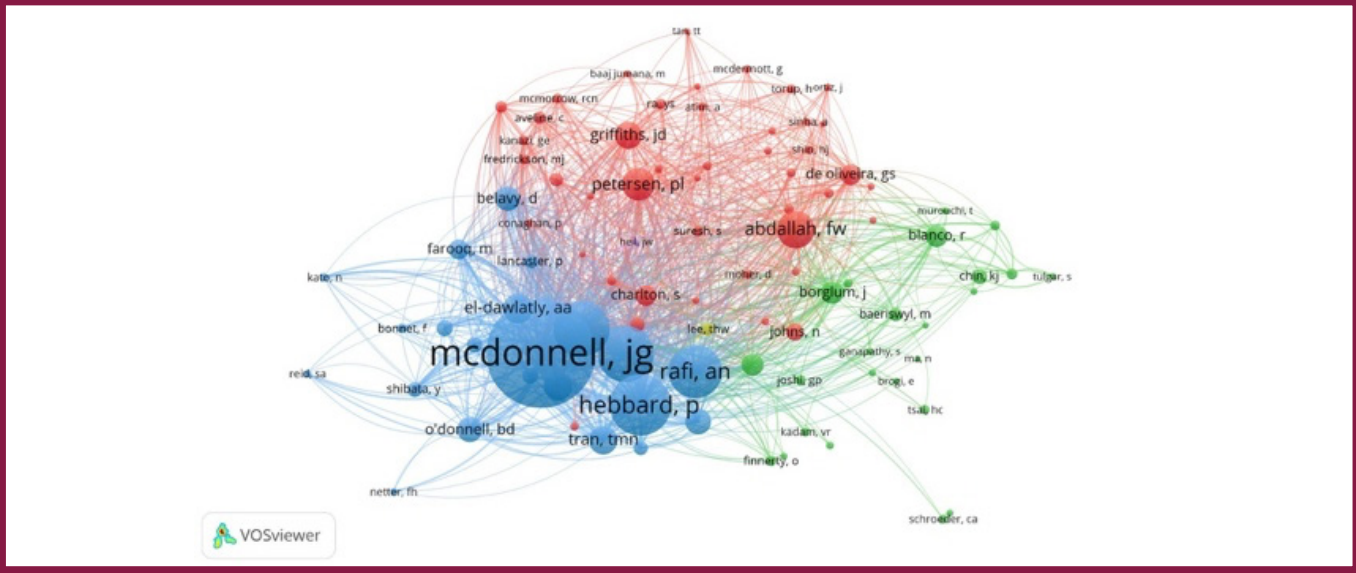

Figure 3. Bibliometric visualization of co-citations/cited authors

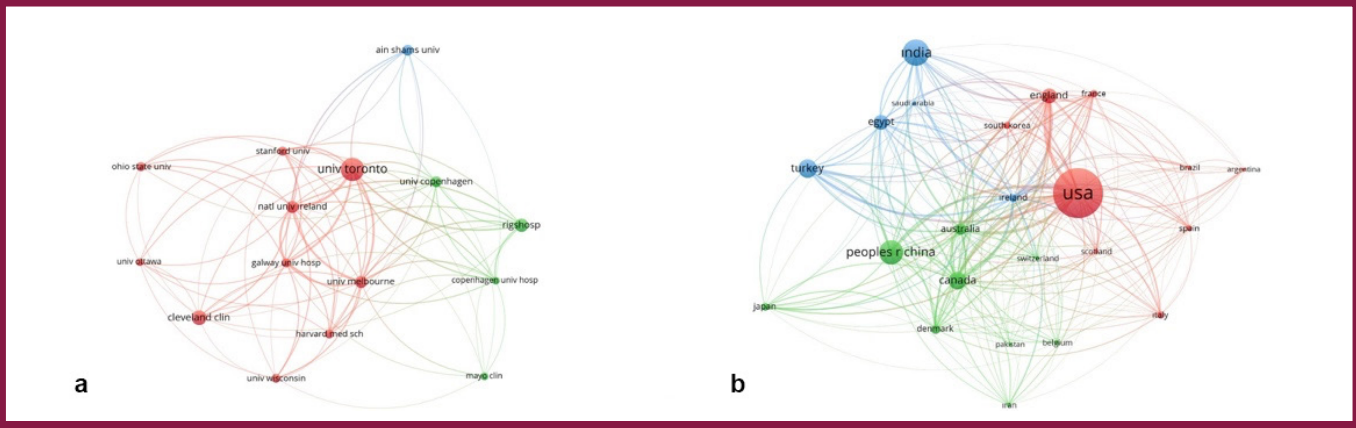

Figure 4. a) Bibliometric visualization of Institutions; b) bibliometric visualization of countries

like bupivacaine, ropivacaine, and dexmedetomidine, followed by China (21%) and then the United States (15%). The United States boasts the highest overall publication count (122), with 90 original articles appearing in journals indexed by the Science Citation Index Expanded (SCI-E). Their research impact is further reflected by an h-index of 28, 2316 total citations, an average of 19 citations per item, and a most-cited article garnering 170 citations. Their publication trend appears stable since 2018, averaging around 13 studies per year.

Following the United States, India emerges as a notable contributor with 59 publications, of which 51 are original articles and 8 are indexed in the prestigious SCI-E. Their research impact is reflected in an h-index of 9, 337 total citations, a most-cited article garnering 95 citations, and an average of 6 citations per item. Interestingly, their publication trend experienced a surge between 2019 and 2021, but it has since shown a slight decline.

Similarly, China stands out with 53 publications, with 41 classified as original articles and all 41 indexed in the SCI-E. Their robust research portfolio boasts an h-index of 13, 540 total citations, a most-cited article achieving 76 citations, and an impressive average of 11 citations per item. China's publication trend demonstrated a consistent upward trajectory until 2021, but it has also mirrored the downward trend observed since then. From 2019 to 2021, China ranked among the most prolific contributors to TAP-B research in abdominal surgery.

Beyond total citation counts, it is crucial to acknowledge the significance of the average citation rate per article as a vital metric for gauging academic relevance and publication quality.

The first study on this topic was conducted in 2011 in Türkiye. A total of 39 studies were authored as original articles, resulting in an h-index of 11, 450 total citations, and 29 publications falling under the SCI-E category. The most cited publication, authored by Öksüz et al. (8), was published in Regional Anesthesia and Pain Medicine (JCI: 1.91, Q2) in 2017, accumulating 94 citations.

Bibliometric Analysis of the Keywords

Our study analyzed 747 keywords extracted across all articles, with Figure 5 depicting the cluster of 62 keywords recurring more than 5 times. The font sizes of the keywords reflect their repetition frequency. The most frequently repeated term was "transversus abdominis plane block", appearing 148 times, followed by "analgesia" (n=73) and "postoperative pain" in the second and third positions, respectively. The keywords "efficacy" (n=47), "pain" (n=41), and "postoperative analgesia" (n=36) were most commonly used during the last 5 years (2018 to the present). These studies indicated a nuanced and specialized development of the TAP-B technique in abdominal surgery over the years.

Characteristics of the Top 10 Studies by Number of Citations

The prominence of a journal is determined by the number of top 10 studies cited. Table 1 delineates the 10 leading journals based on the number of citations they have garnered. Anesthesia and Analgesia emerged as the journal with the highest number of publications, notably

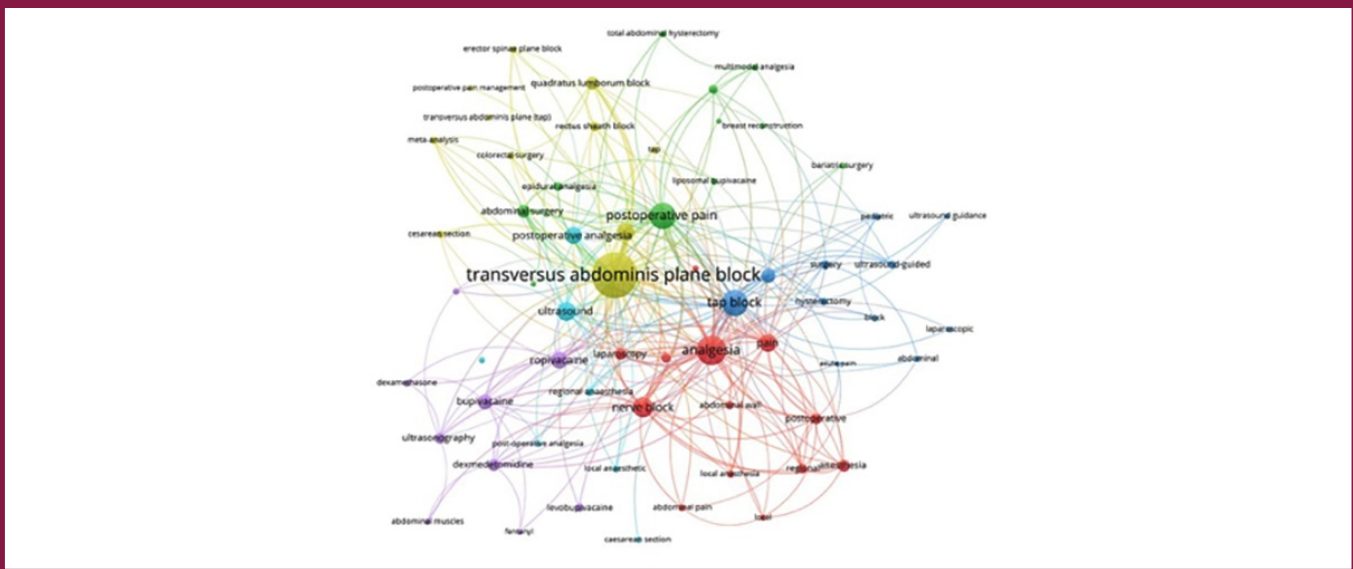

Figure 5. Bibliometric visualization of co-citations/cited authors

Table 1. Analysis of author, journal, keyword, and citation of the 10 most cited studies

Authors	Source title	Quarter	Impact factor	Keywords plus	Times cited	Publication year
McDonnell et al. (7)	Anesthesia and Analgesia	Q1	1.95	Pain	498	2007
McDonnell et al. (9)	Anesthesia and Analgesia	Q1	1.95	Anesthesia, surgery, section, opioids	391	2008
Carney et al. (10)	Anesthesia and Analgesia	Q1	1.95	Randomized controlled trial, efficacy, delivery, surgery	298	2008
Chin et al. (11)	Regional Anesthesia and Pain Medicine	Q2	1.91	Randomized controlled trial, quadratus lumborum block, postoperative pain, gastric bypass, bupivacaine	241	2017
Belavy et al. (12)	British Journal of Anesthesia	Q1	2.63	Randomized controlled trial, efficacy	221	2009
Tran et al. (13)	British Journal of Anesthesia	Q1	2.63	Randomized controlled trial, analgesic efficacy, tap block	210	2009
Rozen et al. (14)	Clinical Anatomy	Q2	1.08	Epigastric perforator flap, free trap flap, plane block, breast reconstruction, sensory recovery, muscle, sensibility, analgesia, anatomy	207	2008
McDonnell et al. (15)	Regional Anesthesia and Pain Medicine	Q2	1.91	Postoperative pain treatment, analgesia, surgery	199	2007
Charlton et al. (16)	Cochrane Database of Systematic Reviews	Q1	1.33	Rectus sheath block, postoperative analgesia, pain, efficacy	191	2010
Niraj et al. (17)	British Journal of Anesthesia	Q1	2.63	Surgery, pain	190	2009

featuring the most cited study (498 citations) concerning the implementation of TAP-Bs in abdominal surgery. The cumulative number of studies published in this journal is 26. The top 10 journals enumerated in Table 1 are categorized as either "Q1" or "Q2" following the Journal of Clinical Research 2019 standards.

Discussion

Postoperative pain is a significant concern for both patients and clinicians, and globally, inadequate management of postoperative pain persists as a prevalent clinical challenge (18). Various approaches exist for postoperative pain management, including the use of morphine, epidural analgesia, intramuscular and intravenous pain relief, intrathecal analgesia, local anesthetics, and nerve blocks. Among these approaches, the TAP-B was initially described in 1993 and formally documented in 2001 (3,4,19). TAP-B has been recognized as a successful adjunctive procedure for postoperative analgesia, albeit with potential complications such as block failure, abdominal organ injury, nerve injury, and vascular injury (20,21,22). Fortunately, the application of ultrasound facilitates visualizing the injection point, the plane of touch, and the needle, leading to improved accuracy in ultrasound-guided punctures and a reduction in associated complications (23). Numerous comprehensive studies and reference books have delved into the detailed application of ultrasound-guided techniques, particularly in the abdomen and subcostal region (24,25).

The TAP block reduces the need for postoperative opioid use, provides superior analgesia for up to 48 h, and prolongs the time to first request for further analgesia. Moreover, it provides more effective pain relief and significantly reduces opioid-related side effects and perioperative opioid consumption. In addition, USG-guided administration ensures precise placement of the TAP-B local anesthetic and minimizes complications (8,26,27,28).

The transversus abdominis plane (TAP) block demonstrated a notable enhancement in both early and late pain scores, resulting in a decreased use of postoperative opioids within the initial 24 hours. It has been associated with a shorter ambulation time and a reduced incidence of postoperative nausea and vomiting additionally (29).

In Hafeman et al. (30), TAP block offers analgesia following pediatric procedures for a longer period than caudal block. It is also linked to a lower analgesic dosage during the first 24 hours without increasing pain scores (21).

According to the study by Viderman et al. (31), TAP block groups had considerably reduced opioid requirements 24 hours following laparoscopic and combined types of procedures than did the 'no block' groups (22).

Effective management of postoperative pain has been linked to early mobilization, enhanced patient satisfaction, shorter hospital stays, reduced healthcare costs, and overall improved outcomes (32). In this regard, the transversus abdominis plane (TAP) block could serve as a viable alternative to epidural analgesia, considering clinically significant differences in pain intensity. Furthermore, this alternative could mitigate the rare but serious risks associated with epidural analgesia, including fatal cardiovascular collapse, meningitis, spinal cord ischemia, and vertebral canal abscess or hematoma (33).

In the last 16 years, 546 articles on the application of TAP-B in abdominal surgery were found in the WoS database, and the number of articles showed a gradual increasing trend. The most published author was J.G. McDonnell, from the Departments of Anesthesiology and Surgery, University of Galway-Ireland, who suggested that TAP block provides highly effective postoperative analgesia within the first 24 hours after major abdominal surgery.

With a bibliometric study, we can make suggestions for future research. Although TAP-B is a simple intervention, practitioners need to customize treatment strategies according to various variables (drugs, catheters, etc.). Therefore, good practice guidelines are needed. The lack of analysis of adverse events encountered during TAP-B implementation is a serious gap.

Study Limitations

Because this study is based on keywords in the WoSCC, it may not capture all research on TAP-B. In cases where more than one database is used, including the same article in the analysis more than once may affect the reliability of the results. Future software for bibliometric analyses may include interdisciplinary indicators and data sharing standards to overcome these limitations by analyzing search results from multiple databases. The fact that the database we used is one of the most popular multidisciplinary databases used scientifically was instrumental in identifying research gaps and potential areas for future research on TAP-B.

Conclusion

The potential applications of TAP-B extend beyond its established role in postoperative analgesia for various surgical procedures. The accumulated research underscores the efficacy of TAP-B in postoperative pain management following lower abdominal surgery, signifying a growing trend in its use. In addition, they are proposed for use in conjunction with general anesthesia for chronic pain management, muscle disease diagnosis, and treatment, as well as complication prevention. TAP-B can be acknowledged as a foundational element in postoperative multimodal analgesia, particularly in situations where central neuraxial blocks are contraindicated or technically challenging.

Ethics

Ethics Committee Approval: Ethics committee approval was not required because this was a bibliometric study.

Informed Consent: Not required as this was a bibliometric study.

Authorship Contributions

Surgical and Medical Practices: E.A., H.Y., E.E., Concept: E.A., H.Y., E.E., Design: E.A., H.Y., E.E., Data Collection or Processing: E.A., H.Y., E.E., Analysis or Interpretation: E.A., H.Y., E.E., Literature Search: E.A., H.Y., E.E., Writing: E.A., H.Y., E.E.

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ORIGINAL ARTICLE

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Impact of Anti-Tumor Necrosis Factor Alpha Treatment on Lipid Profile in Patients with Rheumatoid Arthritis

Romatid Artritli Hastalarda Anti-Tümör Nekroz Alfa Tedavisinin Lipid Profili Üzerine Etkisi

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ABSTRACT

Background: Rheumatoid arthritis (RA) primarily causes joint deformities. Epidemiologic and clinical studies have shown that chronic inflammation in RA increases the risk of cardiovascular disease. The physiopathology of the phenomenon has been attempted to be explained by the alteration of the lipid profile by inflammation triggered by cytokines such as tumor necrotizing factor (TNF). However, studies investigating the effect of anti-TNF agents used for treating RA on lipids are still needed.

Materials and Methods: Between January 2006 and March 2010, 93 RA patients admitted to the University of Health Sciences Türkiye, İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, Clinic of Rheumatology Outpatient were included in the study. Anti-TNF treatment was administered to 46 patients, and 47 patients who were not administered anti-TNF were kept under control. Cholesterol and triglyceride levels were evaluated separately by averaging. The mean lipid levels at the beginning of the study and 12 months later were statistically compared.

