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Ersin ARSLAN, MD - Special Issue

They are working
for our health!

Avoid violence against
Health Workers...

T.C. Sağlık Bakanlığı

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ABOUT

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The policy of top priority of MSD is to put forward and highlight medical innovations and inspiring patents.

MSD offers an exceptionally fast publication schedule including prompt peer-review by the experts in the field and immediate publication upon acceptance. The editorial board aims at reviewing the submitted articles as fast as possible and promptly including them in the forthcoming issues.
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CONTACT US

Lycia Press Inc., 3rd Floor 86 - 90 Paul Street, EC2A 4NE, London, UK.
Phone : +44 0 203 322 3097
E-mail : office@lycians.com
E-mail : editor@medscidiscovery.com

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Şifa Veren Ele Vefa

Bundan tam 4 yıl önce meslektaşımız Dr. Ersin Arslan'ı görevi başındayken zalim bir saldırı sonucunda kaybettik. Bu tarih milat olurken, sağlıkta şiddete dur demek için Ersin Arslan ismi de bir sembol oldu. Hastalarına canı gönülden koşan Dr. Ersin Arslan, bir caninin hedefi oldu. Bizleri o gün kahreden bu olayın tıp camiamız tarafından unutulması asla mümkün değildir. Yaşanan her şiddet olayından sonra şehit Dr. Ersin Arslan'ın acısı, yüreğimizi yeniden yangın yerine çeviriyor. Amacı insana hizmet etmek ve sağlığına kavuşturmak olan bir doktora şiddetle karşılık vermenin hiçbir gerekçesi olamaz.

Allah'ın insanlara bahşettiği en büyük hazine olan sağlığı korumayı ve iyileştirmeyi amaçlayan hekimlik en kutsal mesleklerdendir. Elbette ki her mesleğin kendine özgü zorlukları ve özel durumları vardır. Ama doğrudan insan yaşamını konu alması nedeniyle hekimlerimizin üstlendiği sorumluluk, mesleklerine ayrı bir önem katıyor. Çünkü hekimlerimiz hiçbir beklenti içinde olmadan insanlara hakkaniyetli ve kaliteli bir sağlık hizmeti için gece gündüz demeden çaba sarf ediyor. Zira ülke olarak ideallerimize ulaşabilmemiz için bedensel ve zihinsel yönden sağlıklı ve güçlü bireylere sahip olmamız gerektiğinin bilincindeler.

Hekimlerimiz mesleki sorumlulukları gereği insanlarımız arasında hiçbir ayrım gözetmeksizin en iyi şekilde hizmet veriyor. İnsanlarımızın endişe duymadan canlarını onlara emanet etmelerinin karşısında yapılması gereken de budur. Bu nedenle toplumumuz, hekimlerimize ve sağlık çalışanlarımıza karşı büyük bir saygı gösterir. Ancak münferit de olsa hiçbir şekilde inanç ve kültür değerlerimizle bağdaşmayan şiddet olaylarına şahit olabiliyoruz. Milletimize yakışmayan bu tablonun önüne geçmek için vatandaşlarımızın, şiddet uygulayanlara karşı sağlık çalışanlarımıza sahip çıkmalarını bekliyoruz.

Bunun yanı sıra hekimlerimizi ve sağlık çalışanlarımızı korumak bakanlığımızın ve ilgili kamu kurumlarımızın önceliğidir. Bu kapsamda bugüne kadar birçok yasal düzenleme yaptık. Başbakanlık Genelgesi ile Sağlıkta Şiddete Sıfır Tolerans Eylem Planı'nı hayata geçirdik. Buna göre sağlık çalışanlarına şiddet uygulayan hasta ve hasta yakınları, gözaltına alınacak. Türk Ceza Kanunu'nda yapılacak düzenlemeyle de sağlık çalışanlarına yapılacak tehdit ve hakaret suçlarında var olan tutuklama yasağı kaldırılacak. Bu suçu işleyenlerin tutuklanmasının önü açılacak. Ancak istenilen sonucu alabilmemiz için yaptığımız ve bundan sonra yapacağımız yasal düzenlemelere kadar vatandaşlarımızın da destek vermesini çok önemsiyoruz. Böylece 'sağlık' ve 'şiddet' kavramlarının artık yan yana anılmayacağından emin olabilirsiniz.

Bu duygu ve düşüncelerle Dr. Ersin Arslan kardeşimiz başta olmak üzere bu kutlu yolda hayatını kaybeden meslektaşlarıma bir kez daha Allah'tan rahmet diliyorum.

T.C. Sağlık Bakanı

Dr. Mehmet Muezzinoglu

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Bilgi Değerlidir / Knowledge is Precious

Medical Science and Discovery (MSD) 30 Nisan 2014 yılında ülkemizin değerli bilim adamlarının katkılarıyla kurulmuş sağlık bilimleri alanında aylık olarak yayınlanan İngilizce bilimsel, açık erişimli (Open Access) bir dergidir.

Ücretli kütüphanelerin üniversitelere eklediği ek maliyetlerin ulaştığı devasa boyut, bilgiye erişimi ciddi oranda sınırlamakta, bu sebeple MSD açık erişimli bilimsel yayıncılık ilkelerini uygulamaktadır. MSD'de yayınlanan tüm makalelere araştırmacılar ücretsiz erişebilir, aynı zamanda da kriterlere uygun referanslanmak koşuluyla bu bilgiler ücretsiz biçimde paylaşabilmektedir.

Bilimsel dergicilik konusunda önümüzü açan, bizi teşvik eden ve yanında doktora eğitimimi tamamladığım Prof. Dr. Aziz Sancar hocama desteği için teşekkür ediyorum. Aldığı Nobel ödülü bir süredir coğrafyamızda yaşanan negatif atmosferde bize pozitif enerji olmuştur.

İnsanlık olarak yaşadığımız tüm sorunların temelinin bilgisizlik ve cehalet olduğu açıktır ve çıkış yolu da sadece eğitimdir. Bu sebeple bilginin üretilmesi ve erişime sunulması hem ülkemiz hem de insanlık geleceği açısından son derece önemlidir.

Cehaletin bir yansıması olarak maalesef çok değerli bir meslektaşımız ve arkadaşımız Uzman Doktor Ersin Arslan 17 Nisan 2012'de 85 yaşındaki son dönem akciğer kanser hastası dedesini kaybeden 17 yaşındaki bir "çocuk" tarafından "çocuğun" kendi ifadesiyle intikam amacıyla bıçaklanarak katledilmiştir.

Merhum arkadaşımız Ersin Arslan'a bu özel sayı vesilesiyle Allah'tan rahmet, ailesine de sabırlar diliyoruz. Ülkemizde son dönemde sıkça karşılaştığımız, yaş, ırk, din, mezhep ve cinsiyet ayırt etmeksizin, insana yönelen psikolojik, fiziksel ve toplumsal şiddeti esefle kınıyoruz...

Kullanılabilirse ve İnsanlığa Bir Değer Katıyorsa, Bilgi Önemlidir...

Bilginin üretilmesinde olduğu gibi paylaşılmasına aracı olan bilimsel yayıncılık konusunda da gelişmiş ülkelerin gerisinde kaldığımız can sıkıcı bir gerçektir. Ülkemizde bilimsel yayıncılık hizmeti veren yayınevleri sayısı bir elin parmakları sayısını geçmemektedir, bunun iki önemli sebebi;

-Bilimsel yayıncılığın hedef kitlesinin ülkemizdeki boyutu,

-Ülkemiz vergi politikalarıdır.

Eğitim, araştırma ve geliştirme ve bilimsel faaliyet alanlarında hizmet veren girişimciler için farklı vergilendirme kurallarının geliştirilmesi veya Avrupa Birliği müfredatına uygun hale getirilmesi bu alandaki sorunumuzu çözmek için ülkemize avantaj sağlayacaktır.

Ülkemiz bilimsel yayıncılığına yeni bir dinamizm ve motivasyon sağlamak ve dünyanın önemli bilimsel platformları arasına Türkiye markaları eklemek için bilim adamı arkadaşlarımızla özverili bir gayret içerisindeyiz.

Lycia Press Inc, bu gayretler sonucunda 2015 yılında Londra'da kurduğumuz, ülkemiz bilim adamlarının bilimsel çalışmalarını uluslararası platformlara taşımayı hedefleyen bir yayınevidir. Lycia Press bilimsel dergilere sunduğu yayıncılık hizmeti yanında bilimsel yayıncılık otomasyon sistemleri geliştirmekte ve bilginin olabildiğince hızlı biçimde kullanıcılara aktarılmasını sağlayacak platformlar üzerinde de çalışmaktadır.

Bu özel sayının hazırlanmasında katkı sunan Galenos yayınevi ve çalışanlarına sonsuz teşekkür ediyorum.

Editör
Zafer AKAN

Ersin'in ardından hiçbir şey söyleyemem ki ben...

Sözlerim yarım kaldı, ben yarım kaldım...

Adını haykırmak istiyorum, kelimeler boğazımda düğümleniyor, gözyaşlarım isyan ediyor, sol yanım acıyor...