Results: Among 93 female patients diagnosed with RA, adalimumab was administered to 18, etanercept to 18, and infliximab to 10 of 46 patients who received anti-TNF. The 47 patients who were not administered anti-TNF were kept under control. There was no statistical difference between baseline and 1-year postoperative lipid levels between the groups (p>0.05).

Conclusion: In approximately half of patients with RA, mortality is due to cardiovascular causes. Anti-TNF agents reduce inflammation and alter the lipid profile. In the literature, studies have shown that anti-TNF therapy has a negative effect on the lipid profile. The reason for the absence of this result in our study may be the exclusion of patients with diabetes mellitus and the short duration of the study. In conclusion, we believe that monitoring lipid levels is important in patients with high cardiovascular mortality. We believe that this should be considered in the selection and continuation of treatment.

Keywords: Rheumatoid arthritis, anti-TNF, lipid profile

ÖZ

Amaç: Romatoid artrit (RA), öncelikle eklemlerde deformitelere neden olur. Epidemiyolojik ve klinik çalışmalar RA'de gözlenen kronik enflamasyonun kardiyovasküler hastalık riskini artırdığını göstermiştir. Olayın fizyopatolojisi, tümör nekrotizan faktörü (TNF) gibi sitokinlerle tetiklenmiş olan enflamasyonun lipid profilini değiştirmesi ile açıklanmaya çalışılmıştır. Ancak RA tedavisi için kullanılan anti-TNF ajanlarının lipitler üzerindeki etkisini araştıracak çalışmalara halihazırda ihtiyaç duyulmaktadır. Bu çalışmanın amacı; RA hastalarında anti TNF tedavinin serum lipid düzeylerine etkisini araştırmaktır.

Gereç ve Yöntemler: Ocak 2006-Mart 2010 tarihleri arasında Sağlık Bilimleri Üniversitesi, İstanbul Kartal Dr. Lütfi Kırdar Eğitim ve Araştırma Hastanesi Romatoloji Polikliniğine başvuran 93 RA hastası çalışmaya alındı. Kırk altı hastaya anti-TNF tedavi verildi, anti-TNF verilmeyen 47 hasta ise kontrol altında tutuldu. Diabetes mellitus tanılı ve antihiperlipidemik tedavi alan hastalar çalışmaya alınmadı. Kolesterol ve trigliserid seviyeleri ayrı ayrı ortalaması alınarak değerlendirildi. Çalışma başlangıcı ve 12 ay sonraki lipid düzeylerinin ortalamaları istatistiksel olarak karşılaştırıldı.

Bulgular: RA tanılı 93 kadın hastadan anti-TNF verilen 46 hastanın 18'e Adalimumab, 18'e Etanercept, 10'a İnfliksimab verildi. Anti-TNF verilmeyen 47 hasta ise kontrol altında tutuldu. Gruplara göre başlangıç ve 1 yıl sonrası lipid düzeyleri arasında istatistiksel farklılık bulunmadı (p>0,05).

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ÖZ

Sonuç: RA'lı hastaların yaklaşık yarısında mortalite kardiyovasküler nedenlere bağlıdır. Sistemik enflamasyon direkt endotel fonksiyonu üzerine, indirekt olarak da lipid profiline olan etkisiyle kardiyovasküler riske neden olur. TNF-alfa kronik enflamasyonda odak sitokindir. Lipid metabolizması, insülin rezistansı ve endotel fonksiyonunu etkiler. TNF-alfa blokerlerinin tedavi amaçlı kullanımı enflamasyonu azaltır ve hastaların lipid profilinde değişiklik yapar. Literatürde anti-TNF tedavinin lipid profilini olumsuz etkilediğini gösteren çalışmalar vardır. Bizim çalışmamızda bu sonucun olmamasının nedeni; diabetes mellituslu hastaların çalışmaya alınmaması ve kısa süreli olması olabilir. Sonuç olarak RA gibi kardiyovasküler mortalitesi oldukça yüksek olan bir hastalıkta, lipid düzeylerinin takibinin oldukça önemli olduğu inancındayız. O nedenle tedavi seçiminde ve devamında da bu durumun dikkate alınması gerektiği inancındayız.

Anahtar Kelimeler: Romatoid artrit, anti-TNF, lipid profili

Introduction

Rheumatoid arthritis (RA) primarily affects the joints, causing chronic inflammation and deformities. It is characterized by primary synovitis, which leads to the formation of pannus in the synovia and subsequent destruction of cartilage, bone tissue, and adjacent tissues, resulting in joint deformations (1). Inflammation can also affect other organs (2,3). RA can affect the cardiovascular system through various mechanisms, such as vasculitis, amyloidosis, serositis, valvulitis, fibrosis, and lesions resembling rheumatoid nodules (4). This involvement can lead to serious complications, such as pericarditis, myocardial dysfunction, coronary arthritis, conduction system involvement, heart valve involvement, aortitis, and pulmonary hypertension, which are associated with early mortality (5,6). Chronic inflammation is recognized as a risk factor for atherosclerosis and heart failure in patients with RA. Epidemiologic and clinical studies have shown that RA increases the risk of cardiovascular disease with chronic inflammation. Atherosclerosis is associated with disease duration and blood lipid levels (7,8). Cardiovascular causes account for approximately half of the mortality in patients with RA. Systemic inflammation increases the risk of cardiovascular disease by directly affecting endothelial function or indirectly affecting the lipid profile. The lipid profile is altered by the acute phase response activated by inflammation or infection. Cytokines, such as tumor necrosis factor (TNF), regulate an organism's immunological, inflammatory, and restorative responses to an agent. These hormone-like polypeptides are primarily secreted during immunological and inflammatory responses and act as signals in intercellular communication (9,10,11,12). TNF-α functions as a chemotactic agent for monocytes and neutrophils, stimulating phagocytosis and adhesion to the endothelium. In addition, it induces the release of superoxide derivatives and procoagulant activity in the endothelial tissue, leading to early vasodilation and leukocyte accumulation in the vessel (13,14). These effects include the suppression of cytokine/receptor functions, conversion of the immune response from Th1 to Th2, and inhibition of the three-molecule complex (TCR/peptide/MHC) (15). Anti-TNF agents reduce inflammation in the treatment of RA and are commonly used for this purpose.

The study investigated the impact of anti-TNF therapy on serum lipid levels in patients with RA.

Materials and Methods

This single-center study enrolled 93 patients with RA who applied to University of Health Sciences Türkiye, İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, Clinic of Rheumatology January 2006 and March 2010. The study group comprised 46 RA patients who were scheduled to start anti-TNF treatment, whereas the control group consisted of 47 RA patients who did not receive anti-TNF treatment. In this study, all patients provided informed consent to participate. The disease was diagnosed according to the revised RA diagnostic criteria of the American Rheumatism Association in 1987. This study excluded patients with liver or kidney failure, malignancy, systemic diseases other than hypertension, and additional inflammatory diseases. Patients using antihyperlipidemic drugs and those diagnosed with diabetes mellitus were also excluded because of their potential impact on the lipid profile. The study participants were interviewed regarding their symptoms, systemic diseases, medication use, and family medical history. A comprehensive physical examination, including an assessment of the musculoskeletal system, was conducted for all participants. Routine laboratory tests were performed to obtain a complete blood count and measure biochemical markers, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and rheumatoid factor (RF) levels. Blood samples were collected from the forearm vein between 08:30 and 09:00 after a 12 hours fast. Normal CRP measurement values range from 0 to 5 mg/L, while values higher than 5 mg/L are considered abnormal. A sedimentation value between 6 and 12 mm is considered normal. The normal value for RF is 0-15 IU/mL,

whereas values over 15 IU/mL are considered high. Lipid levels were evaluated separately by calculating the mean. Statistical comparison was conducted between the mean sedimentation, CRP, and lipid levels at the beginning and 12 months after the start of the study.

This study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University of Health Sciences Türkiye, İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, with decision number 89513307/1009/389.

Statistical Analysis

Statistical analysis was performed using Number Cruncher Statistical System 2007 and PASS 2008 software (Utah, USA). Descriptive statistical methods, including mean and standard deviation, were used for data analysis. The Student's t-test was used to compare normally distributed parameters between the two groups. Furthermore, the Paired Samples t-test was used to compare changes after treatment with those before treatment. The data were compared using the chi-square test.

Results

Ninety-three female patients were included in the study, with 46 patients in the study group and 47 patients in the control group. The patients were screened between January 2006 and March 2010. The age range of the patients was 25-64 years, with a mean of 48.52±9.96 years.

Age at onset and disease duration were similar in both groups. The study analyzed CRP, ESR, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, and total cholesterol levels, as well as smoking, presence of hipertension (HT), RF levels, and use of Methotrexate (MTX), Hydroxychloroquine (HQ), Deltacortil (Prednisolone) (DC), Arva (Leflunomide), and Salazopryn (Sulfasalazine) (SA) (p>0.05) (Table 1, Table 2).

The study group consisted of 18 patients who received Adalimumab, 18 patients who received Etanercept, and 10 patients who received Infliximab (Table 3).

Baseline CRP levels were comparable between the groups. Additionally, CRP levels did not show any statistically significant difference between the groups 1 year later (p>0.05). Baseline CRP levels were similar among the groups. No significant change in CRP levels was observed in the control group after 1 year compared with baseline levels (p>0.05) (Table 4).

Baseline sedimentation values were also not significantly different between the groups (p>0.05). After 1 year, there was no statistically significant difference in sedimentation levels between the groups (p>0.05). However, both groups showed a statistically significant decrease in sediment levels compared with baseline (p<0.01) (Table 5).

Additionally, there were no significant differences in total cholesterol, LDL cholesterol, and HDL cholesterol levels between baseline and 1-year follow-up measurements in

Table 1. Patient characteristics

	Study (n=50)	Control (n=47)	p-value
	Mean ± SD	Mean ± SD	
Age	47.60±10.15	49.42±9.78	**0.386**
Age at disease (month)	89.92±27.93	85.70±14.54	**0.414**
CRP	18.35±20.11	14.11±27.77	**0.402**
ESH	43.02±19.36	35.17±24.63	**0.092**
HDL	55.95±1.68	58.63±14.61	**0.195**
LDL	108.62±26.03	110.27±21.78	**0.798**
Triglyceride	116.71±41.21	124.21±55.05	**0.764**
Total cholesterol	86.32±42.42	191.31±25.43	**0.515**
Resume			
Smoking	2 (4.3%)	8 (17%)	**0.091**
HT	19 (41.3%)	22 (46.8%)	**0.593**
DM	0 (0%)	0 (0%)	-
RF			
Positive	25 (54.3%)	23 (48.9%)	**0.602**
Negative	21 (45.7%)	24 (51.1%)	

SD: Standard deviation, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, RF: Rheumatoid factor, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HT: Hypertension, DM: Diabetes mellitus

Table 2. Therapeutic agents

	Study	Control	p-value
	n (%)	n (%)	
MTX	28 (56%)	20 (42.6%)	**0.186**
HQU	17 (37%)	23 (48.9%)	**0.243**
DC	21 (45.7%)	15 (31.9%)	**0.174**
ARAVA	12 (26.1%)	7 (14.9%)	**0.181**
SA	16 (32%)	9 (19.1%)	**0.148**

Chi-squared test, p<0.05, p<0.01, TX: Methotrexate, DC: Deltacortil, SA: Sulfasalazine, HQU: Hydroxychloroquine

Table 3. Anti-TNF usage and duration

	n	%
Currently using anti-TNF		
Adalimumab	18	39.1
Etanercept	18	39.1
Infliximab	10	21.7

TNF: Tumor necrotizing factor

either group (p>0.05). One year later, there was no significant difference in cholesterol levels between the study and control groups (p>0.05). Similarly, there was no statistically significant difference in triglyceride levels between the groups at baseline and after 1 year (>0.05). However, a significant difference in triglyceride levels was found in the control group 1 year after the first measurement (p<0.05) (Table 6).

Discussion

The treatment of RA, a condition characterized by chronic inflammation, joint deformity, and systemic complications, reduces inflammation and prevent joint deformity and systemic complications. Chronic inflammation is primarily caused by TNF-alpha, a cytokine that affects lipid metabolism, insulin resistance, and endothelial function. The therapeutic use of TNF-alpha blockers reduces inflammation and induces changes in the lipid profile of patients (16). Short-term anti-TNF therapy resulted in a significant increase in HDL cholesterol. However, this effect was temporary. Longer anti-TNF use leads to increased levels of cholesterol and LDL cholesterol (17,18).

The relationship between chronic inflammation and lipid metabolism is not yet fully understood (19,20). Biologic drugs targeting proinflammatory cytokines, such as TNF-alpha and IL-6, appear to increase lipid levels, but the mechanism underlying this effect is not yet fully understood (21,22,23).

The study compared the mean lipid levels of patients with RA who received anti-TNF at the beginning of the study and after 1 year. The mean lipid levels of patients with RA in the control group who did not receive anti-TNF were also compared after a 1-year follow-up. The study found no significant difference between the initial and one-year later total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride levels in patients with RA who received anti-TNF. Cholesterol levels did not significantly differ between the control and study groups. However, the study group experienced a significant decrease in triglyceride levels. The lipid averages at baseline and 1 year later were similar between the two groups.

In their study on patients with RA who received anti-TNF therapy, Cauza et al. (24) found no significant difference in

Table 4. CRP assessment

CRP	Study	Control	p-value
	Mean ± SD	Mean ± SD	
Beginning	18.35±20.11	14.11±27.77	**0.402**
1 year later	10.79±16.42	10.35±11.79	**0.883**
Beginning - 1 year later	**0.001**	**0.272**	

Student t-test, Paired Samples t-test, p<0.05, p<0.01
CRP: C-reactive protein, SD: Standard deviation

Table 5. Sedimentation assessment

ESR	Study	Control	p-value
	Mean ± SD	Mean ± SD	
Beginning	43.02±19.36	35.17±24.63	**0.092**
1 year later	28.50±16.13	24.27±14.99	**0.186**
Beginning - 1 year later	**0.001****	**0.001****	

Student t-test, Paired Samples t-test, **p<0.01
ESR: Erythrocyte sedimentation rate, SD: Standard deviation

Table 6. Cholesterol and triglyceride assessment

		Study	Control	p-value
		Mean ± SD	Mean ± SD	
Total cholesterol	**Beginning**	186.72±42.23	191.31±25.43	**0.515**
	1 year later	188.90±35.48	191.30±26.99	**0.718**
Beginning - 1 year later		**0.691**	**0.732**	
LDL	**Beginning**	109.02±25.79	110.27±21.78	**0.798**
	1 year later	103.30±29.11	107.72±24.82	**0.437**
Beginning - 1 year later		**0.229**	**0.634**	
HDL	**Beginning**	55.00±12.80	58.63±14.61	**0.195**
	1 year later	56.52±13.20	59.04±16.81	**0.419**
Beginning - 1 year later		**0.364**	**0.688**	
TG	**Beginning**	121.06±48.21	124.21±55.05	**0.764**
	1 year later	121.26±45.06	115.34±51.65	**0.557**
Beginning - 1 year later		**0.968**	**0.036***	

Student t-test, Paired Samples t-test, *p<0.05
SD: Standard deviation, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglyceride

the levels of total cholesterol and LDL cholesterol before and after 48 months. However, they found a significant increase in triglyceride levels after treatment and a significant decrease in HDL cholesterol levels (24). Our study did not find any negative effects, which may be due to the shorter follow-up period and the exclusion of patients with diabetes mellitus.

Two weeks after treatment, RA patients receiving anti-TNF therapy experienced a decrease cholesterol, LDL, and triglyceride levels. However, evaluations performed 6 months and 1 year later showed an increase in total cholesterol, LDL, and triglyceride levels, as well as a decrease in HDL cholesterol. These findings differ from those of our study (25). Our study suggests that the observed result may be attributed to the inclusion of patients with a higher average age and those diagnosed with diabetes mellitus who received antihyperlipidemic drugs. Seriolo et al. (26) reported an increase in total cholesterol, LDL cholesterol, and triglyceride levels 16 and 24 weeks after initiating anti-TNF treatment in patients with RA. Similarly, Tam et al. (27) found that total cholesterol, LDL cholesterol, and triglyceride levels increased at the 6-week evaluation and continued to increase at the 14th week evaluation. The result may have emerged due to the short control period compared with our study, the presence of additional chronic diseases in all patients, and high lipid levels before treatment initiation.

Study Limitations

One of the reasons why we found different results in similar studies may be that the height, weight, and body mass index of the patients were not considered. This is one of the important limitations of our study.

Conclusion

In conclusion, it is crucial to monitor lipid levels in patients with RA, a disease with high cardiovascular mortality. Therefore, it should be considered when selecting and continuing treatment.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the University of Health Sciences Türkiye, İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital, with decision number 89513307/1009/389.

Informed Consent: In this study, all patients provided informed consent to participate.

Authorship Contributions

Surgical and Medical Practices: R.Ç., G.G.O., Concept: R.Ç., G.G.O., Design: R.Ç., G.G.O., Data Collection or Processing: R.Ç., Analysis or Interpretation: R.Ç., G.G.O., Literature Search: R.Ç., Writing: R.Ç.

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Breast Ultrasound and Dynamic Contrast-Enhanced Magnetic Resonance Imaging Findings of Idiopathic Granulomatous Mastitis: A Retrospective Single-Center Clinical Study

İdiyopatik Granülomatöz Mastitin Meme Ultrasonu ve Dinamik Kontrastlı Manyetik Rezonans Görüntüleme Bulguları: Retrospektif Tek Merkezli Bir Klinik Deneyim

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ABSTRACT

Background: We aimed to evaluate the effectiveness of breast ultrasound (US) and dynamic contrast-enhanced magnetic resonance imaging (DC-MRI) in the diagnosis of idiopathic granulomatous mastitis (IGM).

Materials and Methods: Breast US and DC-MRI findings of 42 female patients diagnosed with IGM histopathologically were retrospectively evaluated. Patient's age, pregnancy history, symptoms, prolactin level, and Breast Imaging-Reporting and Data System (BI-RADS) category of breast lesions were recorded.

Results: The median age of patients was 39 years (range, 20-71 years, 76.2% were under 40 years of age). Pregnancy history, elevated serum prolactin levels, and complaints (breast pain, swelling, or rash) were evident in 40.5%, 23.8%, and 95.2% of the patients, respectively. Breast lesions were mostly categorized as BI-RADS category 3 (38.1%) or BI-RADS category 4A (40.5%). The most common additional findings detected in both imaging modalities were edema (95.2%; 90.5%), reactive lymph nodes (95.2% each), and skin thickening (90.5%; 52.4%). The most common findings specific to US are lesions with irregular borders (88.1%) and hypo-heterogenic echo pattern (92.9%); tubular expansion and connecting tracts (88.1%), cystic component (69.0%), floating debris (64.3%), and ductal ectasia (52.4%). The most common findings specific to DC-MRI are; localized collective abscess (57.5%) and micro-abscess (53.7%), minimal background parenchymal enhancement (66.6%), non-mass enhancement with heterogeneous (48.3%) or cluster (44.8%) internal pattern, and regional distribution (44.8%). Median values for abscess size, lymph node short axis, and apparent diffusion coefficient were 25 mm, 10 mm, and (1.064x10-3 mm^2/s), respectively, while the mean lymph node long axis was 18.0 mm.

Conclusion: Some findings detected on US (heterogeneous hypoechoic lesions, tubular expansion and connection paths, cystic component, floating debris and ductal ectasia) and breast MRI (regionally distributed heterogeneous or clustered internal pattern, non-mass contrast enhancement and minimal background staining, localized collective abscess or microabscess) largely support the diagnosis of IGM.

Keywords: Idiopathic granulomatous mastitis, breast, magnetic resonance imaging, ultrasonography

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ÖZ

Amaç: İdiyopatik granülomatöz mastit (İGM) tanısında meme ultrasonu (US) ve dinamik kontrastlı manyetik rezonans görüntülemenin (DK-MRG) etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Histopatolojik olarak İGM tanısı konulan 42 kadın hastanın meme US ve MRG bulguları geriye dönük olarak değerlendirildi. Hastanın yaşı, gebelik öyküsü, semptomları, prolaktin düzeyi ve meme lezyonlarının Meme Görüntüleme-Raporlama ve Veri Sistemi (BI-RADS) kategorisi kaydedildi.

Bulgular: Hastaların ortanca yaşı 39 idi (aralık, 20-71 yıl, %76,2'si 40 yaşın altındaydı). Gebelik öyküsü, yüksek serum prolaktin seviyeleri ve şikayetler (meme ağrısı, şişlik veya kızarıklık) sırasıyla hastaların %40,5, %23,8 ve %95,2'sinde belirgindi. Meme lezyonları çoğunlukla BI-RADS kategori 3 (%38,1) veya BI-RADS kategori 4A (%40,5) olarak kategorize edildi. Çoğu hastada US ve DK-MRG bulguları sol taraflı (sırasıyla %52,4; %57,1), kitlesiz (%69,0; %59,5), düzensiz şekilli (%90,5; %66,7) ve 1-3 kadran yerleşimli (%66,7; %45,2) lezyon olarak tanımlandı. Her iki görüntüleme yönteminde de en sık saptanan ek bulgular ödem (%95,2; %90,5), reaktif lenf nodları (%95,2) ve deri kalınlaşması (%90,5; %52,4) idi. US'ye özgü en sık bulgular, düzensiz sınırları olan (%88,1) ve hipo-heterojenik eko paternli (%92,9) lezyonlara ek olarak; tübüler genişleme ve bağlantı yolları (%88,1), kistik bileşen (%69.0), yüzen debris (%64.3) ve duktal ektazi (%52.4) idi. DK-MRG'ye özgü en yaygın bulgular; lokalize kollektif apse (%57,5) ve mikro-apse (%53,7), minimal arka plan kontrastlanması (%66,6), heterojen (%48,3) veya kümesel (%44,8) iç patern ve bölgesel dağılım (%44,8) ile kitlesel olmayan kontrastlanma. Apse boyutu, lenf nodu kısa ekseni ve görünür difüzyon katsayısı için medyan değerler sırasıyla 25 mm, 10 mm ve (1,064x10-3 mm^2/s) iken, ortalama lenf nodu uzun ekseni 18,0 mm idi.

Sonuç: US (heterojen hipoekoik lezyonlar, tübüler genişleme ve bağlantı yolları, kistik komponent, yüzen debris ve duktal ektazi) ve meme MRG'de saptanan bazı bulgular (bölgesel dağılımlı heterojen veya kümelenmiş iç paternli, kitlesel olmayan kontrastlanma ve minimal zemin boyanması, lokalize kollektif apse veya mikroabse) IGM tanısını büyük ölçüde destekler.

Anahtar Kelimeler: İdiyopatik granülomatöz mastit, meme, manyetik rezonans görüntüleme, ultrasonografi

Introduction

Idiopathic granulomatous mastitis (IGM) is a rare chronic inflammatory breast disease of unknown etiology that primarily affects premenopausal women with a history of pregnancy and lactation (1,2,3). Diagnosis of IGM poses a challenge because of its resemblance to infectious mastitis or inflammatory breast carcinoma both clinically and radiologically (2,3,4,5). Clinical diagnosis, often delayed and achieved through exclusion, can be facilitated by imaging, with radiologists playing a crucial role in suggesting a diagnosis in appropriate clinical contexts (1,2,4,6). Accurate interpretation of imaging results is vital for establishing a timely and definitive diagnosis, which is supported by histopathological examination (2,3,5,6,7). Although traditional radiological modalities like mammography and ultrasound (US) are commonly used for assessing IGM, they often yield non-specific findings such as focal asymmetries, masses, and skin thickening (2,8,9,10). Magnetic resonance imaging (MRI) has emerged as a key diagnostic tool, offering advantages over mammography and US in evaluating various breast conditions (8,10,11). However, initial imaging assessment for IGM typically relies on US because of its predominance in premenopausal women presenting with mastitis symptoms and palpable masses (5). Consequently, the literature on MRI findings associated with IGM is limited, consisting mainly of small case series. Despite normal US findings not excluding IGM, MRI findings may lack specificity because of overlapping features suggesting malignancy or other granulomatous breast disorders (4,11,12,13,14)

In this study, we aimed to evaluate the effectiveness of breast US and dynamic contrast-enhanced magnetic resonance imaging (DC-MRI) in the diagnosis of IGM.

Materials and Methods

Study Population

A total of 42 female patients (median age: 20 years, ranged 39 to 71 years) with confirmed pathology of IGM who underwent breast US and DC-MRI were included in this cross-sectional study conducted between May 2015 and December 2020 in a tertiary care radiology clinic. This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by Recep Tayyip Erdoğan University Hospital Non-interventional Clinical Research Ethics Committee (date: 21/01/2021; protocol number: 2021/18). Written informed consent was obtained from all patients.

Assessments

Data on the patient's age, history of pregnancy, symptoms (pain, swelling, rash), prolactin level, and Breast Imaging-Reporting and Data System (BI-RADS) category were recorded. US imaging findings [lesion's side, location, shape, echo pattern, margin, fistula to skin, cystic component, floating debris, ductal ectasia, skin thickening, edema, reactive lymph node, nipple retraction, tubular extension and connecting tracts and BI-RADS results) and breast DC-MRI findings (lesion's side, location, type, shape, fistula to skin, micro-abscess, abscess size, localized collective abscess, skin thickening, edema, lymph node long-short

axis, reactive lymph node, nipple retraction, background parenchymal enhancements (BPE), non-mass enhancement (NME) characteristics (internal pattern, lesion distribution type), diffusion restriction and apparent diffusion coefficient (ADC) value] of breast lesions were also recorded.

Imaging Assessments

High-definition US images (LOGIQ P6, GE, USA) were acquired using a linear-array transducer with a central frequency of 7.5 MHz. MRI indications encompassed the exclusion of inflammatory cancer in cases resistant to treatment, further evaluation for patients with inconclusive mammography and/or sonography results, and determination of disease extent. MRI was conducted after conventional examinations in all patients, ensuring no treatment delays occurred. MRI procedures were performed using a 1.5-T whole-body imaging system (Siemens Magnetom Aera Syngo MR D13, Erlangen, Germany) or a 3-T whole-body imaging system (GE Healthcare Discovery MR750, Waukesha, WI).

Statistical Analysis

For statistical analysis, IBM SPSS Statistics for Windows, version 23.0, was used (IBM Corp., Armonk, NY). The assessment of variables' adherence to normal distribution was conducted visually through histograms and probability graphs, and using the Kolmogorov-Smirnov method. Data are presented in terms of mean (standard deviation), median (minimum-maximum), and percentage (%) as deemed appropriate.

Results

Baseline Characteristics

The median age of female patients diagnosed with IGM was 39 years (range: 20 to 71 years), with 57.1% and 76.2% of patients below 40 and 50 years, respectively. Notably, 40.5% had a history of pregnancy, 23.8% showed elevated serum prolactin levels, and 95.2% presented with breast pain, swelling, or rash (Table 1). Most lesions were classified as probably benign (38.1%) or with low suspicion of malignancy (40.5%) (Table 1). US imaging (n=42) predominantly revealed left-sided (52.4%) and non-mass (69.0%) lesions distributed across 1-3 quadrants (66.7%), characterized by irregular shape (90.5%), indeterminate margins (88.1%), and hypo-heterogeneous echo pattern (92.9%). Common associated findings included edema (95.2%), reactive lymph nodes (95.2%), and skin thickening (90.5%) (Figures 1, 2). Nipple retraction or fistula to the skin

Table 1. Baseline characteristics

Age (year)	Mean (SD)	41.9 (12.1)
	Median (min.-max.)	39 (20-71)
Age group, n (%)	≤40 years, n (%)	24 (57.1)
	≤50 years, n (%)	32 (76.2)
Pregnancy history, n (%)	Yes	17 (40.5)
	No	25 (59.5)
Elevated serum prolactin levels (>25 ng/mL), n (%)	Yes	10 (23.8)
	No	32 (76.2)
Breast pain, swelling, rash, n (%)	Yes	40 (95.2)
	No	2 (4.8)
BI-RADS classification, n (%)		
3 (probably benign)		16 (38.1)
4A (low suspicion for malignancy)		17 (40.5)
4B (moderate suspicion for malignancy)		3 (7.1)
4C (high suspicion for malignancy)		6 (14.3)

BI-RADS: Breast Imaging Reporting and Data System, min.: Minimum, max.: Maximum, SD: Standard deviation

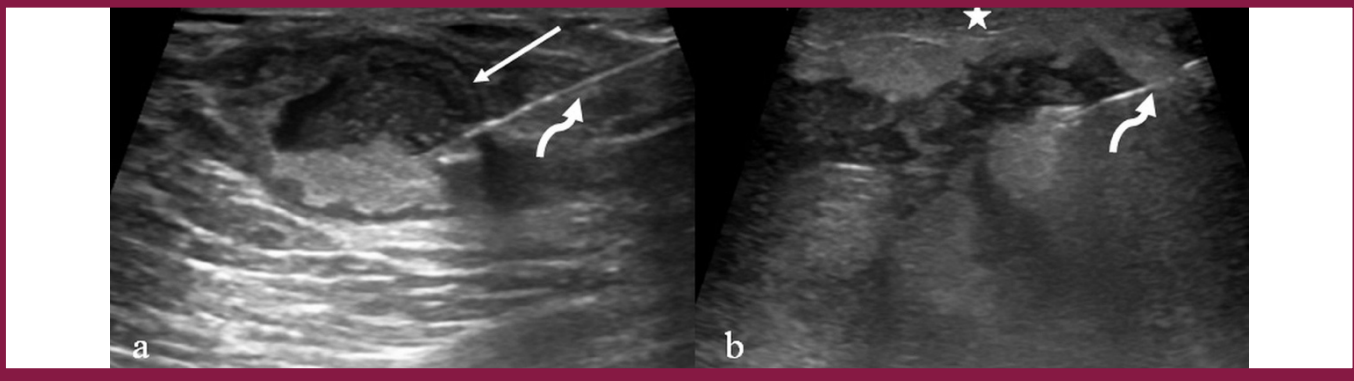

Figure 1. In a 28-year-old patient who was histopathologically diagnosed with idiopathic granulomatous mastitis, a complicated cyst (arrow) with dense floating debris and edema (star) on the skin are observed in the images obtained during US-guided biopsy (curved arrow)
US: Ultrasonography

was absent in the majority (78.6% and 66.7%, respectively) (Table 2).

DC-MRI findings (n=42) also showed left-sided (57.1%), non-mass (59.5%) lesions, often irregular in shape (66.7%). Diffusion restriction (100.0%), reactive lymph nodes (95.2%), and edema (90.5%) were frequently observed, with minimal edema in 61.9% of the cases (Figure 3). Notably, nipple retraction or fistula to the skin was absent in 57.1% and 69.0% of lesions, respectively (Table 3).

BPEs were minimal in 66.6% of cases. NME internal patterns were predominantly heterogeneous (48.3%) or clustered (44.8%) with regional (44.8%), multiple regional (20.7%), or segmental (20.7%) distributions (Figures 4, 5) (Table 3).

Median values for abscess size, lymph node short axis, and ADC were 25 mm, 10 mm, and ($1.064x10^{-3}$ mm^2/s), respectively, while the mean lymph node long axis was 18.0 mm (Table 3).

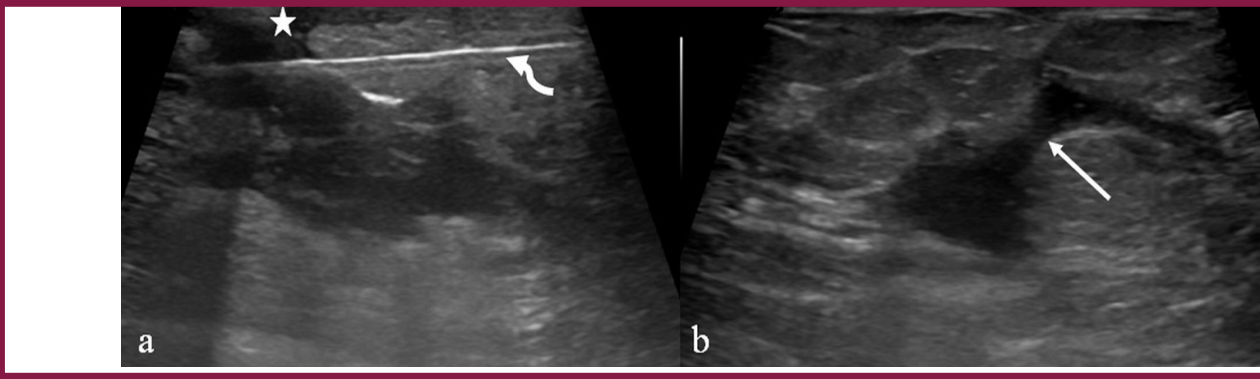

Figure 2. Images of a 25-year-old patient diagnosed with IGM obtained during the US-guided biopsy procedure (curved arrow) show a dense collection of skin fistulization (star), connecting tracts, and tubular extension (arrow)
IGM: Idiopathic granulomatous mastitis, US: Ultrasonography

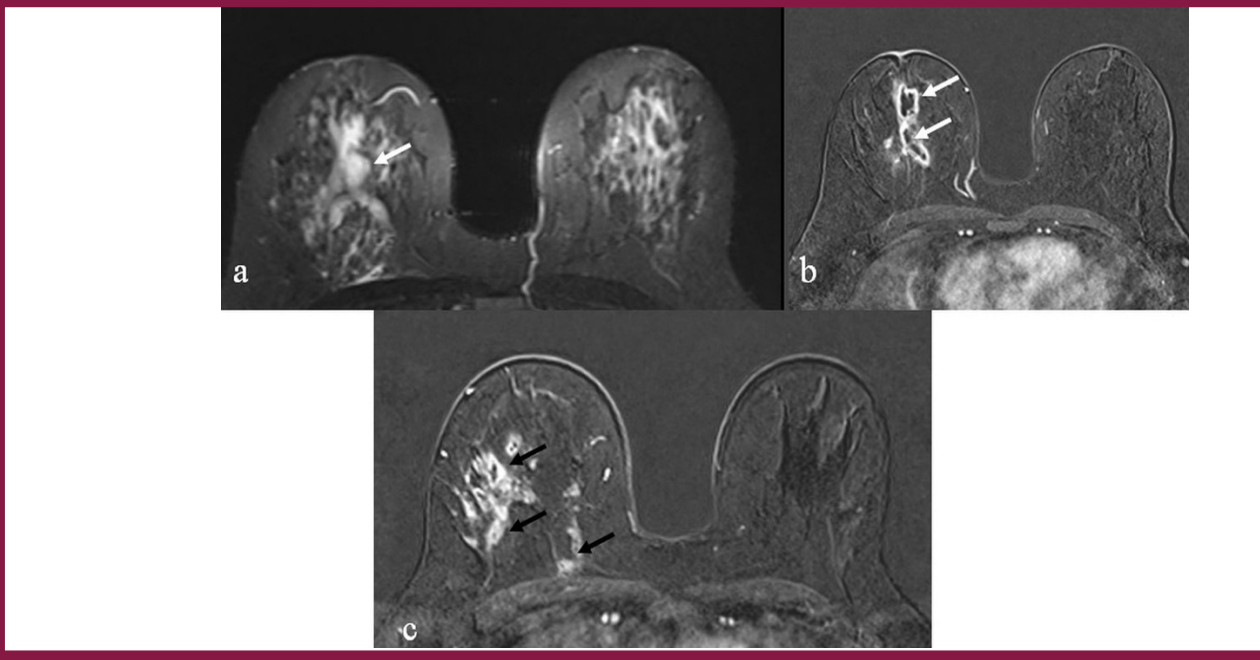

Figure 3. In the dynamic contrast-enhanced MRI examination of a 38-year-old female patient diagnosed with IGM, macro (white arrow) and microabscess foci (black arrow) are observed in the nonmassive enhancement area in the T2W fat-suppressed series (a) and postcontrast dynamic series (b, c)
MRI: Magnetic resonance imaging, IGM: Idiopathic granulomatous mastitis

Discussion

The results of our study indicate that the most commonly observed findings on US in patients diagnosed with IGM include indistinct margins characterized by a hypo-heterogeneous echo pattern, tubular extensions and connections, and the presence of cystic components containing floating debris. Furthermore, our analysis of MRI images in patients with IGM revealed a predominance of localized collections of abscesses or micro-abscesses, heterogeneous or clustered internal patterns, and NMEs exhibiting a regional distribution across most lesions. These findings underscore the diagnostic value of both US and MRI in the evaluation and characterization of IGM.