Hayatının en güzel günlerini mesleğinin hakkını vererek yapmak için çalışarak geçirdikten sonra, 6 yıl tıp fakültesi, 5 yıl göğüs cerrahisi eğitimi, uykusuz geceler, yorgun günlerden sonra, onlarca bilimsel çalışma ve yayından sonra, dinlenmek için sıcak yatağının değil de kara toprağın layık görülmesi kalbime bıçak gibi saplanıyor, canım yanıyor; çünkü "canım" toprağın altında yatıyor...

Dr. Sibel ARSLAN
EŞİ

Yaşanabilecek en büyük acılardandır evlat, eş, kardeş, amca, dayı acısı ...

Yüreği dağlanan ademoğlunun acısı nice olur? Dağa taşa mı haykırır? Başını duvarlara mı vurur? Sinesini mi yumruklar? Kendini Mecnunvari çöllere mi atar? Yoksa içine kapanıp tortop mu olur, kabuk mu bağlar? Yitik ciğerpareyse, spiker anne-baba nasıl sunar bu haberi? Bir gazetenin köşe yazarı, acaba nasıl yazar evladının kaybını? Gassal/gassale nasıl yıkar eline doğmuş çocuğunun soğumuş bedenini? Hele birde doktorsa eşi, ameliyathanede cana can katansa abi nasıl verir bu haberi ailenin tüm fertlerine? Evet, insanoğlunun acısı, illa da evlat, eş, kardeş, amca, dayı, enişte acısıysa düştüğü yeri yakıp kavurur; dile vurur, yüreğe vurur. Ağıt olur, mersiye olur, türkü olur, mani olur, roman olur, hikaye olur. Dilden dile, kuşaktan kuşağa nakledilir. Ölüm acı şeydir de eşin, evladın, kardeşin, amcanın, dayının sızısı ömür boyu çıkmaz. Küllendikçe deşilir, deşildikçe tütmeye, yakmaya devam eder. Asla sönmez.

"Allah böyle acıyı düşmanımın başına vermesin. Allah evlat acısını, hayat arkadaşının acısını, kardeş acısını bir daha göstermesin" yollu sözler duyulur içine kor düşmüşlerin dilinden. "Allah sabır versin, sabrınızı artırsın, geride kalanların ömrü uzun olsun" türünden teselli sözleriyle yanan yüreklere derman olmaya, acıyı paylaşmaya çalışır çevredekiler. Bağırlar yırtılsa da, yürekler için için kanasa da yıllar yıllara ulanmakta gecikmez.

Meğer candan öte bir can daha varmış.

Ve onun adı evlatmış, eşmiş, kardeşmiş, amcaymış, dayıymış...

Dr. Ersin Arslan'ın AİLESİ

Ne pis bir şeymiş yaaaa ...

Ne bitmek tükenmek bilmez bir acıymış ...

Ne acıymış ama ...

Her geçecek dediğinde daha da kanatır mı içini?

Her hayata tutunmaya çabaladığında kaydırır mı ellerini nemli, çentikli urgan ...

Zaman her şeyin ilacı diyorlar ya.

Değil arkadaş.

Bunun ilacı değil.

Bunda zaman yeni acılar getiriyor beraberinde.

Sadece ölümü değil çünkü acı çektiren.

Meğer o sadece başlangıçmış.

Kardeşinin ölümü ile başlayan o süreç ... O pis, kaba ve içi tahmin edemeyeceğin yük, sıkıntıları ile dolu sürecin ilk damlasıymış meğer.

Önce yokluğuna alışmaya çalışıyor insan. Gördüğünde hemen gönderdiği komik resimleri, karikatürleri, videoları kime göndereceğini bilemiyor. Bu ne demek biliyor musunuz? Bu artık kiminle güleceğini bilememek demek. Bilemiyor insan kiminle güleceğini.

Sonra onun diğer sevdiklerini sevmeye başlıyorsun. Onun sevdiği her şeyi, herkesi sen de seviyorsun artık. En sevmediklerini bile seviyor içinde bir yer ...

Ona ait her şey senin oluyor.

İki kişilik yaşıyorsun. Onunla ilgili her şey hem gülümsetiyor hem de bir elin göğsünün içine dalıp kalbini sıktığını hissediyorsun.

"Yıllarca aynı odada uyuduğun, aynı sofrada yemek yediğin, öpüp kokladığın, bayramlarda harçlık verip sevindirdiğin, verdiğin bayram harçlığınla neler yaptığını anlatmasını büyük bir mutlulukla dinlediğin, üniversiteyi kazandığında evden ilk kez ayrılırken arkandan sabaha kadar ağlayan, gurbette açtığı telefonlarla sizi yalnız bırakmayan can ciğerin, kavga ettiğin, sonra öpüp gönlünü aldığın kardeşinin bir gün bilinmeyen ve dönüşü olmayan yolculuğa çıkması.

Tabutta kefeni son kez açıp son kez o masum yüzünü görmek, acı içinde istemeyerek de olsa mezarına iki kürek toprak atmak, evlat acısının ne olduğunu anne babanın yüzünden, telefondaki ses tonundan, sokakta gördüğü çocuklara bakışından anlamak. Ailenin toplandığı bayramların zehir olması, arife günlerinde ziyaret edilen mezarı, okunan iki satır dua, buruk geçen bayram ziyaretleri, ondan geriye kalan eşyalar, sınıf arkadaşlarını görürken içimize dolan hüzün.

Kısacası aklımızdan bir an bile çıkmaman ...

Daha yapacak işleri vardı ...

O kötü günün ardından üç beş gün sonra çekti birileri hatırlamıyorum. Ersin'in kullandığı çantayı getirdi hüzünlenerek açtım, içinden çıkanlar şunlardı siteteskop, abeslang, bir pansuman seti, birkaç rifocin ve bir furocin krem hiç şaşırmadım o güzel insan Dr. Ersin Arslan'ın çantasından ne çıkabilirdi ki ...

Birde dört hastanın dosyası dosyaların içerisinde sonuçlar ve tomografi CD'leri peki bu dosyaları çantasına niye koymuştu? Ersin kendisini insanlığa adamış bir bilim adamıydı bu dosyaları uzmanlık aldığı üniversiteden hocalarıyla konsey yapmak tartışıp hastaları için en iyisine karar vermek için koymuştu. O kötü gün hastalarından aldı Ersin'i, yokluğu biz ailesini çok derinden üzdü tabi ama bizim kadar onu tanıyanlar tanımayanlar kısaca içinde biraz insanlık olan vicdan taşıyan tüm insanları üzdü. Onun hekimliğini, işine olan saygısını başkaları anlatsın. Ben şunu söylerim zor şartlarla perfüzyonist olan biri olarak ve senin de zor şartlarda okuyup doktor olduğunu bilen biri olarak hani kötülere inat beraber akciğer nakli yapacaktık. Ersinim küçük kardeşim sırdaşım akıl danıştığım hocam daha yapacak işlerimiz vardı yaaaaaaaaaaaaaa !

Erkan ARSLAN
ABİSİ

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Ülkemizde sağlık hizmetlerinden tüm vatandaşlarımızın en iyi şekilde yararlanmalarının sağlanması, bu hizmetlerin herkese ve her yere eşit olarak, etkili ve sürekli bir şekilde ulaştırılması amacı ile koruyucu ve tedavi edici sağlık hizmetlerinde çeşitli çalışmalar yapılmakta, sağlık sorunlarımızı en aza indirmek üzere programlar uygulanmaktadır. Sağlıkta Dönüşüm Programı ise bunun en güzel örneklerindendir.

Ülkemizde son yıllarda sağlık alanında yaşanan köklü değişim Sağlıkta Dönüşüm Reformu ile yaşanan bu güzel gelişmelerin temel mimarları ise şüphesiz ki insan hayatına ömrünü adamış, özveri ve sabrı içinde barındıran kutsal bir mesleğin mensubu olan fedakar sağlık çalışanlarımızdır.

Dünya Sağlık Örgütü'ne göre bir ülkenin sağlık sistemi, herkese gerekli olan sağlık hizmetinin yüksek kalitede verilmesini sağlayacak şekilde tasarlanmalıdır. Bu hizmet etkili, karşılanabilir maliyette ve toplumca kabul gören tarzda olmalıdır. Henüz Avrupa Birliği ve gelişmiş ülkeler standartlarında bir muayene edilen hasta sayısı rakamlarına inememiş olmamızın da katkısıyla yaşadığımız yoğun çalışma ortamı sağlık çalışanları üzerinde yıpratıcı bir stres gelişmesine sebep olduğu aşikardır. Her şeyden kıymetli sağlığımızı emanet ettiğimiz sağlık çalışanlarının bu özverili hayat tarzı için kendilerine ne kadar teşekkür edilse yeterli olmayacaktır.

Sevgi en iyi ilaçtır diyerek sevgiyle, şefkatle, insanımıza yardım elini uzatan sağlık çalışanlarımıza uygulanan her türlü şiddet ise maalesef ki bizleri derinden üzmektedir. İnsan hayatına ömrünü adamış hekimlerimize, sağlık çalışanlarımıza, insanımıza ve insanlığa yapılan hiçbir şiddet türünü kabul etmiyor, ölümlere kadar uzanan bu saldırıları kınıyoruz.