IGM generally affects young women of childbearing age (32-34 years) (2,6,13,14,15,16), while some reports indicate a wider age distribution ranging from late childhood to the late postmenopausal period (17,18). Likewise, the median age of our patients was 39 years, while 57.1% and 76.2% of patients were under 40 and 50 years of age, respectively. In addition, majority (95.2%) of our patients reported complaints such as breast pain, swelling, and rash, consistent with the most frequently reported manifestations of IGM (i.e., erythema, edema, sensitive-palpable unilateral breast mass, ulceration, discharge) (5,19). In addition, supporting the association between IGM and history of pregnancy and lactation (2), 40.5% of our patients reported a history of pregnancy and 23.8% had elevated serum levels of prolactin.

The majority of our patients had breast lesions considered to be probably benign (BI-RADS category 3, 38.1%) or with low suspicion of malignancy (BI-RADS category 4A, 40.5%). Likewise, IGM imaging studies have

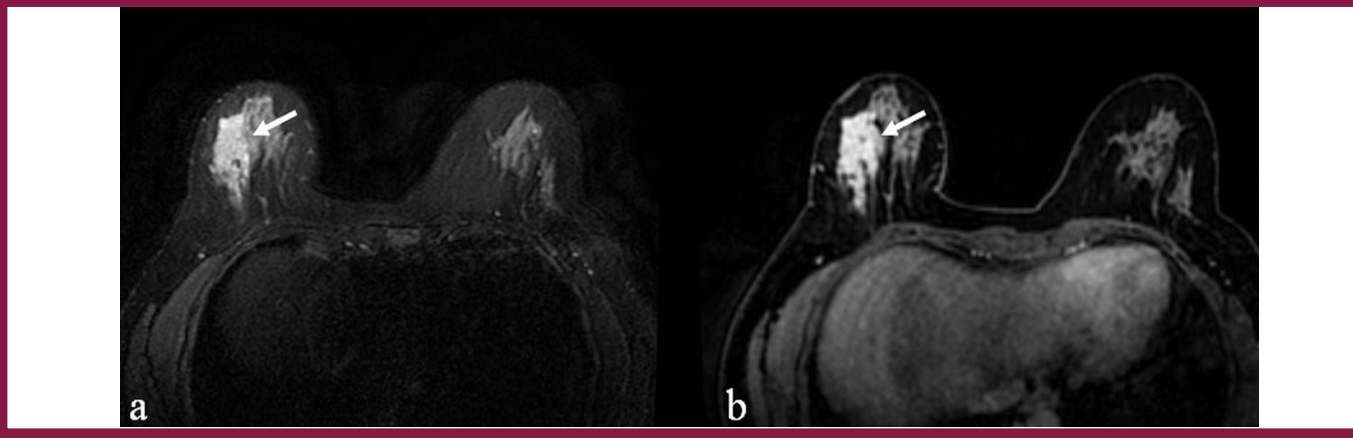

Figure 4. In the DC-MR images of a 40-year-old female patient diagnosed with IGM, a spicular contoured mass (arrow) is observed in the right breast, which is hyperintense in the T2W fat-suppressed series (a) and in postcontrast dynamic displays (b) with intense homogeneous contrast enhancement
IGM: Idiopathic granulomatous mastitis, DC-MR: Dynamic contrast-enhanced magnetic resonance

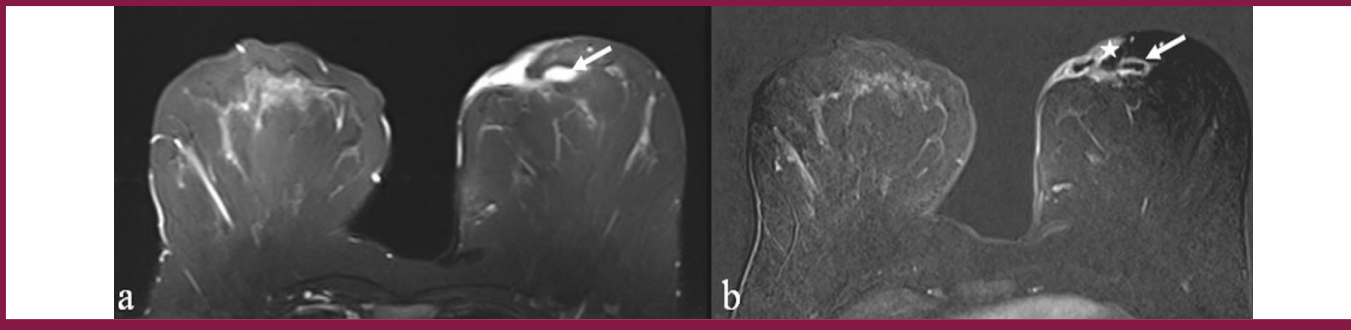

Figure 5. In the T2W fat-suppressed series (a) and postcontrast dynamic series (b) of a 42-year-old female patient diagnosed with IGM, mammary skin thickening (star) and abscess foci (arrow) with fistulization of the skin in the periareolar area are observed
IGM: Idiopathic granulomatous mastitis

indicated a higher prevalence of BI-RADS 3 (82.8% on MR, 55.2% on conventional methods) or BI-RADS 4 (3.4% on MRI and 37.9% on conventional methods) lesions (8).

Considering the imaging findings, representing the largest patient series for IGM in the literature, our findings revealed that breast US imaging and DC-MRI findings were consistent

Table 2. Breast US imaging findings (n=42)

US imaging findings, n (%)		
Lesion side	Right	18 (42.9)
	Left	22 (52.4)
	Bilateral	2 (4.8)
Localization	Retrosternal	2 (4.8)
	1-3 quadrant	28 (66.7)
	Diffuse	12 (28.6)
Lesion type	Mass	13 (31.0)
	Non-mass	29 (69.0)
Lesion shape	Oval-round	4 (9.5)
	Irregular	38 (90.5)
Lesion echo pattern	Hypo-heterogenic	39 (92.9)
	Echogenic-heterogenic	3 (7.1)
Lesion margin	Well-circumscribed lesion	3 (7.1)
	Indeterminate lesion	37 (88.1)
	Spiculated lesion	2 (4.8)
Fistula to the skin	Absent	28 (66.7)
	Present	14 (33.3)
Cystic component	Absent	13 (31.0)
	Present	29 (69.0)
Floating debris	Absent	15 (35.7)
	Present	27 (64.3)
Ductal ectasia	Absent	20 (47.6)
	Ipsilateral	11 (26.2)
	Contralateral	8 (19.0)
	Bilateral	3 (7.1)
Skin thickening	Absent	4 (9.5)
	Present	38 (90.5)
Edema	Absent	2 (4.8)
	Present	40 (95.2)
Reactive lymph nodes	Absent	2 (3.8)
	Present	40 (95.2)
Nipple retraction	Absent	33 (78.6)
	Present	9 (21.4)
Tubular extension and connecting tracts	Absent	5 (11.9)
	Present	37 (88.1)

US: Ultrasonography

Table 3. Breast DC-MRI findings (n=42)

Breast DC-MRI findings, n (%)		
Lesion side	Right	16 (38.1)
	Left	24 (57.1)
	Bilateral	2 (4.8)
Localization	Retrosternal	11 (26.2)
	1-3 quadrant	19 (45.2)
	Diffuse	12 (28.6)
Lesion type	Mass	17 (40.5)
	Non-mass	25 (59.5)
Lesion shape	Oval-round	14 (33.3)
	Irregular	28 (66.7)
Fistula to the skin	Absent	29 (69.0)
	Present	13 (31.0)
Microabscess	Absent	19 (46.3)
	Present	22 (53.7)
Localized collective abscess	Absent	17 (42.5)
	Present	23 (57.5)
Abscess size (mm), median (min.-max.)		25 (0-62)
Skin thickening	Absent	20 (47.6)
	Present	22 (52.4)
Edema	Absent	4 (9.5)
	Minimal	26 (61.9)
	Moderate	11 (26.2)
	Massive	1 (2.4)
Lymph node long axis (n=33, cm), mean (SD)		18.0 (6.8)
Lymph node short axis (n=31, cm), median (min.-max.)		10 (6-21)
Reactive lymph nodes	Absent	2 (3.8)
	Present	40 (95.2)
Nipple retraction	Absent	24 (57.1)
	Present	18 (42.9)
BPEs (n=33)	Minimal	22 (66.6)
	Moderate	6 (18.2)
	Intense	5 (15.2)
NME internal pattern (n=29)	Heterogenic	14 (48.3)
	Homogeny	2 (6.9)
	Cluster	13 (44.8)
NME distribution type (n=29)	Regional	13 (44.8)
	Diffuse	3 (10.3)
	Focal	1 (3.4)
	Multiple regional	6 (20.7)
	Segmental	6 (20.7)
Diffusion restriction	Absent	0 (0.0)
	Present	42 (100.0)
ADC value (x10^{-3} mm^2/s), median (min.-max.)		1.064 (650-1.580)

ADC: Apparent diffusion coefficient, BPE: Background parenchymal enhancements, DC-MRI: Dynamic contrast-enhanced magnetic resonance imaging, NME: Non-mass enhancement, SD: Standard deviation, min.: Minimum, max.: Maximum

in terms of identifying the left-sided (52.4% and 57.1%, respectively), non-mass (69.0% and 59.5%), and irregularly shaped (90.5% and 66.7%) lesions located in the 1-3 quadrant (66.7% and 45.2%) in most patients. The most prevalent associated findings on both US and DC-MRI were the presence of edema (95.2% and 90.5%), reactive lymph nodes (95.2% for each), and skin thickening (90.5% and 52.4%) along with the presence of nipple retraction (42.9% and 21.4%) or fistula to skin (66.7% and 69.0%) in most patients.

US-specific findings in our series indicated lesions with indeterminate margins (88.1%) and hypo-heterogeneous echo pattern (92.9%) in addition to the presence of tubular extension and connecting tracts (88.1%), cystic component (69.0%), floating debris (64.3%), and ductal ectasia (52.4%) in most patients. DC-MRI-specific findings indicated localized collective abscess (57.5%) and micro-abscess (53.7%), as well as minimal BPEs (66.6%) and NMEs with heterogeneous (48.3%) or cluster (44.8%) internal pattern and a regional distribution (44.8%) in most lesions.

Similarly, in a radiological investigation involving 36 patients diagnosed with IGM, the predominant observations on breast US imaging included a heterogeneously hypoechoic mass displaying an irregular shape and indistinct margin (72.2%), tubular extension with connecting tracts, and tunneling around the lesions (50.0%). In addition, fluid collection with floating debris accounted for 27.8% of cases, and anechoic cystic components were observed in 13.9% of cases. The authors also highlighted two novel imaging indicators of IGM, namely duct ectasia containing secretion and a high-flow pseudocyst appearance (6).

In line with our US-based findings in IGM lesions, irregular hypoechoic lesions with tubular extensions (indicating the insinuating rather than destroying effect of IGM on breast lobules) are considered the most frequently reported US imaging findings in patients with IGM, whereas isolated ill-defined hypoechoic or heterogeneous lesions are the second most common finding (3,8,20,21,22,23,24). The ancillary US imaging findings reported in studies among patients with IGM are variable, including parenchymal edema, skin thickening, fluid collection, and axillary lymphadenopathy (2,4,8,13,20,22,24,25,26,27).

While studies investigating the MRI features of IGM also indicate a variable set of findings depending upon the severity of inflammation, heterogeneous ill-defined masses and segmental-regional NMEs are identified in most cases, and NME lesions are more frequent than mass-like lesions, in line with our findings (4,5,8,12,13,20,24,26,28,29).

Prediagnosis imaging observations in 29 patients with IGM revealed heterogeneous hypoechoic lesions with tubular extensions in 55.2% of cases, mild to moderately enlarged axillary lymph nodes in 41.4%, and fistula tracts in 10.3% of cases on US. MRI findings indicated the involvement of multiple quadrants (52.2%), heterogeneous segmental and regional NME, enlarged axillary lymph nodes (52.2%), and abscesses with marked peripheral ring enhancement (86.2%), suggesting edematous inflammation in the peripheral parenchyma (8). In a retrospective study of 20 patients with IGM, MRI identified a total of 29 lesions, with 14 appearing as mass enhancements and the remaining 15 characterized as NMEs with segmental distribution (40%) and diverse enhancement patterns (53%) (13). Analyzing DC-MRI results in 39 patients with IGM, the authors reported significantly lower ADC values for the lesion compared with the contralateral normal parenchyma, with NME and abscess noted in 92.3% and 33.3% of patients, respectively (12).

Similarly, our study predominantly observed regional distribution (44.8%) and heterogeneous enhancement patterns (48.3%) in the NME lesions, coupled with localized collective abscess (57.5%) and micro-abscess (53.7%). Furthermore, the presence of diffusion restriction in all lesions and the median ADC values ($1.064x10^3$ mm^2/s) in our analysis align with data from IGM imaging studies indicating restricted diffusion in the affected parenchyma, consistently yielding lower mean ADC values ($1.0x10^3$ mm^2/s) than those observed in normal breast parenchyma ($2.3x10^3$ mm^2/s) (4,30). However, despite the likely impact of the chronic inflammatory response in IGM on reducing water diffusion capacity and relative ADC values (4), the diminished ADC sequence signal in diffusion-weighted imaging in IGM is considered to play a minimal role in distinguishing it from inflammatory breast cancer (14,31).

In our study, BPEs were minimal in most patients, and segmental enhancements were noted in only 20.7% of patients. In contrast, some studies reported segmental heterogeneous enhancements and rim enhancement features rather than regional distribution as the most commonly encountered MRI findings of IGM lesions (8,9,13,26,32,33,34). Notably, segmental enhancements are considered to be features of ductal carcinoma *in situ* on MRI (35). In addition, although IGM is a benign pathology showing non-mass-like lesions with restricted diffusion, it may also show clustered ring-like enhancement similar to malignant lesions (9,12,13,32).

In our study, the most prevalent associated findings on both US and DC-MRI were the presence of edema (95.2% and 90.5%), reactive lymph nodes (95.2% for each), and skin thickening (90.5% and 52.4%). Along with the findings of floating debris (64.3%) on US and localized collective abscess (57.5%) and micro-abscess (53.7%) on DC-MRI, the imaging findings of IGM in the current study support the consideration of parenchymal heterogeneity with abscess formation and axillary lymphadenopathy as well as focal mastitis with interstitial edema to favor an inflammatory

granulomatous process (3,16,31). Indeed, associated diffuse parenchymal edema, which is a well-known feature of IGM (33), as well as associated lesions such as microabscesses or larger fluid collections in advanced cases (4,20,24) are considered likely to play a role in volume enlargement of the affected breast related to IGM (10).

Our results corroborate the established notion that skin thickening is a frequently observed imaging characteristic in IGM, evident in more than 90% of cases (27,34). Conversely, the involvement of the nipple and nipple-areolar complex is infrequent (4,10), and sinus tracts extending to the skin surface may become apparent in cases of delayed diagnosis or a history of prior intervention (4,20,22,32).

A collection of imaging features plays a role in the differential diagnosis of IGM, such as an indistinct mass with the long axis of the lesion parallel to the chest wall and multifocal abscess cavities on US. Infective mastitis, on the other hand, exhibits characteristics like diffuse or focal skin thickening, inhomogeneous breast tissue with or without an irregular hypoechoic mass, and fluid collection on US. Malignancy is distinguished by skin thickening and breast edema with dilated lymphatics on US, along with extensive NME featuring areas of a clustered ring-like pattern or contiguous irregular breast masses with rapid enhancement on MRI (2,11,35). Our imaging findings underscore the capability of US to propose an IGM diagnosis in a suitable clinical context (6), while MRI can aid in the differential diagnosis and evaluation of disease extent in patients with inconclusive conventional findings (4,8). Nevertheless, a definitive histopathological diagnosis is deemed indispensable for IGM before any surgical procedures are considered (3,5).

Indeed, MRI or DC-MRI was also considered not discriminatory in differentiating IGM from inflammatory carcinoma because of overlapping signs of inflammation and intense early enhancement (3). However, MRI-enhanced imaging has higher accuracy in assessing the extent of lesions compared with US imaging alone or combined with mammography (31).

Hence, MRI is a supplementary instrument that enhances the visibility of lesions not adequately visualized by conventional imaging modalities because of parenchymal edema. It aids in ruling out a diagnosis of inflammatory breast cancer (3,5,24) and functions as a subsequent imaging tool for diseases that are diffuse, aggressive, and non-responsive (4,5,8,20,31).

Study Limitations

The comprehensive presentation of breast US imaging and DC-MRI findings in the largest patient series for IGM in the literature seems to be the major study strength. However, our study has certain limitations. First, the potential lack of generalizability is an important limitation due to the relatively small sample size. Second, lack of data on other inflammatory breast pathologies considered in the differential diagnosis of IGM as well as more comprehensive data on socioeconomic characteristics and breastfeeding history and their relation to US-MRI findings seem to be another limitation that would otherwise extend the knowledge achieved in the current study.

Conclusion

In our series of IGM, both breast US imaging and DC-MRI commonly revealed non-mass lesions with irregular shapes, accompanied by edema, reactive lymph nodes, and skin thickening in the majority of patients. Noteworthy US-specific findings included a hypoheterogeneous echo pattern, tubular extension and connecting tracts, cystic components, floating debris, and ductal ectasia. On the other hand, DC-MRI-specific findings predominantly featured localized collective abscesses or microabscesses, minimal BPEs, and NMEs with heterogeneous or clustered internal patterns and a regional distribution in most lesions. Our findings underscore the diagnostic significance of US in an appropriate clinical context, particularly when complemented by MRI for aiding differential diagnosis. However, it is essential to emphasize that histopathology remains the cornerstone for the definitive diagnosis and appropriate management of IGM.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by Recep Tayyip Erdoğan University Hospital Non-interventional Clinical Research Ethics Committee (date: 21/01/2021; protocol number: 2021/18).

Informed Consent: Written informed consent was obtained from all patients.

Authorship Contributions

Surgical and Medical Practices: F.T., N.O.M., E.T., Concept: F.T., Y.M., M.G.G., Design: Y.M., N.O.M., M.G.G., E.T., Data Collection or Processing: F.T., N.O.M., E.T., Analysis or Interpretation: Y.M., M.G.G., E.T., Literature Search: Y.M., N.O.M., M.G.G., Writing: F.T.

Conflict of Interest: xxxxxx

Financial Disclosure: xxxxxx

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ORIGINAL ARTICLE

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Our Approach and Results for Congenital Nasolacrimal Duct Obstruction in a Tertiary Hospital

Üçüncü Basamak Bir Hastanede Konjenital Nazolakrimal Kanal Tıkanıklığına Yaklaşımımız ve Sonuçlarımız

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ABSTRACT

Background: To evaluate the effectiveness of probing and nasolacrimal duct intubation in patients with congenital nasolacrimal duct obstruction (CNLDO).

Materials and Methods: CNLDO data collected between June 1, 2014, and June 1, 2023, were retrospectively reviewed. canalicular Crawford intubation was performed in all patients after two failed probing procedures.

Results: A total of 121 eyes of 93 patients (45 male and 48 female) were included in the study. The first probing procedure was successful in 94 (80.3%) eyes and the second probing procedure in 15 (75%). Among the four eyes in the silicone intubation group, the first procedure was successful in two (50%) and partially successful in the remaining two (50%). Silicone intubation was successful in all five eyes (100%) for which the second probing failed.

Conclusion: Nasolacrimal duct intubation with silicone tubes appears to be a less invasive and successful treatment option for CNLDO after failed probing.

Keywords: Congenital nasolacrimal duct obstruction, epiphora, fluorescein disappearance test, probing, silicone intubation

ÖZ

Amaç: Konjenital nazolakrimal kanal tıkanıklığı (KNLKT) olan hastalarda sondalama ve nazolakrimal kanal entübasyon işlemlerinin etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: 1 Haziran 2014 ile 1 Haziran 2023 tarihleri arasında takip edilen KNLKT geriye dönük olarak incelendi. İki başarısız sondalama prosedüründen sonra bikanaliküler Crawford entübasyonu tüm olgularda uygulandı.

Bulgular: Çalışmaya 93 hastanın (45 erkek ve 48 kadın) toplam 121 gözü dahil edildi. İlk sondalama işlemi 94 (%80,3) gözde, ikinci sondalama işlemi 15 (%75) gözde başarılı oldu. Silikon entübasyon grubundaki dört gözün ikisinde (%50) ilk işlem başarılı, kalan ikisinde (%50) kısmen başarılı oldu. İkinci sondalamanın başarısız olduğu beş gözün hepsinde (%100) silikon entübasyon başarılı oldu.

Sonuç: Silikon tüplerle nazolakrimal kanal entübasyonu, başarısız problamadan sonra KNLKT için daha az invaziv ve başarılı bir tedavi seçeneği gibi görünmektedir.

Anahtar Kelimeler: Konjenital nazolakrimal kanal tıkanıklığı, epifora, floresan kaybolma testi, sondalama, silikon entübasyon

Introduction

The incidence of congenital nasolacrimal duct obstruction (CNLDO) in the general population has been previously reported to be 20% of all infants in the first year of life (1). According to another source, it is seen in one out of every nine infants (2). In the majority of newborns (73.3%), there is a membranous barrier between the nasolacrimal duct and inferior meatus; i.e., the lumen of the nasolacrimal duct does not open into the nose at birth (3). 95% of cases with CNLDO become symptomatic in the first month of life. Spontaneous remission has been observed before the age of 1 year in 96% of symptomatic patients (1). The diagnostic criteria for CNLDO are the presence and appearance of epiphora and the formation of mucopurulent discharge

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following pressure on the affected lacrimal sac. It has been suggested that most such cases are resolved under conservative treatment (topical antibiotic and massage on the lacrimal sac) (4). In cases where conservative treatment fails, probing is successfully used to treat CNLDO in most children aged six to <15 months of age. The success rate is lower in older age, in the presence of bilateral disease, or when there is more than one clinical manifestation of CNLDO (5,6). Balloon catheter dilatation of the nasolacrimal duct and nasolacrimal duct intubation been similarly successful in the surgical treatment of permanent CNLDO (7). However, the appropriate timing of surgery remains a long-debated issue. While some researchers recommend early probing, some ophthalmologists prefer to perform this procedure after the first year (5,6).

The aim of this study was to evaluate the effectiveness of probing and silicone intubation procedures in treating patients with CNLDO.

Materials and Methods

The records of all patients with a diagnosis of CNLDO who were followed up in the oculoplasty unit of our clinic between June 1, 2014, and June 1, 2023, were retrospectively reviewed. The study was approved by the Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval number: 2020-01/237, date: 11.06.2020) and was consistent with the tenets of the Declaration of Helsinki. Patients diagnosed with CNLDO on the basis of typical signs and symptoms, such as epiphora, increased tear meniscus, recurrent or persistent mucopurulent discharge, and an abnormal fluorescein disappearance test (FDT) result, were included in the study. All patients received conservative medical treatment, including nasolacrimal sac massage until spontaneous resolution or interventional procedures were performed. FDT was performed by an ophthalmologist without topical anesthesia. Five minutes after fluorescein application to the eye surface, the result was classified as normal, abnormal, or indeterminate. The presence of no or a very thin fluorescein-colored tear meniscus was considered a normal result, whereas a thick fluorescein-colored tear meniscus was considered abnormal. The presence of minimally increased tear film or residual fluorescein in the tear was evaluated as an indeterminate result (8). Surgical success in probing was defined as the complete resolution of previous signs and symptoms and a normal or indeterminate FDT result. Partial success was defined as reduced symptoms accompanied by intermittent watering depending on environmental conditions. The failed probing criteria were recurrent epiphora, mucoid discharge, lacrimation, and an abnormal FDT result. Canalicular Crawford intubation was performed on all patients whose findings did not regress after two fail probing procedures. The success of treatment was defined as the absence of epiphora, mucoid discharge, and lacrimation in the examination undertaken 1 month after tube removal.

Observation and Follow-up

After both surgical procedures, the patients were administered topical moxifloxacin four times a day for 7 days. Follow-up examinations were performed on the seventh day and at the fourth week during the procedure. Treatment was considered successful or partially successful if CNLDO symptoms (epiphora, increased tear meniscus, and mucopurulent discharge) were reduced and the FDT result was normal or indeterminate. If the first probing was not successful, a second procedure was planned to be performed 4 weeks later. If symptoms and signs still did not improve after the second probing, nasolacrimal duct intubation was planned. In patients whose age was not suitable for probing, nasolacrimal duct intubation was performed as the primary procedure.

Surgical Procedures

Probing

The procedure was performed using the patients under general anesthesia by the same surgeon. The upper and lower canaliculi were enlarged using a punctal dilator. To confirm the diagnosis of occlusion, the nasolacrimal duct was irrigated using a syringe and a lacrimal cannula attached to its tip. The flow of fluid from the other canaliculi during irrigation confirmed the diagnosis of occlusion. A Bowman probe suitable for the patient was first advanced 2 mm vertically, and then horizontally toward the medial until reaching bone sensation; then, the probe was verticalize. It slowly advanced along the nasolacrimal duct until it passed the occluded part. Patency was confirmed by allowing a second probe to touch the probe in the nasopharynx, visualizing the probe under the inferior turbinate, or aspirating the fluorescein-colored solution from the nasopharynx after irrigation through the nasolacrimal system.

Nasolacrimal Duct Intubation

The surgical procedure was performed under general anesthesia. All procedures were performed by the same surgeon. Both upper and lower canaliculi were enlarged using a punctal dilator. To confirm the diagnosis of occlusion, the nasolacrimal duct was irrigated using a syringe and a lacrimal cannula attached to its tip. The flow of fluid from the other canaliculi during irrigation confirmed the diagnosis of occlusion. Probing was performed using an appropriate Bowman probe selected by the surgeon.

Canalicular Crawford intubation was performed. The ends of the tube were seen and removed through the nose, cut and knotted outside the nose, and the knot was inserted back into the nose. The tube was planned to remain in place for at least 3 months. When it was time to remove the tube, the knot was cut and the tube was removed from the nose by an otolaryngologist while the child was awake or under conscious sedation.

Statistical Analysis

The Statistical Package for the Social Sciences v. 21 (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. Quantitative variables were defined as mean and standard deviation and qualitative variables as percentages. The mean values were standardized to within 1.0 standard deviation for all determined values. Statistically significant differences were determined using the chi-square test. Values were considered statistically significant if $p<0.05$.

Results

A total of 121 eyes of 93 patients (45 male and 48 female) who underwent probing and/or silicone intubation were included in the study. Probing and/or silicone intubation were performed bilaterally in 28 patients and unilaterally in 65 patients. Of the operated eyes, 63 were right eyes and 58 were left eyes (Table 1).

As the primary procedure, probing was performed in 117 eyes (96.7%) at a mean age of 18 months (3-64 months) and silicone intubation in four eyes (3.3%) at a mean age of 50 months (47-60 months) (Table 2).

Table 1. Distribution of sex and affected eyes for the primary procedure

		n	%
Gender	Male	45	48.4
	Female	48	51.6
	Total	93	100.0
Affected side	Right	63	52.1
	Left	58	47.9
	Total	121	100.0

In cases where probing was performed as the primary method, the first procedure was successful in 94 (80.3%) eyes and unsuccessful in 23 eyes (19.7%) (Table 3). The decision for silicone intubation as the primary procedure was made on the basis of the age of the patients at the time of diagnosis. Among the four eyes that underwent silicone intubation as the primary method, the first procedure was successful in two (50%) and partially successful in the remaining two (50%).

In one eye in which the first probing failed, the canalicular system was incomplete; therefore, probing was not repeated. In two further eyes with failed probing, silicone intubation was applied as the second procedure at the 35th month (26-43 months), taking into account the age of the patients. Success was achieved in both eyes (100%). In the remaining 20 eyes in which the first probing procedure had failed, second probing was performed at a mean age of 23 months (12-32 months). The second probing was successful in 15 eyes (75%) and failed in five (25%) (Tables 4, 5).

According to the age evaluation, the first probing procedure was successful in 44 eyes (77.2%) and failed in 13 eyes (22.8%) among patients younger than 18 months. In the ⩾18 months group, the first probing was successful in 50 eyes (83.3%) and unsuccessful in 10 eyes (16.7%). There was no statistically significant difference between the patients aged <18 months and ⩾18 months in terms of probing results ($p>0.05$) (Table 6).

In five eyes in which the second probing failed, silicone intubation was performed at an average of 27 months (21-36 months), and success was achieved in all these cases (100%). In two eyes, the tube was removed at the second week and one month following intubation, respectively, because the patient pulled the tube out of the punctum,

Table 2. Distribution of age at the time of probing or silicone intubation as the primary procedure

			Age (months)		
	n	%	Median	Minimum	Maximum
Probing	117	96.7	18	3	64
Silicone intubation	4	3.3	50	47	60

Table 3. Success rates of probing and silicone intubation performed as primary procedures

	Outcome							
	Success		Failure		Partial success	Total		
	n	%	n	%	n	%	n	%
Probing	94	80.3	23	19.7	0	0.0	117	100.0
Silicone intubation	2	50.0	0	0.0	2	50.0	4	100.0

Table 4. Distribution of age at the time of probing or silicone intubation performed as the second procedure

			Age (months)		
	n	%	Median	Minimum	Maximum
Probing	20	90.9	23	12	32
Silicone intubation	2	9.1	35	26	43

Table 5. Success rates of probing and silicone intubation performed as the second procedure

	Outcome					
	Success		Failure		Total	
	n	%	n	%	n	%
Probing	15	75.0%	5	25.0	20	100.0
Silicone intubation	2	100.0%	0	0.0	2	100.0

Table 6. Distribution of procedure success according to age group

		Outcome					
		Success		Failure			
		n	%	n	%	χ^2	p
Age group	<18 months	44	46.8	13	56.5	0.698	0.404
	≥18 months	50	53.2	10	43.5		

and we were not able to insert it back into its place. For the remaining three cases, the tube was removed at an average of 3 months. No complications related to silicone intubation were observed.

Discussion

This study included 121 eyes from 93 patients. We retrospectively determined the probing success rate of CNLDO cases diagnosed at our clinic. We evaluated the effect of age at the time of probing on the success of the procedure. At the same time, we shared our results of nasolacrimal duct intubation in patients who did not benefit from repeated probing.

The timing of probing, the standard therapeutic procedure used for treating CNLDO, remains a matter of debate (9). In a previous study, it was shown that postponing probing and irrigation for CNLDO after 1 year did not cause an increase in failure or complication rates (10). Zor et al. (11) found the success rate of probing to be 93.7% in patients aged 12 to 84 months. Considering the high spontaneous resolution rates observed in the first 12 months, the authors suggested that probing should not be performed unless complications such as dacryocystitis and canaliculitis develop during this period. Another study concluded that the ideal probing time was between 6 and 12 months (12). We choose to perform conservative approaches and wait for up to 12 months for spontaneous recovery.

Consistent with the literature, we found that the first probing procedure was completely successful in 80.3% of the eyes and unsuccessful in 19.7%. In a recently published study with a large series, it was shown that spontaneous recovery slowed down and plateaued after 9 months in the follow-up of CNLDO (13). Recent reports have shown that age at probing is an important risk factor for failure of the procedure (6,9,14). In a large-series study, it was concluded that probing between 9 and 15 months might be reasonable, considering that the success of the first probing decreases after the 15th month. This timeframe includes both an earlier and narrower age range for intervention compared with probing after 1 year of age (13). Gul et al. (14) reported 100% success in probing performed at 4-12 months, 88.5% success at 7-12 months, and 82.5% success at 13-24 months. In our study, when we grouped the probing patients according to their ages at the time of the procedure, we observed that age did not have a significant effect on the success of the procedure. In one eye in which the first probing failed, probing was not repeated because the canalicular system was incomplete. Among the remaining eyes that underwent the second probing procedure, success was achieved in 15 eyes (75%), whereas the procedure failed in five (25%). Similar to the literature, our results concerning the second probing were not as successful as those of the first probing (15).