Bildiğiniz üzere doğuda yaşanan terör olaylarına rağmen doktorlarımız, hemşirelerimiz ve tüm sağlık çalışanlarımız canları pahasına halkımıza hizmet vermeye devam etmektedir

Gaziantep kamu hastanelerine bağlı sağlık tesisimize adını verdiğimiz kıymetli doktorumuz Ersin Arslan gurur duyduğumuz çalışanlarımızdan biriydi, maalesef kendisini, son zamanlarda sıkça yaşadığımız sağlık çalışanlarına şiddet olayında kaybetmiştik, merhuma Allah'tan rahmet, ailesine sabrı cemil niyaz ediyoruz.

Bölge ve eğitim araştırma hastanelerinden beklentilerimiz ve yönetim olarak hedefimiz kaliteli sağlık hizmeti olduğu kadar sağlık teknolojilerine katkı sağlayacak bilimsel çalışmalara da öncü olmaktır.

Bu bağlamda Dr. Ersin Arslan Eğitim Araştırma Hastanesi ve Kamu Hastaneler Birliği Genel Sekreteri Doç. Dr. Hayati DENIZ ve yöneticilerini uluslararası bilimsel gruplarla yapmış oldukları bilimsel işbirliklerinden dolayı tebrik ediyorum.

Prof. Doç. Dr. Alper CIHAN
Türkiye Kamu Hastaneleri Kurum Başkanı

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Dünyanın en eski şehirleri arasında yer alan Gaziantep, tarihi ve zengin kültürünün yanında, sanayi ve ticaretteki başarıları ile de dikkatleri üzerinde toplayan, ülkemizin yıldızı en hızlı parlayan şehirlerinden birisidir.

Türkiye'nin 6. büyük ili olan Gaziantep'te, 4 Kasım 2015 tarihine kadar Sağlık Bakanlığı'mıza bağlı bir Eğitim ve Araştırma Hastanesi'nin olmaması büyük bir eksiklikti. Dr. Ersin Arslan Eğitim ve Araştırma Hastanesi sadece Gaziantep'in değil, bölgemizde de kamu sağlık hizmetlerinin amiral gemisi konumunda bulunmaktadır. Gaziantep'e Eğitim ve Araştırma Hastanesi ünvanının kazandırılmış olmasından büyük bir onur ve mutluluk duyuyoruz. Dr. Ersin Arslan Devlet Hastanesi'nin, Eğitim ve Araştırma Hastanesi ünvanını almasında, başta Sağlık Bakanlığı, Türkiye Kamu Hastaneleri Kurumu Başkanlığı'na, Gaziantep valimiz Ali Yerlikaya ve Gaziantep milletvekillerimiz olmak üzere, emeği geçen herkese teşekkür ediyorum.

Cumhuriyetin ilk yıllarından itibaren, farklı isimler altında Gaziantep ve bölgemize sağlık hizmeti sunan hastanemizin Eğitim ve Araştırma Hastanesi ünvanı alması ile birlikte yeni bir dönem başlamış oldu. Eğitim ve Araştırma Hastanesi ünvanı ile birlikte hastanemizde verilen sağlık hizmetlerine ek olarak eğitim hizmetleri de başlayacak. Eğitim ve Araştırma Hastaneleri için bilimsel çalışmalar ve bu çalışmaların yayınlanacağı bilimsel dergiler çok önemlidir. Tıp biliminin gelişmesine, bu alanda yapılacak çalışmaların ve tecrübelerin paylaşılmasına önemli katkılar sağlayacağına inandığımız Medical Science and Discovery dergisi özel sayısını görevi başında şehit verdiğimiz Dr. Ersin Arslan'ın anısına basılı yayın olarak sunması, ayrı bir anlam ifade etmektedir.

Ayrıca, asistanlığından beri birlikte çalıştığım, gerek hekimliği, gerekse de kişiliği ile hem sağlık çalışanlarının, hem de hastaların gönlünde taht kuran Dr. Ersin Arslan'ın adını taşıyan bu hastanede hizmet vermekten de büyük onur duyduğumu ifade etmek istiyorum. Bu vesile ile genç yaşta, hayatının baharında, kutsal bir görev olan hekimlik hizmetini yerine getirirken şehit edilen Dr. Ersin Arslan'a bir kez daha Allah'tan rahmet diliyorum.

İnsanın en temel hakkı yaşam hakkıdır. Ve bu hak kutsaldır. Dolayısıyla sağlık hizmeti de kutsal bir görevdir. Büyük bir fedakarlıkla, ırk, din, dil ayrımı yapmadan, Gaziantep ve komşu ülkelerden gelen misafirlerimize sağlık hizmeti sunan tüm sağlık çalışanlarını kutluyorum. Hepsine ayrı ayrı göstermiş oldukları fedakarlıktan, sabırdan, özverili hizmetlerinden dolayı teşekkür ediyorum.

Doç. Dr. Hayati DENIZ
Gaziantep İli Kamu Hastaneleri Birliği Genel Sekreteri

Ne giden anlar kalanın halini, ne de kalan gidenin neden gittiğini ...∞∞

Bütün açıklamalar anlamsız kalır o noktada. Eğer gitmek elzem ise, yaşananların bir anlamı kalmamıştır. Sonuçta giden de kalan da acı çeker. Yaşanmıştır, hissedilmiştir tüm duygular ...

Ama o bütün bunları sanki hiç hissetmemiş gibi gitmiştir. Anlamanın imkanı yoktur. Yalan mıdır tüm yaşananlar? Tek başına mı yaşanmıştı? Geçen günler rüya mıydı? Kendinden şüphe edersin ... Gerçek hiç de öyle değildir halbuki. Giden gitmeden önce, kalan geride kalmadan önce, paylaşılmıştır hepsi. Hissedilenler, yaşananlar yalan değildir, rüya değildir. Mutluluk paylaşılmış, hayaller beraber kurulmuştur. Bunun üzerine yapılacak pek de bir şey kalmaz. Dünyaya daha gerçekçi bakmak gerekir. Ne kendini ne de başkasını kandırmaya gerek yoktur. Onun için artık gitmek elzem olmuştur. Nasıl bir anda girdiyse hayatımıza, o şekilde de çıkar gider. Kalanın tek hissettiği acısıdır ve kelimeler bir anlam ifade etmez. Yani ne giden anlar kalanın halini, ne de kalan gidenin neden gittiğini ... Bütün açıklamalar anlamsız kalır o noktada. Sonuçta tamamı boşa sarf edilmişlerdir o sözlerin. Ne söyleyen inanır o sözlere, ne de dinleyen ...

Hayatın acımasız bir gerçeği olsa da hangi yaşta olursa olsun bütün ölümler erken sayılır.

Canım kardeşim, iki gözüm;

Ben şimdi zihnimde, içimde asılı duran bugünkü fotoğraftan bahsetmek istiyorum sana. Günlük güneşlik bir vakitte ansızın yağan yağmurlar gibi hayattan düştüğünün 4 yılını geride bıraktık. Adını her an telaffuz ettiğimiz hastanedeki fotoğraflarda yoksun ama senlik kareler var. İki gözüm, kardeşim ... Silüetin yok artık bu fotoğraflarda! Ama hatıran, ama ruhun, ama her şeyinle sen buralardasın.

Biliyorum Turgenyev haklı;

"Ölüm eski bir şeydir ama, her insana yeni görünür."

İnsanın yakınına bu kadar sokulunca, nefesini böylesine bırakınca inanılası bir şey gibi gelmiyor insana. Dışımızda, uzağımızda birinin ölümü değildi seninkisi; artık bize ait olmuş bir şeyin ölümü oldu ölümün. Hem ölümle iç içe hem de yaşıyor olmak garip bir çelişki. Kabullenmekte zorlansak da hakikat bu! Doğar doğmaz, yaşarken ölüme yürüyoruz. Ölüm hayatın dışında değil, hayat ölümün içinde saklı.

Farkında olmadan insana maruz kalırız. Zamanın içinde öylece kıvrılırken biri hikayemizin kapılarından içeri girer. Esaslı dostlar böyle ansızın girerler hayatımıza ama zor çıkarlar. Ölüm ayırır dostları birbirinden. Kim önce ölmüşse, kalanın kalbinde derin bir kuyu oluşturur. Sen de bize bunu yaptın. Ölümün, içimizde açılmış bir kuyu gibi duruyor şimdi.

Ayak uçlarına çömelen, fotoğrafını öpüp toprağına bırakan eşini düşündüm epey. Gidişinle yüreğinde açtığın boşluğun derinliğini gördüm. Yakınlarının hepsi hüzne sürgündü.

Hayır, ölüm, lanet bir şey değildir! Hayata düşen aydınlıktır, her gelişiyle hayatın altını çizer. Ölümlü varlıklar olduğumuzu, haddimizi hatırlatır.

Böyle söyleniyorum ama Sebnem Ferah'ın şarkısındaki nakarat da içimde çınlıyor;

"Sen hiç öldün mü, birden durulduk mu?