Silicone intubation has been frequently used for many years for treating many conditions such as congenital nasolacrimal duct occlusion, canalicular lacerations, primary canalicular disease, and complicated Dacryocystorhinostomy (16). Some researchers apply intubation, primarily as canalicular or monocanalicular for treating CNLDO in older children or in cases where the duct is narrow during probing (17). In our study, due to the age of the patients at the time of the procedure, probing was not performed in four eyes, and silicone intubation was undertaken as the primary procedure. Silicon intubation was also performed in two eyes in which the first probing had failed, and the second probing was not considered appropriate because of the age of the patients. Silicone intubation was performed in five additional eyes because the second probing procedure was unsuccessful. In addition, all intubations were performed canalicularly.

Many studies have demonstrated the success of silicone intubation for treating CNLDO. In the literature, the success rate of silicone intubation in pediatric eye diseases has been reported as 90.9% by Pashby and Rathbun (15),86% by

Yazıcı et al. (17), and 84% by Repka et al. (7). In the current study, according to the first-month follow-up results, there was partial improvement in two eyes that underwent silicone intubation as the primary procedure, whereas all the other eyes on which silicone intubation was performed as the second procedure had complete recovery.

The recommended time for tube removal varies between 6 weeks and 18 months after surgery (19). In our study, the tubes were removed after an average of 2.5 months. Although the initial plan was to remove the tubes at the third month, we had to remove them at the second week after the procedure in one patient and at one month in another patient because the tubes had been pulled out of the punctum. In both of these cases in which the tubes were removed early, the symptoms disappeared completely. Complications such as pyogenic granuloma formation, punctal or canalicular damage, crusting, runny nose, and corneal abrasion were not observed.

Conclusion

Our results show that probing is a very safe and effective procedure, and it has very successful results when applied after 12 months of age. Considering its less invasive nature, nasolacrimal duct intubation with silicone tubes appears to be a successful treatment option for CNLDO after failed probing. In the future, we plan to share our nasolacrimal duct intubation with silicone tubes results from our increasing number of cases to further contribute to the literature.

Ethics

Ethics Committee Approval: The study was approved by the Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval number: 2020-01/237, date: 11.06.2020)

Informed Consent: Patient inform consent is not required for this study.

Authorship Contributions

Surgical and Medical Practices: G.K.H., Concept: A.K., Design: A.K., B.İ.S.A., Data Collection or Processing: G.K.H., Analysis or Interpretation: M.S.K., B.İ.S.A., Literature Search: A.K., Writing: G.K.H., A.K.

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Evaluation of IKK-β, NF-kβ, p53, and Ki-67 Protein and Gene Expression in Neuroblastoma Cells Treated with Cisplatin

Sisplatin ile Tedavi Edilen Nöroblastoma Hücrelerinde IKK-β, NF-kβ, p53, Ki-67 Protein ve Gen Ekspresyonunun Değerlendirilmesi

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ABSTRACT

Background: Neuroblastomas are extracranial solid tumors caused by the differentiation and uncontrolled proliferation of immature sympathetic nervous system cells. This study investigated the effects of the anticarcinogenic cisplatin (Cis) on IKK-β, NF-κβ, p53, Ki-67 protein, and gene expression in neuroblastoma cells.

Materials and Methods: SH-SY5Y cells were treated for 48 hours with various doses of Cis (1, 3 and 10 μM). *IKBK1, MKI67, TP53,* and *NFKB1* gene expression analyses were completed by transcription-quantitative polymerase chain reaction (RT-qPCR). The levels of IKK-β, NF-κβ, p53, and Ki-67 proteins were detected by Western blotting.

Results: IKBKB gene expression was significantly increased at 1 and 3 μM and reduced significantly 10 μM compared to the control. *NFKB1* gene expression significantly increased at 1 μM Cis, whereas it decreased when Cis concentration increased. *TP53* gene expression significantly increased at 1 and 3 μM. MKI67 gene expression decreased with an increase in Cis concentration. In the low concentration (1 μM) of Cis group, while there was no significant change in IKK-β and p53 protein expressions, NF-κβ expression significantly increased. However, in the groups administered with high-dose Cis (3 μM, 10 μM), where Cis showed a significant antiproliferative effect, IKK-β expressions decreased significantly, while NF-κβ and p53 expression increased. The expression of the proliferation marker Ki-67 was also reduced in this group.

Conclusion: These results highlight the antiproliferative activity of Cis and its related NF-κβ/IKK-β, p53, and Ki-67 proteins and the marked changes in gene expression in neuroblastoma cells.

Keywords: SH-SY5Y, neuroblastoma, NF-kβ, p53, IKK-β, Ki-67

ÖZ

Amaç: Nöroblastomlar, olgunlaşmamış sempatik sinir sistemi hücrelerinin farklılaşması ve kontrolsüz çoğalmasının neden olduğu ekstrakraniyal katı tümörlerdir. Çalışmada nöroblastom hücrelerinde antikanserojen sisplatinin IKK-β, NF-κβ, p53, Ki-67 protein ve gen ekspresyonu üzerine etkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: SH-SY5Y hücrelerine, 48 saat boyunca çeşitli dozlarda sisplatin (1, 3 ve 10 μM) uygulanmıştır. *IKBK1, MKI67, TP53, NFKB1* gen ekspresyon analizi transcription-quantitative polymerase chain reaction (RT-qPCR) ile gerçekleştirildi. IKK-β, NF-κβ, p53, Ki-67 protein düzeyleri Western blot yöntemiyle tespit edildi.

Bulgular: IKBKB gen ekspresyonu, kontrole kıyasla 1 ve 3 μM'de önemli ölçüde arttı ve 10 μM'de önemli ölçüde azaldı. *NFKB1* gen ekspresyonu 1 μM sisplatinde önemli ölçüde artarken, sisplatin konsantrasyonu arttığında azaldı. *TP53* gen ekspresyonu 1 ve 3 μM'de önemli ölçüde arttı. MKI67 gen ekspresyonu sisplatin konsantrasyonunun artmasıyla azaldı. Düşük konsantrasyonlu (1 μM) sisplatin grubunda IKK-β ve p53 protein ekspresyonlarında anlamlı bir değişiklik olmazken, NF-κβ ekspresyonunda anlamlı artış görüldü. Ancak sisplatinin anlamlı antiproliferatif etki gösterdiği yüksek doz sisplatin (3 μM, 10 μM) uygulanan gruplarda IKK-β ekspresyonları anlamlı derecede azalırken NF-κβ ve p53 ekspresyonları arttı. Bu grupta prolifrasyon belirteci Ki-67'nin ifadesi de azalmıştır.

Sonuç: Bu sonuçlar, sisplatinin ve bununla ilişkili NF-κβ/IKK-β, p53 ve Ki-67 proteinlerinin antiproliferatif aktivitesini ve nöroblastoma hücrelerinde gen ekspresyonlarının belirgin şekilde değiştiğini vurgulamaktadır.

Anahtar Kelimeler: SH-SY5Y, nöroblastoma, NF-kβ, p53, IKK-β, Ki-67

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Introduction

Neuroblastoma is a type of cancer that develops from the uncontrolled proliferation of precursor nerve cells. Metastasis is one of the most common causes of mortality in patients with neuroblastoma (1). Surgery, chemotherapy, and radiotherapy are the current treatment methods for neuroblastoma. Although these current treatments are effective in patients with neuroblastoma, the prognosis of these patients is still poor (2). Cisplatin (Cis) is a cytotoxic drug that inhibits cancer cell proliferation by damaging DNA and is generally accepted as an effective drug used in chemotherapy for neuroblastoma (3). Cis plays a role in inflammation by activating proinflammatory cytokines and nuclear factor kappa-B kinase subunit beta (IKK-β) /nuclear factor-κβ (NF-κβ) or p53 pathways (4).

The IKK complex is activated in the immunoresponse, cell survival, and cancer. The IKK complex comprises catalytic subunits (IKK-α, IKK-β kinases) and a regulatory subunit (IKK-γ). IKK-β mediates phosphorylation of IκB, an important step in multiple signaling pathways leading to NF-κβ activation (5). Inflammation is a process that is often associated with the development and progression of cancer through the activation of multiple signaling pathways, including the NF-κβ pathways (6). It has been shown that over expression of NF-κβ promotes cancer cell proliferation, survival, and metastasis (7). In addition, it was reported that NF-kβ expression increased significantly in mice kidney tissue after Cis administration compared with the control group (8).

The protein complex known as NF-κβ is responsible for regulating the expression of genes that play important roles in immune response and cell survival. *NFKB1* encodes the p105 protein, which is a precursor of the NF-κβ transcription factor that gives rise to the p50 subunit of NF-κβ upon proteolytic processing. NF-κβ p65, on the other hand, is a constitutively expressed subunit of NF-κβ that directly participates in gene regulation upon nuclear translocation, often forming heterodimers with other NF-κβ subunits. Both subunits play an important role in the NF-κβ signaling pathway and are involved in various cellular processes, including inflammation, immunity, cell proliferation, and apoptosis (8,9).

The tumor suppressor p53 protein is a multifunctional protein that regulates a multitude of cellular processes. The p53 protein is a nuclear transcription factor that activates numerous target genes related to multiple cellular events and regulates cell cycle progression and DNA repair (10). P53 is an important transcription regulator in Cis nephrotoxicity. It has been shown that Cis treatment induces p53 phosphorylation and protein accumulation in p53 knockout C57BL/6 mice (11). Increased p53 and NF-κβ expression was observed in neuroblastoma cells treated with the anti-carcinogenic Doxorubicin. Loss of NF-κβ activity inhibited p53-induced apoptosis. These results show that NF-κβ plays a critical role in p53-mediated cell death (5).

We analyzed the protein and gene expression profiles of IKKβ, NF-κβ, p53, and Ki-67 to investigate the mechanism of action of Cis in Neuroblastoma. We report the functional importance and interconnection of IKK-β, NF-κβ, and p53 in Cis-induced neuroblastoma cell death. Comprehending the intricate molecular processes that underlie the development of neuroblastoma is of utmost importance for devising tailored treatment strategies and enhancing the prognosis of patients. Comprehending the interactions and regulatory mechanisms of these genes may offer insights into the etiology of neuroblastoma and facilitate the identification of potential targets for therapeutic intervention.

Materials and Methods

Because a commercially purchased cell line was used in the study, ethical approval is not required in terms of the method.

Reagents

Cell Counting Kit 8 (CCK-8) was purchased from Sigma-Aldrich (St. Louis, MO, USA). The neuroblastoma cell line (SH-SY5Y-CRL-2266) was obtained the American Type Culture Collection [(ATCC), USA]. Dulbecco's modified Eagle's medium (DMEM), heat-inactivated fetal bovine serum (FBS) and Antibodies against IKKβ, NF-κβ-p65, p53, Ki-67, β-Actin were purchased from Invitrogen (Thermo Fisher Scientific Inc. USA).

Cell Culture

Neuroblastoma cells were cultured in DMEM containing 10% FBS and 1% penicillin-streptomycin at 37 °C in a 5% CO_2 environment.

Proliferation Assay

Neuroblastoma cells ($3x10^3$ cells/well) were seeded into 96-well plates. After 24 hours, cells were treated with increased Cis concentrations (1, 3,10 μM) for 48 hours at 37 °C. 10 μl of CCK-8 solution was added to the wells, and the cells were further incubated for 4 hours at 37 °C. The absorbance was then determined at 450 nm using a plate (Thermo Scientific Mutilskan FC, Thermo Fischer Scientific, USA). Cell viability was measured compared with the optical density value of the control group. Proliferation analysis was performed in four replicates.

Western Blotting

After treatment, cells were washed twice with phosphate-buffered saline and lysed with radioimmunoprecipitation assay buffer supplemented with protease inhibitors (Santa Cruz Biotechnology, Inc. Europe). The protein concentration of samples was determined using a Bicinchoninic acid protein assay kit (Thermo, Rockford, IL, USA). 30 µg of protein was subjected to SDS-PAGE on 12% gel. The protein was then transferred onto a nitrocellulose membrane (Bio-Rad, Philadelphia, PA, USA). Nitrocellulose membranes were blocked with 5% non-fat dried milk in TBS with 0.1% Tween for 1 hour. After blocking, the membrane was incubated with primary antibodies at 4 °C overnight and then washed three times in Tris-buffered saline with 0.1% Tween® buffer. Mebrane was incubated in horseradish peroxidase-conjugated secondary antibody (Thermo Fisher Scientific Inc. USA) for 1 hour. Specific protein bands were detected using an enhanced chemiluminescence Western Blotting Substrate (Thermo Fisher Scientific Inc. USA). Bands were quantified using ImageJ Software.

RNA Extraction and Genetic Analyses

Total RNA was extracted from SH-SY5Y cells using PureZole (#7326890, Biorad, USA) for genetic analysis. The purity and quantity of the RNA samples were determined using Nanodrop ND-1000 spectrophotometer V3.7. Following this, all RNA samples were converted into cDNA (1708890, Biorad, USA). The transcription-quantitative polymerase chain reaction (RT-qPCR) method with the Step-One-Plus Thermocycler (Applied Biosystems) was employed to analyze the expression of *IKBKB*, *NFKB1*, *MKI67*, and *TP53* mRNA. The amplifications were performed using cDNA, site-specific primers (Oligomer Biotechnology, Ankara), SYBR Green (1725270, Biorad, USA), and nuclease-free water. To ensure internal control, *GAPDH* was used. The primer sequences of *IKBKB*, *NFKB1*, *MKI67*, and *TP53* were designed on the basis of the FASTA format from NCBI (Table 1) (12).

The subsequent RT-qPCR protocol was employed: for *IKBKB*, *NFKB1*, and *TP53*, 95 °C for a duration of 30 s, 40 cycles consisting of 5 s at 95 °C and 30 s at 60 °C. Additionally, for MKI67, 30 s at 95 °C, 40 cycles consisting of 5 s at 95 °C and 30 s at 58 °C. For confirmation of singular product amplification, a melting curve analysis was performed at the conclusion of the PCR. Each run was executed in triplicate.

Table 1. Primer sequences

Gene	Forward primer 5'→3'	Reverse primer 5'→3'
TP53	CCGGGGACACTTTGCGTT	AGTCTGGCCAATCCAGGGAAG
MKI67	GTGGTTCGACAAGTGGCCTT	AGTTGGGTCTCCCCCTGTAA
NFKB	TGTGCTTCGAGTGACTGACC	TCACCCCACATCACTGAACG
IKBK	TCTCACGTCTGACGGACTCT	CCTGGCATTCCTTAGTGGCA
GAPDH	CATTGCCCTCAACGACCACTTT	GGTGGTCCAGGGGTCTTACTCC

Statistical Analysis

Data were analyzed using the ordinary One-Way analysis of variance test with GraphPad Prism 8.0 software (GraphPad Software, Inc., San Diego, CA). Statistical significance was considered *p<0.05, **p<0.01 compared with the control group. Genetic analysis was performed using REST 2009 V2.0.13 (13) where p<0.05 is considered to be statistically significant.

Results

Genetic Analysis

The mRNA levels of *IKBKB*, *NFKB1*, *TP53*, and *MKI67* genes expressed in SH-SY5Y neuroblastoma cancer cell lines exposed to 1, 3, 10 µM Cis for 48 hours were compared with control cells. The mRNA levels of *IKBKB* were increased in 1 µM and 3 µM Cis and decreased 10 µM Cis compared with the control (2.27*; 5.61*; 0.47*, fold change, respectively, *p<0.001). The mRNA levels of *NFKB1* were increased in 1 µM and 3 µM Cis and decreased 10 µM Cis compared with the control (1.34*; 1.05; 0.81*, fold change, respectively, *p<0.001). The mRNA levels of *TP53* were increased in 1 µM and 3 µM Cis and decreased 10 µM Cis compared with the control (2.86*; 2.36*; 0.40, fold change, respectively, *p<0.001). The mRNA levels of *MKI67* were decreased in 1 µM and 3 µM Cis compared with the control (0.76; 0.68 fold change, respectively, no data obtained at 10 µM amplification plot) (Figure 1).

Cis-induced Antiproliferative Effect on Neuroblastoma Cells

To investigate the antiproliferative effect of Cis, we tested a human neuroblastoma cell line using the CCK-8 kit. According to our results, Cis inhibited cell proliferation in a dose-dependent manner. In the 3 µM Cis-treated group, 19% proliferation inhibition was determined, and in the 10 µM Cis-treated group, 77% proliferation inhibition was determined compared with the untreated control. 1 µM of Cis did not affect the proliferation of the cells compared with the untreated control (Figure 2).

Determining IKKβ, NF-κβ, p53, and Ki-67 Expression Profiles

We examined total protein levels of IKKβ, NF-κβ, p53, and Ki-67 in neuroblastoma cells treated with 1 µM, 3 µM and 10 µM Cis. NF-κβ signaling has an essential role in the regulation of inflammation, cell survival, and cell proliferation. NF-kβ signaling is also active in neuroblastoma and has various functions in cancer progression (14). As shown in Figure 2, the NF-κβ protein expression significantly increased after

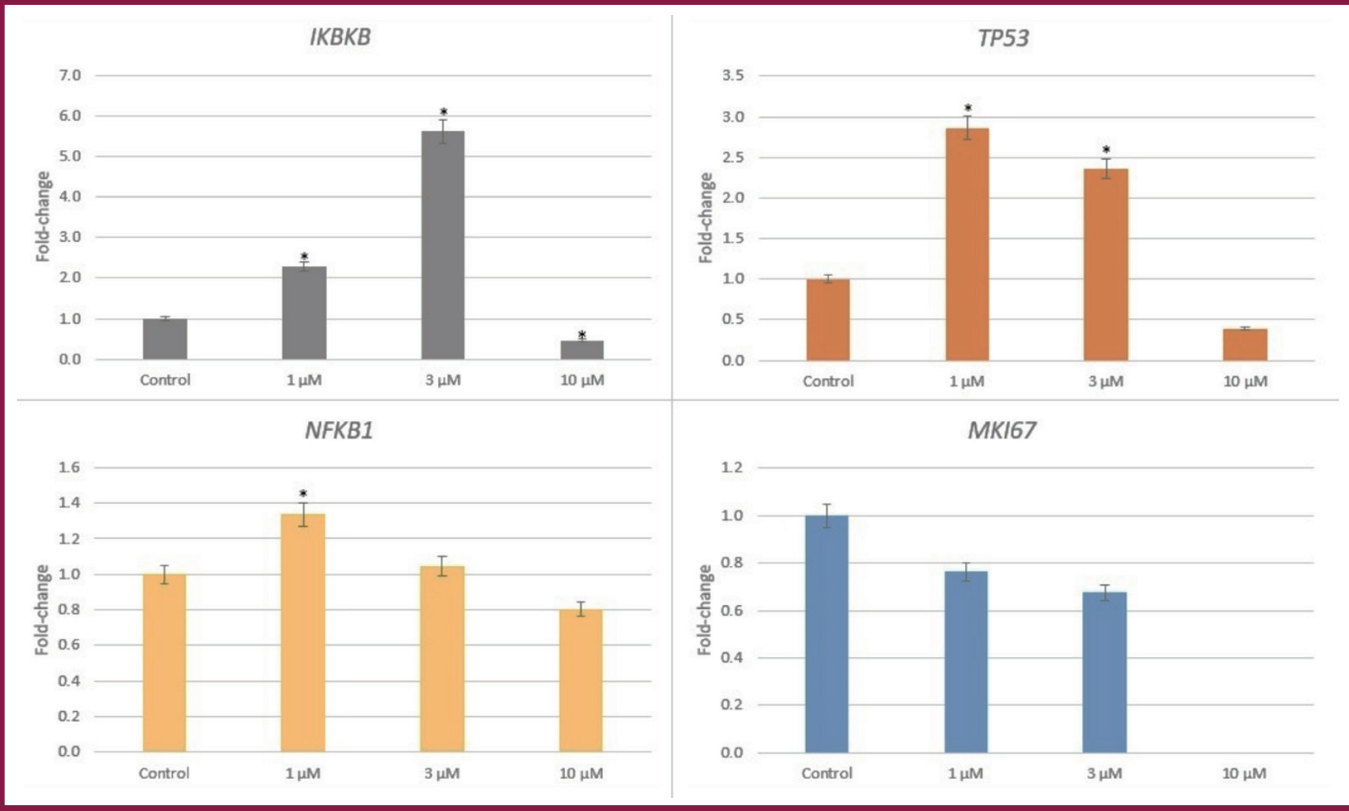

Figure 1. The results of real-time PCR. Relative mRNA expression of *IKBKB*, *NFKB1*, *TP53*, and *MKI67* genes in SH-SY5Y neuroblastoma cells exposed to Cis are given as fold change compared with the control. *Represents the significance of p<0.001. *GAPDH* was the reference gene for normalization

PCR: Polymerase chain reaction, Cis: Cisplatin, GAPDH: Glyceraldehyde-3-phosphate dehydrogenase

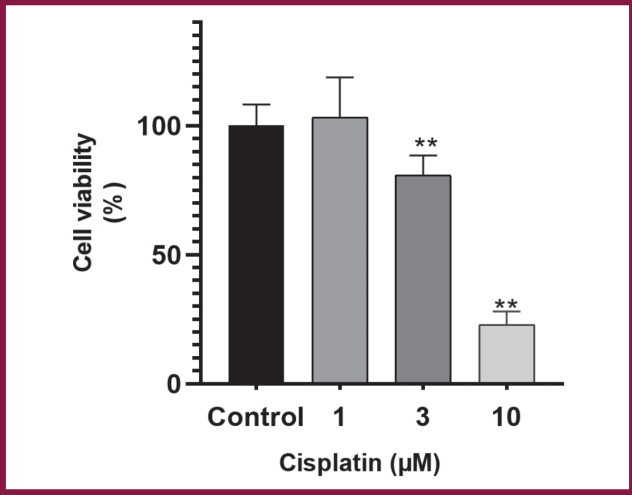

Figure 2. Cytotoxicity analysis of Cis (1, 3, and 10 µM) in SH-SY5Y neuroblastoma cells for 48 hours. Results are presented as mean ± SD of triplicate experiments. **p<0.01 compared with control

Cis: Cisplatin, SD: Standard deviation

exposure to Cis (1, 3 and 10 µM) compared to untreated control in neuroblastoma cells.

The IKK complex is an important regulator for NF-κβ Activation in cancer progression. The kinase IKK activates NF-κβ signaling molecules by phosphorylating the inhibitor I-κβ. As shown in Figure 3, the IKKβ protein markedly increased in the 1 µM and 3 µM Cis treated groups but decreased in 10 µM Cis group compared with the control. Ki-67 is an important prognostic marker in various tumors, including neuroblastoma (15). As shown in Figure 3, Ki-67 expression significantly decreased in 10 µM Cis group compared with the control.

P53 protein expression was analyzed in 64 human esophageal squamous cell carcinoma tumor tissues, and it was shown that p53 expression was higher than that in non-neoplastic tissues (16). P53 protein acts as an activator for apoptosis induced by DNA damage, such as Cis (17). Similarly, p53 protein expression levels increased in the 3 µM and 10 µM Cis treated groups compared with the control group (Figure 3).

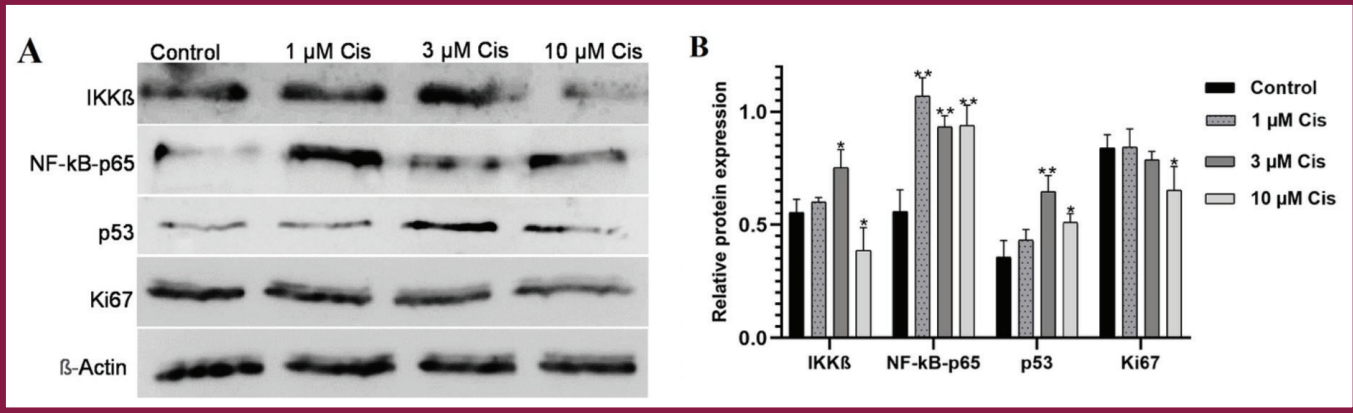

Figure 3. A) Western blot results of protein expression of IKKβ, NF-κβ, p53, Ki-67, β-actin. Cells were treated with increased Cis concentrations (1, 3, and 10 μM). **B)** Densitometric analysis of each band was performed using ImageJ. The relative density ratio of each band was normalized to β-actin as the internal control. Results are presented as mean ± SD. *p<0.05, **p<0.01 (n=3)

Cis: Cisplatin, SD: Standard deviation

According to the results, protein expression changes were correlated with Cis doses. The expression of IKKβ, NF-κβ, p53, and Ki-67 proteins was increased in the low-dose Cis (1, 3 μM) treated group. However, IKKβ expression significantly decreased in 10 μM Cis treated group. Similarly, Ki-67 expression was decreased in the high-dose Cis (10 μM) treated group.

These results highlight the antiproliferative activity of Cis and its related IKK-β/NF-κβ, p53 and Ki-67 protein expression changes in neuroblastoma cells.

Discussion

Neuroblastoma, an oncological condition originating from nascent nerve cells distributed across various regions of the human anatomy, predominantly affects infants and children. Elucidating the interconnection between genetic elements within the ambit of neuroblastoma can offer valuable knowledge regarding the molecular processes underpinning its formation and to identify potential targets for therapeutic interventions. Treatment of neuroblastoma usually includes surgery, chemotherapy, and radiotherapy. However, poor prognosis in the metastatic stage limits treatments (1).

The genes *NFKB1*, *TP53*, *IKBKB*, and *MKI67* are involved in different cellular processes and pathways, but they can interact indirectly through various signaling networks. Although these genes may not directly interact at the gene or protein level, their functions intersect within broader cellular signaling networks involved in inflammation, apoptosis, cell cycle regulation, and tumorigenesis. In the context of neuroblastoma or other cancers, dysregulation of these pathways can contribute to tumor development and progression. Within the realm of neuroblastoma, the interplay between these genes can influence tumor development, progression, and response to therapy.

Dysregulation of NF-κβ signaling, often through aberrant activation or overexpression of *NFKB1*, has been implicated in various cancers (18,19), including neuroblastoma (1,20). NF-κβ signaling is known to be dysregulated in neuroblastoma, and increased expression of *NFKB1* mRNA and NF-κβ-65 protein may indicate activation of the NF-κβ pathway. Zhi et al. (1) suggested that targeting NF-κβ signaling or its downstream target *CXCR4* may be a potential therapeutic strategy for inhibiting neuroblastoma metastasis and improving patient outcomes. The suppression of neuroblastoma cell migration and invasion is postulated to result from the inhibition of NF-κβ activity (21). In the present study, treatment resulted in a significant increase in *NFKB1* mRNA at 1 μM Cis compared with the control, whereas it decreased when the Cis concentration was increased. Beside, NF-κβ-65 protein level was increased, especially at 1 μM Cis concentration in cultured SH-SY5Y cells. Both subunits (*NKFB1* p105 and NF-κβ-65) play an important role in the NF-κβ signaling pathway.

IKBK1, is inhibitor for IKK-β, encodes a protein referred to as IKK-β. This protein functions as a subunit within the IKK complex and is responsible for initiating the NF-κβ signaling pathway. It is plausible that *IKBK1* contributes to the promotion of neuroblastoma cell growth and survival using activating NF-κβ. The IKK-β functions as an inhibitor within the Iκ-β kinase (IKK) complex, which in turn stimulates the activation of the transcription factor NF-κβ (22). Decreased *IKBKB* expression and *IKBKB* protein activity increase

anticancer treatment effectiveness (23). Inactive NF-κβ/I-κβ complex is activated by phosphorylation at specific serine residues of Iκ-β proteins. Phosphorylated I-κβ is degraded by the proteasomal system, resulting in NF-κβ activation and translocation to the nucleus (24). It has been shown that the migration and invasion properties and IKK-β/NF-κB activity of Cis-resistant HNSCC cells have increased compared with the control groups (25). Cis treatment results in a cardiac inflammatory response accompanied by an increase in tumor necrosis factor-alpha and interleukin-6 levels. These results showed that Cis treatment caused a significant upregulation of cardiac NF-κβ, STAT-3, and p-STAT-3, and Iκβ levels were significantly reduced (26). In our study, the content of IKK-β protein significantly increased at 3 μM and decreased significantly at 10 μM; similarly, *IKBKB* gene expression significantly increased at 1 and 3 μM and decreased significantly at 10 μM. This indicates that Cis treatment modulates the transcriptional regulation of *IKBKB* in a dose-dependent manner. Overall, these results suggest that Cis treatment modulates the expression of *IKBKB* and *NFKB1* in neuroblastoma cells, with complex effects on both protein and mRNA levels. In addition, the response of NF-κβ protein levels to Cis treatment may involve regulatory mechanisms distinct from *NFKB1* mRNA expression. Further studies are needed to elucidate the precise molecular mechanisms underlying these observed effects and their implications for neuroblastoma biology and treatment.

p53, a widely recognized tumor suppressor protein, plays a critical role in upholding genomic stability and averting cancer development. It governs cell cycle progression, apoptosis, DNA repair, and senescence. Genetic analyses indicate that the p53 protein plays a pivotal role in safeguarding cells from both genome instability and malignant transformation. It is noteworthy that the majority of neuroblastomas exhibit wild-type p53 with unimpaired transcriptional function, thereby suggesting that the mutated *TP53* gene, which encodes p53, is not commonly implicated in this particular type of cancer. In fact, the mutation rate of *TP53* in neuroblastomas does not surpass a mere 1-2% (27). The p53 tumor suppressor plays a pivotal role in triggering cell death or halting cell division in response to DNA harm and stress within the cell (28,29). Mutations or aberrant regulation of p53 are frequently observed in diverse malignancies, including neuroblastoma. The absence of functional p53 can instigate unbounded cell proliferation, survival, and resistance to therapeutic interventions in neuroblastoma. Moreover, research has suggested that the signaling pathway of p53 is operational in neuroblastoma (30,31,32). p53 protein expression was analyzed in 64 human esophageal squamous cell carcinoma tumor tissues and it was shown that the p53 expression level was higher than that in non-neoplastic tissues (16). p53 protein acts as an activator for apoptosis induced by DNA damage, such as Cis (17). Similarly, p53 protein expression levels increased in the 3 μM and 10 μM Cis treated groups compared with the control group. Similarly, *TP53* mRNA levels were increased by Cis treatment. The increase in mRNA and protein levels may indicate the anti-proliferative effect of Cis. In contrast, *TP53* is a tumor suppressor gene mostly mutated in neuroblastoma. The increase in p53 protein levels and *TP53* gene expression at 3 and 10 μM Cis concentrations may indicate the activation of p53-mediated apoptotic pathways in response to Cis-induced DNA damage.

The tumor suppressor p53 is involved in cell signaling, apoptosis, and DNA repair. It can interact with NF-κβ signaling by modulating the activity of NF-κβ target genes and influencing cell fate decisions. Cis treatment in neuroblastoma can influence p53 expression and activation. The functional status of p53 plays a significant role in determining cellular responses to Cis-induced DNA damage, apoptosis, and overall treatment outcomes. Further research into the molecular mechanisms underlying the interaction between Cis and p53 signaling pathways is needed to develop more effective treatment strategies for neuroblastoma.

MKI67 is a protein-coding gene. *MKI67*, also known as the marker of proliferation Ki-67, is responsible for the synthesis of the Ki-67 protein. This protein serves as a cellular indicator of cell proliferation. For decades, the Ki-67 protein has served as a prominent marker for measuring the proliferation of human tumor cells. Recent studies have shed light on the diverse molecular functions of this sizable protein. Ki-67 is involved in various activities in both interphase and mitotic cells, with its cellular localization undergoing significant alterations throughout the cell cycle (33). Ki-67 expression is observed during the active phases of the cell cycle, namely G1, S, G2, and M phases, but is absent in resting G0 cells. Its widespread application in cancer diagnostics and prognosis stems from its role as a marker of cell proliferation. Notably, an elevated level of Ki-67 expression often correlates with heightened tumor cell proliferation and increased aggressiveness (34,35). Ki-67 is a marker of cell proliferation, and its increased expression at lower Cis concentrations (1 μM) followed by a decrease at higher concentrations suggests a potential cytotoxic effect of Cis on neuroblastoma cells. Similarly, the changes in *MKI67* gene expression parallel the alterations in Ki-67 protein levels, reflecting changes in cell proliferation dynamics in response to Cis treatment. The genes *NFKB1*, *TP53*, and *IKBKB* are all associated with the NF-κβ signaling pathway. In the context of neuroblastoma, the interaction

between these genes can influence tumor development, progression, and response to therapy.

We analyzed the predictive value of *IKBK1*, *MKI67*, *TP53*, *NFKB1*, protein, and gene expression for the efficacy of Cis in neuroblastoma cell lines. We reported the functional importance and interconnection of *IKBK1*, *NFKB1*, *TP53*, *and MKI67* in Cis-induced neuroblastoma cell death. The results show that increasing concentrations of Cis was induced NF-κβ, p53 activation, and cell death in neuroblastoma cells. IKK-β/NF-κβ/p53 signaling can be suggested as an alternative therapeutic target for increasing the effectiveness of Cis treatment in neuroblastoma.

Conclusion

In brief, the aforementioned genes fulfill significant functions in the molecular pathways that underlie the development and progression of neuroblastoma. Disruption of these genes may contribute to irregular cell proliferation, survival, and other characteristic features of cancer. Comprehending the interactions and regulatory mechanisms of these genes may offer insights into the etiology of neuroblastoma and facilitate the identification of potential targets for therapeutic intervention.

Overall, our results provide insights into the molecular mechanisms underlying the response of neuroblastoma cells to Cis treatment, highlighting the relationship between NF-κβ signaling, p53-mediated apoptosis, and cell proliferation pathways. These results highlight the antiproliferative activity of Cis and related NF-κβ/IKβ/p53 and Ki-67 proteins and gene expression changes in neuroblastoma cells.