Bulanıkmış berrakmış her suyu içtin mi?

Altında ağ olmadan yerden yükseldin mi?

Tam zevkine varmışken birden yere düştün mü sen?"

...

Güzel ahlaklı, yüreği zengin kardeşim seni çok kısa bir süre içinde akademisyen olarak göreceğimizi beklerken gönlümüzün profesörü olarak gittin ama biz senin isminin altında bil ki çok akademisyenlerin yetişmesine katkıda bulunacağız.

Sana rahmet diliyor, buradan çok selam gönderiyoruz ...

Isik Betil KUTLU

Eğitim ve AR-GE Koordinatörü

Ersin ARSLAN'ı Anarken

Onsuz geçen yılların sayısı arttıkça hasretimiz de çoğalmakta. Neden derseniz, bunun cevabını anlamak için Ersin'i tanımak gerekir de ondan. O ölümünün ardından sadece onu tanıyanlara değil, bir ülkeye ve hatta dünyaya meslek onurunu yaşamın anlamını ve hakikati hatırlattı. Onu ebediyete uğurlarken gördük ve hatırladık ki hekimlik mesleğinin değeri kaybedilmiş bir toplumda yaşıyoruz. Aslında insan değerinin azaldığı ve belki de yok olmaya doğru gittiğini gördük. İşte tam bu anda Ersin Arslan ışık oldu, güneş oldu aydınlattı dünyamızı. Yaradanın nuru oldu. Ersin ile çalışmak, ve de en yakınında olmak güzeldi, mutluluktu. Sağlam bir kişilik, iyi bir insan meslek ile barışık Allah vergisi yetenek. Kısa bir ömre sığan muhteşem bir kimlik. Onu ölümsüzleştiren isim hiçte boş değil. Umuyorum ve diliyorum bu ülke çok sayıda Ersin Arslan'lara sahiptir ve olacaktır. Onların kıymetini bilelim.

Son yıllara bakıldığında görevi başında öldürülen hekim sayısında artış olmuştur. Bunun toplumun son yıllarda yaşadığı sosyo-ekonomik sorunlarla ilgisi olduğu aşikar olup, niteliğe, bilgiye insana olan değer azalmıştır. Beşikteki bebekten başlayarak bu değerin artırılacağı bir eğitim sürecine gereksinim vardır. Toplum önderlerinin, siyasi erkin ve biz hekimlerin önderliği ve öncülüğü esas olmalıdır.

Ersin Arslan'ı anarken gözümün önüne onu yanımda genç ve ulusuna örnek bir doçent, karşımda sihirli parmakları ile hastasına hayat veren bir cerrah olarak görüyorum. Öyle bir kişiliktir ki Ersin daha asistanlığı sırasında kapsamlı çalışmaları ile bilimsel verilerini tamamlamış, bugün hepimizin göğsünü kabartacak bir bilim insanı olmuştu. Yazık değil mi ona ve ona emek verenlere, sevdiklerine sevenlerine ve yazık değil mi bu ülkeye. Sizlere onu daha çok anlatmak isterdim, ancak kelimelere sığmayan kimliği ve kişiliği ile ifade etmekte güçlük çekiyorum.

Onu çok özlüyorum ve bir kez daha rahmetle anıyorum.

Prof. Dr. Levent ELBEYLI

Tıp Fakültesi Dekanı

Hasta haklarının, değişen sağlık ihtiyaçlarının, hasta ve hasta yakınlarının beklentilerinin karşılanması ile etkili, verimli ve duyarlı sağlık hizmeti sunulmasında önemli bir misyonu yerine getiren çalışma arkadaşlarımızın, bu önemli görevi yerine getirirken gösterdikleri özveri ve gayret takdire şayandır. Irk, renk, inanç, yaş, cinsiyet, siyasi ve sosyal statü hiçbir şekilde ayrım yapılmaksızın doktoru, hemşiresi, ebesi ve tüm sağlık çalışanlarımızla kısaca insanımızla birlik beraberlik içerisinde topluma fayda sağlamak üstlendiğimiz en büyük görevdir.

Çok uzak değil 4 sene önce şehrimizin yetiştirdiği gencecik bir hekimimizi, Dr. Ersin ARSLAN'ı gözyaşları ile toprağa verdik.

Bir hasta yakını tarafından bıçaklı bir saldırı ile hayatını kaybetmesiyle, sağlık sistemi ve Gaziantep halkı yetenekli ve bilgili bir uzman doktorunu kaybetmekle kalmadı, ülkemiz ve bizler de geleceğimizin bir parçasını kaybettik.

Tıp bilimi ve mesleğinin gerektirdiği onurlu ve bilimsel duruşu, özverili çalışması, yeteneği, zekası ve hep daha iyi için uğraşı ile hocalarının ve arkadaşlarının dikkatini çekerek sevgisini kazanan başarılı hekimimiz Dr. Ersin ARSLAN'ın gayreti, çalışkanlığı ve iyi yüreği ile açtığı yol muhakkak ki gelecek nesillere ışık tutacak, örnek teşkil edecektir.

Bizler de "Şifa Veren Ele Vefa" diyerek birbirimize merhametle ve şefkatle, yaratılmışların en şereflisi gözüyle bakarak yolumuza devam edeceğiz. Nitekim dinimiz de bizlere hiddet ve şiddet yerine ülfet ve şefkat yolunda ilerlemeyi emretmiştir.

Bu duygularla şiddeti bir kez daha kınıyor, yürekleri kanatan, vicdanları sızlatan şiddet olaylarının yaşanmaması temennisiyle herkese sağlıklı günler diliyorum.

Dr. Sadettin YAZI

Gaziantep İl Sağlık Müdürü

O Hep Yanımızda

Yılların emeği bir anda, hunharca, canice, kabul edilemez bir şekilde kayboldu gitti. Geride çok acılar bırakarak...

Bugün ise hala içimizde sızısı, acısı, hüznü devam ediyor. Bu çok erken ayrılış hiç yakışmadı yakışmayacak. Ersin tanıdığım en çalışkan, en fedakar, akademik yönü kuvvetli, geleceğin en iyi öğretim üyelerinden olmaya aday değerli bir insan, iyi bir arkadaş, parlayan yıldız unvanına yakışan bir meslektaşımdı. Şu anda birçoğumuzun çocuklarımıza eğitimleri için sağladığı imkana o sahip değildi belki ama o kadar idealist o kadar çalışkan bir insandı ki asistanlığı döneminde dahi hocalarının medar-ı iftiharı idi.

Üzüldük, üzülüyoruz! Yıkıldık, yıkılıyoruz! Yıprandık, yıpranıyoruz! Kızdık, kızıyoruz!

Ama artık fedakarca bu mesleği yapan insanlar olarak bizler, hiçbir meslektaşımız, çalışma arkadaşımız, dostumuz için üzülmek istemiyoruz. Uykusuz geçen gecelerin, ailemizden çalıp hastalarımıza verdiğimiz zamanın karşılığı asla şiddet olmamalı. Bu mesleğin saygınlığı tekrar geri verilmeli.

Tek tesellimiz şu ki: Ersin geriye büyük bir iz ve farkındalık bırakarak gitti.

Sevgili Ersin,

Yaptığın çalışmaların, ayrılışından sonra bile kıymetini bulan yayınların, en önemlisi de Sen ve binlerce anıların kaldı bize. Seni yaşatacağız. Seni anacağız ve bil ki asla unutmayacağız! Nurlar içinde uyu! Hoşçakal demiyorum sevgili kardeşim: Hoş geldin...

Doç. Dr. Senem KORUK

Uzmanlık eğitimine başladığı ilk günden itibaren tıp bilimi ve mesleğinin gerektirdiği onurlu ve bilimsel duruşu, özverili çalışması, yeteneği, zekası ve hep daha iyi için uğraşısı ile dikkati çekti. Dürüstlüğü, çalışkanlığı ve potansiyali ile akademisyen olması gerektiği konusunda anabilim dalındaki öğretim üyeleri arasında fikir birliği oluşmuştur. Anlayacağınız katledilmesiyle, sağlık sistemi ve Gaziantep halkı yetenekli ve bilgili uzman doktoru kaybetmekle kalmadı, ülkemiz ve kliniğimiz geleceğimizin bir parçasını kaybettik. Kendisini tanıma şansını elde eden herkesin ortak görüşü şudur;

"Bu sistem içerisinde böyle bir davranışı hak eden en son kişi Ersin'dir."

Ersin'le beraber çalıştığı Devlet Hastanesi'nde ilk defa bu düzeyde göğüs cerrahisi operasyonlarının yapıldığı ve bu operasyonların onun canına mal olduğunu bilerek, "keşke bu seviyeye gelecek kadar eğitmeseydik " şeklinde mantıksız ve sağlıksız düşünmeden edemiyorum.

Allah doktor olanlara ve doktor olmayı düşünenlere sabır ve cesaret versin.

Hepimizin başı sağ olsun.