Ethics

Ethics Committee Approval: In the study, ethical approval is not required in terms of the method.

Informed Consent: Ethical approval is not required for our study so we do not need consent.

Authorship Contributions

Surgical and Medical Practices: E.K., Z.S., Concept: E.K., S.K., Design: E.K., S.K., Data Collection or Processing: E.K., S.K., Analysis or Interpretation: E.K., Z.S., Literature Search: E.K., Z.S., S.K., Writing: E.K., Z.S., S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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CASE REPORT

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Travel Story of the Double-J Stent in the Patient

Double-J Stentin Hastadaki Seyahat Hikayesi

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ABSTRACT

A ureteric JJ stent is an essential therapeutic tool for urology. JJ stent migration, which is an essential complication, may be limited to the ureter or may cause pelvis/ureter perforation, intra-abdominal solid organ injuries, hematoma, and even life-threatening sepsis. A 33-year-old male patient had stage 3 hydronephrosis and 1.5 cm calculi in the proximal right ureter. During surgery, optimal visualization could not be achieved because of edema. 4.8 Fr 26 cm JJ stent was inserted and checked by scope. On postoperative day 1, plain urinary system radiographs (DUSG) showed that the distal part of the JJ stent was mobilized to the ureter and pulled back into place during reoperation. DUSG taken on postoperative day 1 of reoperation showed that the distal end of the JJ stent migrated to the ureter again. He was given symptomatic treatment, and the JJ stent was planned to be removed after 3 weeks. Postoperative third-week DUSG showed that the JJ stent had migrated entirely to the renal pelvis. He was operated on; calculi was broken with a laser lithotripter, and a new 4.8 Fr 26 cm JJ stent was inserted and checked by scope. The JJ stent did not migrate in the DUSG taken 3 weeks after the last operation of the patient. The best way to avoid JJ stent complications is to avoid unnecessary stent placement. The patient's symptoms and complications should be considered when JJ stents are inserted. We found that a large calculus implanted in the ureter and hydronephrosis facilitated proximal migration of the JJ stent. The patient's JJ stent should be checked postoperatively.

Keywords: DJ, stent, ureter, calculi, migration

ÖZ

Üreter JJ stenti üroloji için önemli bir tedavi aracıdır. Temel komplikasyonlardan biri olan JJ stent migrasyonu üreter ile sınırlı olabileceği gibi pelvis/üreter perforasyonuna, karın içi solit organ yaralanmalarına, hematoma ve hatta hayatı tehdit eden sepsise neden olabilir. Otuz üç yaş erkek hasta evre-3 hidronefroz ve sağ üreter proksimalinde 1,5 cm'lik taş ile üroloji polikliniğine başvurdu. Opere edilen hastada ödem nedeniyle optimal görüntü sağlanamadı. Hastaya 4,8 Fr 26 cm JJ stent takıldı ve skopiyle kontrol edildi. Postoperatif 1. günde çekilen direkt üriner sistem grafisinde (DÜSG) JJ stentin distal kısmının üretere mobilize olduğu görüldü ve yeniden operasyonla yerine çekildi. Postoperatif 1. günde alınan DÜSG'de JJ stentin distal ucunun tekrar üretere migre olduğu görüldü. Ciddi semptomu olmayan hastaya semptomatik tedavi verilerek 3 hafta sonra JJ stent çekilmesi planlandı. Postoperatif 3. hafta çekilen DÜSG'de JJ stentin renal pelvise tamamen migre olduğu görüldü. Lazer ile taşı kırıldı ve tekrar 4,8 Fr 26 cm JJ stent takıldı. Skopiyle kontrol edildi. Son operasyondan 3 hafta sonra çekilen DÜSG'de JJ stent yerinde izlendi. JJ stent komplikasyonlarından korunmanın en iyi yolu gereksiz JJ stent takmamaktır. JJ stent takılan hastanın semptomlarına dikkat edilmeli ve olası komplikasyonlar akılda tutulmalıdır. İmpakte büyük taş ve hidronefroz varlığı JJ stentin proksimal migrasyonunu kolaylaştırdığını gördük. Hastanın JJ stenti postoperatif dönemde kontrol edilmelidir.

Anahtar Kelimeler: DJ, stent, üreter, kalkül, migrasyon

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Introduction

Symptomatic or asymptomatic ureteral calculi can affect renal function and cause obstructive neuropathies, such as hydronephrosis.

Medical expulsive therapy, shock wave lithotripsy and flexible-semirigid ureterorenoscopy are among the treatment options.

A ureteric JJ stent is one of the essential therapeutic tools of urology used in open ureteral surgeries, ureteral stricture, and surgical treatment of renal or ureteral calculi (1). JJ stent insertion is frequently preferred because it is a safe and minimally invasive option. However, it may also cause complications. JJ stent migration, which is one of them, is a significant complication that may be limited within the ureter or may cause pelvis/ureter perforation, intra-abdominal solid organ injuries, hematoma, and even life-threatening sepsis (2).

Case Report

After obtaining the patient's consent, we decided to share this case report.

A 33-year-old male patient was admitted to the urology outpatient clinic with complaints of frequent urination, incomplete emptying, and decreased urine pressure for 2-3 months. He also had a gunshot wound to the left groin 1 week ago, and ultrasonography revealed stage 3 hydronephrosis in the right kidney. His medical history included 15 pack years of smoking, hypertension, and a left groin operation due to SCI, and his family history was unremarkable.

A non-contrast abdominal computed tomography (CT) scan showed stage 3 hydronephrosis in the right kidney and a 1.5 cm calculi image in the proximal right ureter (Figure 1A). Endoscopic ureteral calculi treatment was planned, and intravenous pyelography (IVP) was performed preoperatively. IVP showed dilatation of the right renal pelvic structures and opaque calculi in the proximal ureter, but no passage of contrast medium through the ureter was observed at 60 min (Figure 1B).

During the operation, optimal visualization could not be achieved due to edema, and a 4.6 Fr 26 cm JJ stent was inserted and checked by scopy, and the operation was terminated after it was found to be in place. On postoperative day 1, plain urinary system radiograph (DUSG) showed that the lower end of the JJ stent was mobilized into the ureter (Figure 2). The patient had irritative symptoms such as renal colic, pain in the groin, and frequent urinary sensations, and the operation was planned again. When ureterorenoscopy was performed under anesthesia, it was seen that the JJ stent had migrated to the middle ureter, and the distal end of the JJ stent was grasped with the help of a grasper and pulled up to the bladder. The JJ stent was found to be in place when checked with a scope.

Plain urinary system radiograms performed on postoperative day 1 of his reoperation showed that the distal end of the JJ stent had migrated into the ureter again (Figure 3A). On suspicion that the JJ stent was *in situ*, a non-contrast abdominal CT scan was performed, and it was observed that the proximal end was in the inferior renal calyx and the distal end was in the distal ureter (Figure 3B).

He was discharged with symptomatic treatment, and the JJ stent was planned to be removed after 3 weeks, and ureteral calculi lithotripsy was planned in the same session.

No hydronephrosis was observed on USG performed in the outpatient clinic after the first week postoperatively.

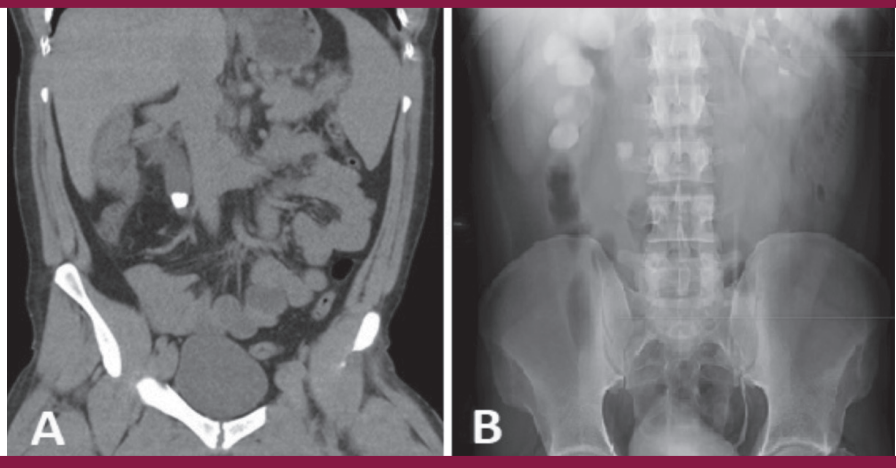

Figure 1. A) Preoperative non-contrast abdominal CT, **B)** Preoperative IVP 60th minute image
IVP: Intravenous pyelography, CT: Computed tomography

In the third week postoperatively, DUSG showed that the JJ stent had migrated entirely to the renal pelvis (Figure 4). The patient was operated on; the calculi was broken with a laser lithotripter, and a JJ stent was seen in the renal pelvis proximally. It was removed in one piece with a grasper. A new 4.6 Fr 26 cm JJ stent was inserted over the guide, checked by scope, and found to be in place.

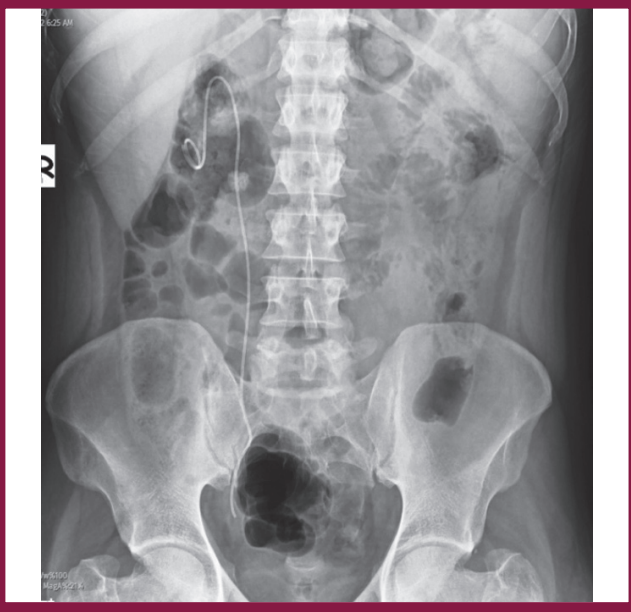

Figure 2. Postoperative day 1 control DUSG
DUSG: Plain urinary system radiographs

When the patient had the JJ stent removed 3 weeks after the last operation, DUSG showed that the JJ stent did not migrate. The JJ stent was removed under local anesthesia (Figure 5).

Discussion

Ureteric JJ stent migration complications have been reported in up to 6% of the literature (3). However, while distal migration toward the bladder usually occurs, proximal migration occurred in our case, which is reported as a rare complication in the literature (4). According to the literature, our patient also had hydronephrosis with an impacted and large ureteral calculus, which are among the factors that increase stent migration (5).

According to the patient, short JJ stent length has also been shown to be among the factors that may increase migration; however, in our case, the stent length was determined according to the patient (6). In our case, the proximal end of the JJ stent was observed to be in the inferior calyx by the preoperative scope and postoperative DUSGs (Figures 3, 4). In their study on the factors affecting JJ stent migration, Slaton and Kropp (7) showed that localization of the proximal end in the calyces (especially in the upper calyx) instead of the renal pelvis increased the proximal migration of the JJ stent.

It has been reported in the literature that JJ stent migration may lead to severe injuries such as duodenal, rectal, and renal parenchymal injuries. However, our patient had no symptoms or findings other than renal colic (8,9,10).

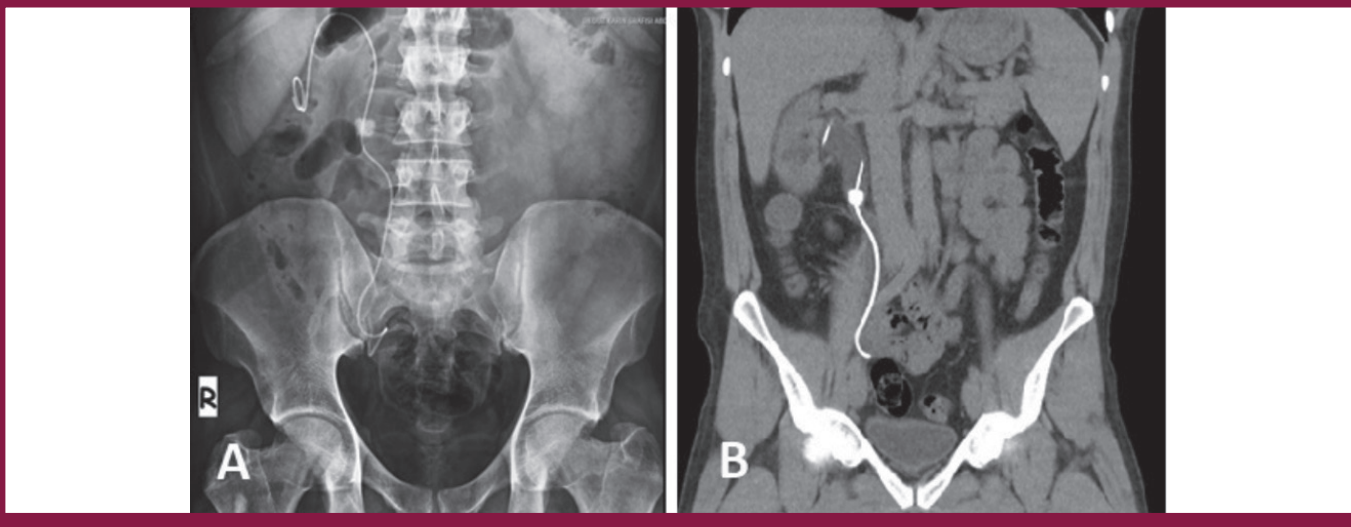

Figure 3. A). Control DUSG taken on the 1st postoperative day of the re-operated patient, **B)** Abdominal CT without contrast
CT: Computed tomography, DUSG: Plain urinary system radiographs

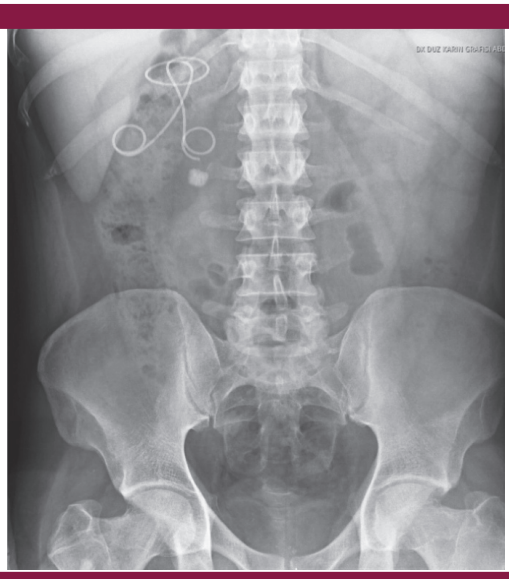

Figure 4. DUSG taken at the 3rd postoperative week
DUSG: Plain urinary system radiographs

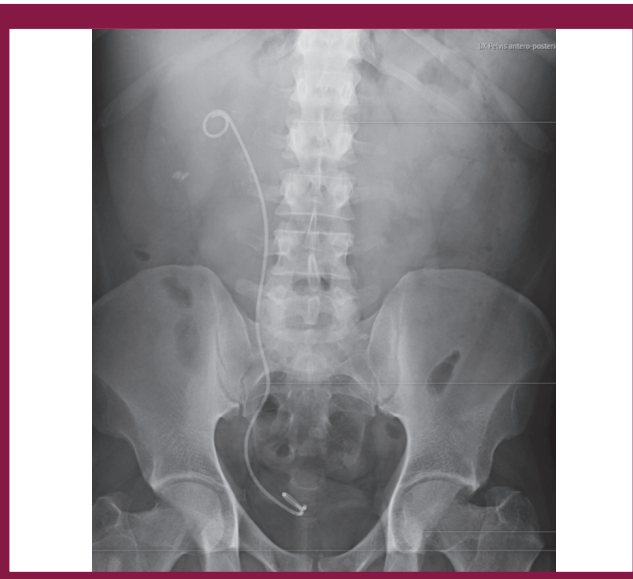

Figure 5. Postoperative 3rd week control DUSG after lithotripsy
DUSG: Plain urinary system radiographs

Conclusion

Although JJ stent insertion is a method commonly used in urologic interventions, it may cause complications. The best way to avoid these complications is to avoid unnecessary JJ stent placement. However, complications should be considered in JJ stents placed in necessary cases according to the signs and symptoms of the patient. We found that the impaction of large calculi in the ureter and hydronephrosis facilitated the proximal migration of the JJ stent. The patient's JJ stent should be checked postoperatively before discharge.

Ethics

Informed Consent: After obtaining the patient's consent, we decided to share this case report.

Authorship Contributions

Surgical and Medical Practices: S.Y., Ö.Y., Concept: H.H., Y.E.K., Ö.Y., Design: S.Y., Y.E.K., Ö.Y., Data Collection or Processing: H.H., Y.E.K., Analysis or Interpretation: C.Y., Y.E.K., Ö.Y., Literature Search: S.Y., C.Y., H.H., Y.E.K., Ö.Y., Writing: S.Y., C.Y., Y.E.K.

Conflict of Interest: There are no conflicts of interest between the authors.

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