Prof. Dr. Bulent Tuncozgur

Ersin, göğüs cerrahisi gibi zor bir uzmanlık dalında, ilk günden itibaren bu işe gönüllü ve uygun olduğunu gösterdi. Hem çok çalışkan hem çok yetenekli, hem de saygılı olması ile de klinikte göze batan isimdi. Yılmadan, öf-pöf demeden çalışınca da uzmanlık eğitim süresi olan 5 yıla, iyi bir göğüs cerrahi eğitimini, uluslararası alanda yayınlanmış 10'un üzerinde makaleyi, bir o kadar ulusal makaleyi, sayısı çok daha fazla olan bildiriyi, Üniversitelerarası Kurul Yabancı Dil Sınavını geçecek İngilizce eğitimini ve çok güzel bir evliliği sığdırdı. Mecburi hizmetini tamamlayıp, tekrar kliniğe döneceği planlarını hep birlikte yaptığımız bir dönemde, görevi başındayken, sabahtan-öğleye kadarki süreye 4 operasyon sığdırdıktan sonra, güpegündüz, devlet hastanesindeyken, klinikteyken, arkadan kalleşçe-haince-insanlık dışı bir şekilde yapılan bıçaklı saldırıyla katledildi. Hem de çalışıp, hastasına baktığı ve can vermeye çalıştığı gerekçesiyle. Oysa 1 gün öncesi akşamında konuştuğumuz gibi, operasyonlarını bitirecek ve yanıma gelip hastalarını ve son yazdığı makalesini konuşacak ve hep birlikte klinikteki hasta vizitini yapacaktık. Olmadı, yapamadı(k). Ciğerine saplanan kalleş acı izin vermedi. Yüzlerce hastanın canına can katmak için çalışan koca beden, bizim de canımızdan bir parça koparak ayrıldı aramızdan. Gelecekte yapmayı istediği pek çok işin planlarını, umutlarını ardında bırakarak. Oysa yapacağı çok şey vardı. Eşi sevdiğini, ailesi gururlandıkları oğullarını, biz dostumuzu-umudumuzu-geleceğimizin bir parçasını, Türk halkı ve dünya çok başarılı işlere imza atacağını bildiğim bir göğüs cerrahını yitirdi. Umarım hükümet ve toplum bunun son olmasını sağlayacak önlemler alır.

Ruhu şad olsun.

Doç. Dr. Maruf Sanli

MSD
Medical Science & Discovery

Dr. Ersin Arslan'a,

Ne söylenebilir ki? Bütün bu 'hekime şiddete hayır' sloganları, yürüyüşler, itirazlar, protestolar ...

Bunları yazmak çizmek başkalarına kalsın, ben abim Ersin Arslan'ı anlatayım. Yıllarca birlikte tuttuğumuz onca gece nöbeti, birlikte girdiğimiz ameliyatlar, baktığımız hastalar ... Bir tek defa bile üşenmeden, gece yarıları her ihtiyacımız olduğunda geldiğin hastalar. Sen bize iyi bir insan olmanın yanında iyi bir hekim olmayı, tanıdan tedaviden önce hastaya sahip çıkmak gerektiğini öğrettin. Hocalarımızdan biri bir gün "Miray'ın gerçek hocası Ersin" demişti, ne doğru söylemişti ... Ama sen bana sadece kıdemli olmadın, yalnız olduğumda, her ihtiyacım olduğunda, canım sıkkın olduğu her anda sen ve eşin yanımda oldunuz. Yani sen gittiğinde yalnızca bir doktorumuzu, bir kıdemlimizi değil, ben abimi kaybettim ... Şimdi bu yazıyı yazarken bütün bunlar için teşekkürlerimi sunmak istiyorum sana ... Cümlelerimizde daima 'Ersin abinin öğrettiği gibi' kelimeleri geçecek ve biz çömezlerin için daima unutulmaz kalacaksın ... Seni çok özlüyoruz ...

Dr. Miray ERSOZ

Uzmanlık eğitimimiz boyunca beraber çalıştığım Ersin çalışkan heyecanlı ve yenliklerin peşi sıra koşturan bir hekim olduğu gibi insani yönü ağır basan bir hekim arkadaşım idi. Uzmanlık eğitimimiz için akademik bir yayını tartışmak için kendisi ile konuşmam gerekiyordu. Poliklinikte hasta baktığı sırada hızla soruyu sorup çıkmak için yanına gittiğimde hasta bakıyordu. Sandalyeye oturup muayeneyi bitirmesini bekledim. Muayenesi biten hasta eve nasıl döneceğini parası olmadığını söyleyince Ersin'in hastaya dolmuş parasından daha fazlasını verince çok şaşırmıştım. Niye soruma verdiği cevap ise daha manidardı; "Bu gün ben vermesem, yarın bana veren olmaz." Ruhun şad olsun dostum.

Dr. Ertugrul KILIC

17 Nisan 2012 tarihinde katledilen şehit kardeşim Dr. Ersin Arslan güler yüzlü işinde son derece yetenekli iyiliksever hasta ve yakınlarıyla ilişkisi mükemmel olan ve bu olayı hak etmeyen bir hekimdi. Kendisini 5 aylık kısa bir çalışma süresinde gördüm ki kendini insanlığa ve bilime adamış enerji dolu hasta ve yakınlarına karşı son derece sevecen yardımsever personel olmadığı durumlarda bile hastayı tek başına tekerlekli sandalye ile taşıyıp film çekilmesini sağlayan insanlık timsali bir hekimdi onun ölümü tüm sağlık camiasını olduğu gibi beni de çok derinden üzdü yokluğunu çok arıyorum onu rahmet ve minnetle anıyorum.

Dr. Muslum POLAT

Ben 1997'de bir yabancı öğrenci olarak gelmiştim, 2008'de ben Türkiye'den ayrılırken, kendi ailemden ve kendi öz vatanımdan ayrıldığımı hissettim ... Kardeşimden ...

Bunu hissetmemi sağlayan Ersin'di. Onun yokluğu, benim öz vatanımda bana yabancılığı hissettiriyordu. Ersin benden 3 yaş daha küçüktü, ama o bana hep abim gibi bakıyordu, benim her türlü sorunuma çözüm bulmaya uğraşıyordu, her attığım adımda arkamdaydı, bense her adımda kendisine hayranlıkla bakıp; "Ben ne zaman Ersin gibi olacağım?" diye kendi kendime soruyordum.

Ersin bana Haydar Haydar'ı öğretendi ...

Kan Çiçekleri'ni ezberletendi ...

Bağlamanın özgün sesiyle bizi ağlatıp, neşeli parçalarla içimizi ferahlatandı.

Birlikte kitaplar okuduk ... Türkü söyledik, yabancı kültürlerin her kapısını çaldık, doktor olduk ve başarılıydık.

Otuz yılda yapabileceği maksimum başarıyı yaparak, verebileceği maksimum sevgiyi vererek, toplayabileceği maksimum saygıyı topladı. Eşini seven, işini kusursuz yapan, ailesine çok bağlı bir insandı Ersin.

Çok acele ettin kardeşim, doyamadık sohbetine, dostluğuna ve sevgine ... Ama sen hep gözümün önünde kalacaksın, hayatımda büyük bir örnek kalacaksın.

Huzur içinde yat, seni hiç unutmayacağız.

Khalid Shilbayeh
Karadeniz Teknik Üniversitesi Tıp Fakültesi'nde sınıf arkadaşı

MSD
Medical Science & Discovery

OP. DR. ERSİN ARSLAN'IN ANISINA

Hastanemize adını veren Op.Dr.Ersin Aslan, 14 Mart 1982'de Gaziantep ilimizde doğdu. 6 çocuklu mütevazı bir ailenin 5. çocuğuydu. İlköğretimine Şehit Nafi Kıvanç İlkokulu'nda tamamladı. Ortaokulu Yavuzeli yatılı Bölge Okulun'nda, liseyi ise 19 Mayıs Lisesin'nde okudu. 2000 yılında kazandığı Karadeniz Teknik Üniversitesi Tıp Fakültesin"nden 2006 yılında tıp doktoru olarak mezun oldu. Aynı yıl kazandığı Gaziantep Üniversitesi Tıp Fakültesi Göğüs Cerrahisi Anabilim dalında, uzmanlık eğitimini Ekim 2011'de tamamladı. 6 Kasım 2009 tarihinde kendisi gibi tıp doktoru olan Dr. Sibel Arslan ile hayatını birleştirdi. Aralık 2011"de Gaziante; Av. Cengiz Gökçek Devlet Hastanesi'nde (şikdiki adıyla Dr. Ersin Arslan Devlet Hastanesi) devlet mecburi hizmetine başladı.

Op. Dr.Ersin Arslan hekimliğe başladığı ilk günden itibaren tıp bilimi ve mesleğinin gerektirdiği şekilde onurlu ve bilimsel duruşu, çalışkan, dikkatli, düzenli kişiliği ile çağdaş ve nitelikli bir Türk hekimi olmanın örneğini verdi. Zor ve çileli asistanlık döneminde bile sürekli güler yüzlüydü. Her şeyden öte hastalarına nazik, sevecen ve insalcil kişiliği ile yaklaşırdı. Mesleği konusunda idealist bir insandı. Hastalarını kendinden düşünürdü. Dürüstlüğü, çalışkanlığı ve potansiyeliyle akademisyen olması gerektiği konusunda Anabilim dalındaki öğretim üyeleri ve meslekdaşları arasında fikir birliği olmuştu.

Mecburu hizmeti bittiğinde Gaziantep Üniversitesi Tıp Fakültesi'nde akademisyen olma ülkü ve azmi olan Op. Dr. Ersin Arslan, mecburi hizmetinin 4. ayında, 17 Nisan 2012 günü, görevi başındayken, sabahtan-öğleye kadarki süreyle 4 cerrahi operasyonu sığdırdıktan sonra, kendi kliniğinde, güpegündüz, insanlık dışı bir şekilde yapılan bıçaklı saldırı sonucu yaşamını kaybetti.

Op. Dr. Ersin Arslan'ın katledilmesiyle, sağlık sistemi ve Gaziantep halki yetenekli ve bilgili bir uzman doktorunu kaybetmekle kalmadı, ülkemiz ve bizler de geleceğimizin bir parçasını kaybettik. Ersin'e saplanan hançer aslında sadece onun naçiz vucuduna değil, sağlk çalışanlarının ve hatta tüm milletimizin bağrına, umutlarımıza, geleceğimize, hayata bakışımıza saplanmıştır. Ölen Ersin değildi aslında... ölen hepimizdik... Onun açtiği yol bizlere ebediyen ışık tutacak, canı ile verdiği mücadele bizlere ilelebet örnek olmaya devam edecektir.

Ruhun Şad Olsun

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Plasma adrenomedullin levels in patients with migraine during naturel attack and attack free period

Aylin Akcalı[1], Sirma Geyik[1]*, Ilker Dogru[2], Arzu Dogru[2], Muhittin Yurekli[3], Abdurrahman Neyal[4], Ayse Balat[5], Ayse Munife Neyal[1]

Abstract

Objective: The role of Calcitonin gene related peptide (CGRP) in migraine has been demonsrated. The aim of this study was to examine the role of Adrenomedullin (AM) which is a member of the calcitonin/CGRP/amylin family in migraine patients during naturel attack and attack free period.

Material and Method: Twenty-six migraine patients (11 with aura, 15 without aura) and 26 healty participants were involved. Blood samples were obtained from each patient in attack and attack free period, then compared with each other and control group.

Results: Mean plasma AM levels were 19 pmol/l during migraine attacks, 25.23 pmol/l between attacks, and 33.01 pmol/l in the control group. AM levels of migraine patients were significantly lower than controls during non-attack periods (p=0.001) and more interestingly, it further decreased during attack periods (p=0.001). A comparison of the mean plasma AM levels of migraine with and without aura cases revealed the same statistically significant difference (p=0.001).

Conclusion: The persistently low AM levels in migraine patients gave the impression that in physiological conditions there may be a balance between CGRP and AM and this may be changed towards to the site of CGRP in migraine pathophysiology while causing a decline in AM levels as we had found. Further studies regarding on AM involvement in migraine pathophysiology are needed to confirm these results.

Keywords: Adrenomedullin, calcitonin/CGRP/amylin family, headache, migraine, pathophysiology

Introduction

Pivotal role of Calcitonin gene related peptide (CGRP) in migraine mechanisms has been recognized long ago (1-4). Although studies have demonstrated that CGRP infusion might trigger and CGRP antagonists effectively limit the migraine attacks in migraine sufferers (5,6). About 20 years ago, Goadsby et al. (1) reported higher serum CGRP levels in the internal jugular vein blood during migraine attacks, but another study couldn't verify these results (7). Due to these conflicting results it is still uncertain whether serum CGRP levels change during the natural course of migraine attack (8). Adrenomedullin (AM) that was originally isolated from human pheochromocytoma cells belongs to CGRP super family (9). Two of the major sources for AM are endothelial and vascular smooth muscle cells. The vasodilator effect of AM may be important in the maintenance of resting vascular tone and regulation of specific blood-brain barrier properties (2,10). Because of higher concentration of AM, it may be especially important in the cerebral circulation (11). Due to its similarities to CGRP, AM was also suggested to have a possible role in migraine pathophysiology (12). Animal studies have all shown the vasodilator effect of AM and increase in cerebral blood flow (CBF) (10,13). However in Petersen et al. (14) study intravenous AM is not a mediator of migraine headache and does not affect CBF and mean blood flow velocity in the middle cerebral artery (VMCA). Therefore

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[1]Gaziantep University Faculty of Medicine, Department of Neurology, Gaziantep-Turkey
[2]Aksaray University Faculty of Science and Letters, Department of Biology, Aksaray-Turkey
[3]Inonu University Faculty of Science and Letters, Department of Biology, Malatya-Turkey
[4]Dr. Ersin Arslan State Hospital, Clinic of Neurology, Gaziantep-Turkey
[5]Gaziantep University Faculty of Medicine, Department of Pediatrics, Gaziantep-Turkey
*Corresponding Author: Sirma Geyik E-mail: drsirmageyik@hotmail.com

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in the present study we aimed to show the relationship between the AM during nature attack, without attack in migraine patients and the control group.

Material and Methods

Study population

Twenty-six patients, aged 18-50 years, diagnosed with migraine, according to International classification of headache disorders-2 criteria (15) and age, gender matched 26 healthy subjects were enrolled to study. Local ethics committee approved the study and written informed consents have been obtained from all included cases before the enrolment. Migraine patients who reported having chronic migraine or headache due to drug overuse were not included in the present study. Exclusion criteria were; presence of high arterial blood pressure (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg), body mass index (BMI) <18 and ≥30 kg/m^2, history of renal functional disorders, endocrinological disorders, rheumatological diseases, peripheral vascular disease, inflammatory conditions, active cancer, diabetes mellitus (hunger plasma glucose ≥126 mg/dL), hypercholesterolemia (>200 mg/dL), pregnancy or lactation and regular use of vasoactive drugs. The medical information and physical and neurological examination findings of the study patients and the control group were recorded on a previously structured form by an experienced neurologist. Routine laboratory studies of the patients included routine blood tests; serum electrolytes, serum creatinine, blood urea nitrogen and fasting blood glucose levels; liver function tests; cranial tomography or cranial magnetic resonance imaging were performed in all patients. The glomerular filtration rate (GFR) was calculated by modification of diet in renal disease (16).

Collection of the plasma samples

Ten mL blood samples were taken from the cubital vein of migraine patients during attacks (when they still had pain and before they took any medicine) and also during non-attack periods when they had no complaints at least for 48 hours and from healthy control group patients on any day. The samples were placed in tubes containing 0.6 trypsin inhibitor unit/mL aprotinin. The tubes were gently shaken shortly and following a 15 minutes rest they were centrifuged for 10 min at 1.600 g/min. The obtained plasma samples were stored in deep-freeze at -20 ˚C until the examination time.

Adrenomedullin study technique

The residual erythrocytes in the plasma were removed from the bottom by filtration and washed with isotonic (9.0 g/L NaCL) for 10 times. Red blood cell sediment was destroyed with adding ice-cold deionized water. Harmless hemolysate was obtained through centrifugation at 10.000 xg for 5 min. Plasma AM level was measured with high performance liquid chromatography (HPLC) in picomole/l. The obtained fluid was applied to Super Coil C18 columns (Cecil 1000 HPLC, Super co, Cambridge UK). The applied material was mixed with 60% acetonitrile in 0.1% trifluoro acetic acid. Rat AM (1-50 pm/mL) (Phoenix Pharmaceuticals Mountain View CA, USA) (Figure 1) was used to determine standard AM levels (14). The investigators who quantified the AM plasma levels were blind to attack, non-attack and control samples.

Statistical analysis

The socio demographic and clinical characteristics of the patients and controls were given as a simple distribution. Chi-square and Fisher's exact tests were used to compare the socio demographic and clinical characteristics of the patients and controls. Student t-test was performed to examine the relationship of quantity variables such as age range between the patients and controls. To compare the two-implementation groups, Student's t tests for normally distributed continuous variables and Mann Whitney U test for non-normal variables, and Anova test was performed to compare groups according to continuous variables. And least significant difference test was used to detect subgroup differences. Spearman correlation analysis was performed to examine the relationship between the laboratory results and the AM levels. The p values lower than 0.05 was accepted as significant. Mean and Standard deviations and percentages were given as descriptive statistics. Package for the Social Sciences for Windows (SPSS, version 20.0, Chicago, IL, USA) software was used for statistical evaluation.

Results

The clinical characteristics of the control group and migraine patients are summarized in Table 1. The patient and control groups were similar in terms of age and gender. No significant differences were found in the mean arterial pressure and

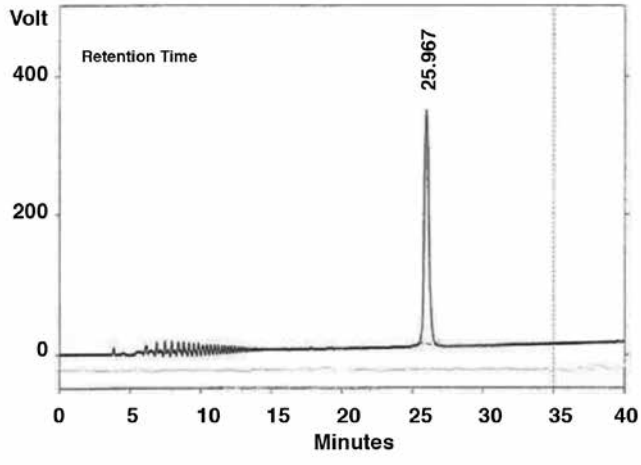

Figure 1. Standart human adrenomedullin retention time

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biochemical laboratory tests (Table 1). Of a total of 26 individuals in the migraine group, 11 had migraine with aura (42.3%) and 15 had migraine without aura (57.7%). Mean plasma AM levels were 19.00±4.25 pmol/l (in a range of 14.65 pmol/l and 25.48 pmol/l) during migraine attacks, 25.23±5.2 pmol/l (in a range of 20.08 pmol/l and 30.98 pmol/l) between attacks, and 33.01±6.8 pmol/l (in a range of 22.47 pmol/l and 41.09 pmol/l) in the control group (Figure 2). The mean serum AM level in attack period was significantly lower than that of the non-attack period samples in migraine cases (p=0.001). There were statistically significant relations between migraine groups and control group (p=0.001). A comparison of the mean plasma AM levels of migraine with aura during attack and attack free period (respectively; 18,62± 5.87 pmol/L and 25.23±4.3 pmol/L, p=0.001) revealed statistically significant difference. The result was the same in migraine patients without aura (respectively; 18.95±3.8 pmol/l / 26.01±4.3 pmol/l, p=0.001). When we compared with the aura group between the group without aura during attack there was no statistically significant difference (p=0.646). The result was the same in with the aura group between the group without aura between attack (p=0.606). The associations between the plasma AM concentration and the BMI, mean arterial pressure (MAP) and GFR in the control and patient groups are summarized in Table 2. When we seperate the groups by gender there were no statistically significant difference in attack period, between attack period and in the control group (Table 3).

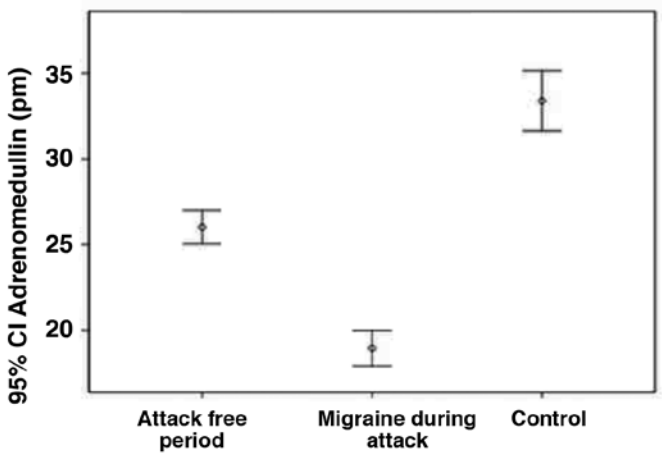

Figure 2. Plasma adrenomedullin levels in migraine patients with and without attacks and in controls

CI: Confidence interval

Discussion

In the present study, the plasma AM levels in migraine patients were significantly lower than that of control cases in attack-free period and it decreased to much lower levels during the

Table 1: Characteristics of the study subjects

	Control, n=26	Patients between attack n=26	Patients during attack n=26	p
Age (years)	28.12±5.89 (18-48)	28.65±5.87 (19-47)		0.349
Male:female ratio (n=n)	17:9	22:4		0.472
BMI	25±2.1	26±2.8		0.285
MAP (mmHg)	50±8	55±6	52±8	0.398
BUN (mg/dL)	20.03±3.36	20.95±4.46		0.416
Scr (mg/dL)	1.3±0.25	1.2±0.3		0.428
GFR (mL/min)	101±9	98±7		0.105
Plasma glucose (mg/dL)	95±8.2	86±6.8		0.286
CRP (mg/dL)	3.4±1.8	2.9±0.9		0.102

BMI: Body mass index, MAP: Mean arterial pressure, BUN: Blood urea nitrogen, Scr: Serum creatinine, GFR: Glomerular filtration rate, CRP: C-reactive protein

Table 2: Correlation coefficients (r) of simple regression analysis for relationships between body mass index, mean blood pressure, glomerular filtration rate, blood urea nitrogen, serum creatinine and plasma levels of adrenomedullinin patients and control groups

	BMI Corr.r/p value	MAP (mm/Hg) Corr.r/p value	BUN (mg/dL) Corr.r/p value	Scr (mg/dL) Corr.r/p value	GFR (mL/min) Corr.r/p value
Plasma levels of AM in patients	0.117/0.17	0.243/0.24	0.34/0.07	0.16/0.09	-0.39/0.068
Plasma levels of AM in control group	0.212/0.19	0.32/0.21	0.46/0.06	0.22/0.08	-0.42/0.06

BMI: Body mass index, AM: Adrenomedullin, MAP: Mean blood pressure, BUN: Blood urea nitrogen, Scr: Serum creatinine, GFR: Glomerular filtration rate

attacks. When we divided the patient group migraine with aura and without aura the results were similar. Low plasma AM levels in migraine cases may suggest a biological interaction and/or a possible variation in AM synthesis and release in migraine patients. Anyway, we can state that migraine cases have persistently low AM plasma levels. It is now well known that CGRP has an important role in migraine pathophysiology. Due to its similarities to CGRP, AM was also suggested to have a possible role in migraine pathophysiology (12). Their physiological properties are similar in some aspects. Additionally, calcitonin receptor-like receptors (CL) function both as CGRP and AM receptor, depending on receptor activity modifying protein (RAMP) function that determines which ligand will be bound by CL (17). RAMP1 transforms CL into a CGRP-binding form, while RAMP2 and RAMP3 give it an AM-binding property.

Kis et al. (2) summarized the similarities and differences of these two peptides in terms of migraine pathophysiology.

AM and CGRP are effective on the same receptors (17), yet there are differences in some aspects. For example, AM receptors are expressed from both the endothelial layer and smooth muscle layer of brain vessels, while CGRP receptors are released from perivasculer sensory nerve endings (11,18). Furthermore, CGRP is not expressed in cerebral endothelial cells; whereas, AM is abundantly secreted in brain vessel endothelium (11,19,20). Additionally, CGRP does not have a significant role in regulating the resting muscle tone of cerebral vessels, while AM may play an important role in regulating the resting muscle tone of cerebral vessels (21,22). In fact, although they belong to the same peptide family and bind to the same receptor, we still have insufficient data whether they have an interbalance, mutual effects and interaction in physiological and pathological conditions in human being. An experimental study investigated the behavior of endothelial endo CL receptors in microvascular endothelial cell culture when AM, CGRP and their antagonists are introduced into the environment (23). Akiyama et al., (24) demonstrated that endo CL internalization as a result of AM introduction could be blocked by both AM and CGRP antagonists (AM22-52 and CGRP8-37) and that desensitized receptor due to binding to AM was also desensitized against CGRP. Akiyama et al. (25) suggested that, the receptor was desensitized against both of these two peptides, regardless of with which it encounters. Also previous studies revealed that AM presynaptically inhibits the neurotransmission of rat mesenteric resistance arteries in perivascular CGRPergic nerves, possibly by reducing CGRP release. The results of these studies raise the question whether an imbalance of CGRP and AM functions may cause physiological or pathological consequence in humans.

A recent study in 12 migraine patients (14) demonstrated that AM infusion didn't alter CBF and VMCA which contrasts to animal studies (10) and didn't trigger migraine attacks in migraine patients. Based on these findings the conclusion of this study was made as AM might not have a role in migraine attacks. However, according to our results, lack of AM may be associated with migraine attacks. In physiological conditions there may be a balance between CGRP and AM and this may be changed towards to the site of CGRP in migraine pathophysiology while causing a decline in AM levels as we had found.

Some studies showed that several factors influence plasma AM levels, e.g. age and eGFR (26,27). Gender was one of the significant factors for plasma AM levels (28). Kawano et al. (28) also showed that plasma AM levels were correlated with BMI and waist circumference in women, but not in men. In our study When we seperate the groups by gender there were no statistically significant difference in attack period, between attack period and in the control group.and there were no significant associations between the plasma AM concentration and the BMI, MAP, GFR in the control and patient groups. However the clinical characteristics of the control group and migraine patients are similar.

In this study, the blood samples were drawn from the cubital vein in all of the included cases and the reported AM levels were from the peripheral circulation. This is one of the limitations of the present study. We would assess the results much accurately if we could obtain blood samples from more central veins. However, permission could not be obtained from our local ethics committee due to the lack of sufficient data on the role of AM in migraine pathophysiology.

Simultaneous CGRP levels were not examined in this study that may be considered as another limitation. However, in the extent

Table 3: Comparison of plasma levels of adrenomedullinin levels (ng/mL) in the patient and control groups

	Female (AM ng/mL)	**Male (AM ng/mL)**	**p**
Migraine patients during attack	18.95±2.3 (n=22)	20.02±1.6 (n=4)	0.215
Migraine patients between attack	26.01±4.2 (n=22)	26.78±2.1 (n=4)	0.416
Control group	33.38±4.8 (n=17)	33.38±5.1 (n=9)	0.698

AM: Adrenomedullin

of our knowledge, this is the first study reporting low plasma AM levels in the natural course of migraine patients.

Conclusions

Our results indicate that low plasma AM levels may be important in migraine pathophysiology. Studying AM together with CGRP and/or other pain modulators in peripheral and maybe also in cerebral circulation may provide new information about migraine pathophysiology. Notifying the potency of CGRP antagonists in terminating migraine attacks, it may be supposed that along with the CGRP itself, the receptor site may be an important partner in pathophysiological mechanisms of migraine. Moreover, since AM is a multifunctional peptide, it may sustain its effect on migraine attacks through some other ways regardless of CGRP. Furthermore, this study is the first about the serum AM levels during the nature attack of migraine patients in literature.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Factors affecting the burden on caregivers of stroke survivors in Turkey

Umit Gorgulu[1]*, Ulku Polat[2], Burcu Bayrak Kahraman[2], Sukru Ozen[2], Ersin Arslan[3]

Abstract

Objective: Caring for stroke patients leads to caregiver strain. Caregiver burden following stroke is increasingly recognised as a significant health care concern. This study was conducted to determine factors affecting the burden on caregivers of stroke survivors.

Material and Method: This was a descriptive study. Eighty caregivers of stroke patients hospitalized in the intensive and intermediate intensive care clinics of the Neurology Department of the Gazi University Health Research and Application Centre were included in the study. The caregiver introductory form, Barthel index (BI), National Institutes of Health Stroke Scale, Pittsburgh sleep quality index (PSQI) and caregiver burden scale (CBS) were used to collect the data.

Results: In our study, a significant negative relationship (r=-0.854, p=0.000) was determined between the mean BI scores (24.55±7.69) and the mean CBS scores (57.52±14.35) and a significant positive relationship was determined between the mean CBS and the mean PSQI daytime dysfunction sub-component scores (1.30±1.42; r=0.223; p=0.046).

Conclusion: The burden of care could become so excessive as to negatively impact the caregivers' sleep quality. Our study has demonstrated that caregiver burden increased as the level of independence of stroke patients decreased and daytime dysfunction sleep disorder became more prevalent as the caregivers' burden increased. To reduce the negative impact of burden of care, influencing factors should be determined.

Keywords: Caregivers, sleep, stroke, survivors

Introduction

Stroke is defined as an acute neurological disorder that develops after the decrease of cerebral blood flow in a certain part of the brain caused by vascular damage (1). Causing mortality and morbidity, stroke is an important disease and is the second leading cause of death in the world and in our country, Turkey (2,3). Complete recovery is not possible for many stroke survivors and these patients have to suffer permanent cognitive and functional sequelae for the rest of their lives. In this period, patients and their caregivers try to cope with many problems such as regression in musculoskeletal system functions, nutritional changes, elimination and loss of senses, and they try to adjust to changes in their daily lives (4). The care of stroke patients is usually undertaken by family members. McCullagh et al. (5) reported that it is identified that 70% of caregivers are the patient's spouse and 22.8% are the patient's child.

In our country, generally caregivers are the family members of the patient and caregiving is perceived to be an interfamilial responsibility (6). In our country, in a similar study conducted by Asiret and Kapucu (7), it is indicated that 42.9% of caregivers are the patient's spouse and 50% are the patient's child. Caregiving, defined as the process of undertaking caregiving activities and responsibilities, does not merely consist of meeting the physical needs of patients, it also requires the caregiver to provide the patient with emotional, social, and financial support (6,7). From this point of view, the multi-dimensional functional disorder of the patient entails extensive and long-term care and affects not only the patient but also the patient's relative who undertakes the caregiving responsibility (8,9). Being a difficult process, post-stroke caregiving may affect the caregiver in certain respects such as her/his physical and emotional health, work life, and social relations (8). As caregiving responsibilities increase, the relationship between the caregiver and care receiver may turn

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[1]Nizip State Hospital, Clinic of Neurology, Gaziantep-Turkey
[2]Gazi University Faculty of Medicine, Department of Nursing, Ankara-Turkey
[3]Dr. Ersin Aslan State Hospital, Clinic of Thoracic Surgery, Gaziantep-Turkey
*Corresponding Author: Umit Gorgulu E-mail: drumitgorgulu@hotmail.com

into a one-sided, dependent, and lasting obligation that causes discomfort in the caregiver's life. This situation is known as 'caregiver burden'. Caregiver burden is defined as the physical, psychological, and financial responses that may be observed during the caregiving process and occurs when the caregiver suffers from difficulties, experiences high levels of strain, feels pressure, and undertakes the caregiving burden (9,10,11). After a while, various problems emerge that influence the health condition of the caregiver. Not allocating enough time for his/her self-care, chronic fatigue, changes in body weight, sleep disorder, muscle pain (myalgia), and concentration impairment are common problems. Doubtless, the caregiving burden of the caregivers of stroke patients is affected by and differentiated according to the level of dependence, personal characteristics, and the duration of the caregiving process. Likewise, in a study conducted by Mollaoglu et al. (6) a significant positive relationship was found between the level of dependence of patients and the caregiving burden of their caregivers. When the related literature on strokes is examined, although the post-stroke caregiving burden and the affecting factors are frequently addressed, it is observed that the problems encountered by caregivers are mentioned less and their sleep quality is not evaluated at all (6,7,9,12-14). In our study, we aimed to compare the level of functional independence of stroke patients and the burden of care and sleep quality of caregivers.

Material and Methods

The caregivers of stroke patients hospitalized in intensive and intermediate intensive care clinics of the Neurology Department of the Gazi University Health Research and Application Centre were included in the population of the cross-sectional study. The study included caregivers of 80 patients, who were literate, did not have communication difficulties, and who participated voluntarily. Data collection instruments used in the study were the caregiver introductory form, Barthel index (BI) and National Institute of Health Stroke Scale (NIHSS) for the identification of the independence levels of the patients, Pittsburgh sleep quality index (PSQI) to identify the quality of sleep of caregivers, and the caregiver burden scale (CBS) to define the burden of caregivers.

Instruments

Barthel index

The BI, is frequently used for the evaluation of daily functions, and was developed by Mahoney and Barthel in 1965 (15). This index measures the independence of a person in activities of daily living without help; such as feeding, toileting, bathing, and movement inside and outside a building. Its validity and reliability studies were conducted by Kucukdeveci et al. (16) with neurology patients. The total score of the index is 100; scores of 0-20 mean a person is fully dependent, 21-61 severely dependent, 62-90 moderately dependent, 91-99 slightly dependent, and 100 fully independent (16).

Caregiver burden scale

The CBS was developed by Zarit et al. (17) in 1980 in order to measure the stress of caregivers providing assistance to a person or elderly people needing care. The validity and reliability studies of the scale in Turkish were conducted by Inci and Erdem (18) in 2006. The scale, which can be filled in by either the caregiver himself or through questions by a researcher, is comprised of a series of 22 questions that determine the effects of caregiving on the life of caregivers. The tool has a five-point Likert-type assessment scale that ranges from '0=never' to '4=almost every time'. The minimum possible score is 0 and the maximum score is 88. The sections on the scale are generally related to social and emotional dimensions and high scores on the scale indicate high levels of discomfort (18).

Pittsburgh sleep quality index

This index was developed by Buysse et al. (19) in 1989 and provides detailed data on the type and severity of sleep quality and sleep disorder during the previous month. Its validity and reliability studies in Turkey were conducted by Agargun et al. (20) in 1996. The scale includes 24 questions and is comprised of seven components. These are: Self-rated sleep quality, sleep latency, sleep duration, habitual sleeping activity, sleep disorder, use of sleeping pills, and daytime dysfunction. The total points received in these seven components give the total scale score, which is between 0-21. A high total score indicates low quality of sleep (20).

National Institute of Health Stroke Scale

This scale, which is used in the observation of stroke patients to determine the severity of stroke, was designed by the US National Institute of Health (21). The scale measures level of consciousness, conscious responses to questions, response to commands, extra-ocular muscle movements, visual fields, facial palsy, motor strength of lower and upper extremities, limb ataxia, sensory loss, aphasia, dysarthria, and neurological neglect. It grades the existing problems on a two- to three-point scale (0-3 points, according to the question) and is comprised of a total of 11 components, one of which has three sub-components. In total 36 points can be scored on the scale and lower scores indicate better post-stroke clinical condition (21).

Statistical analysis

The Statistical Package for Social Sciences version 16.0 program was used in the evaluation of the data in our study. Percentage, average, Student's t-test (for independent samples), Mann-Whitney U test, Kruskal-Wallis test, one-way analysis of

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variance (ANOVA), and Pearson correlation analysis were used in the statistical analysis.

Ethical considerations

In order to conduct the study, written permission was received from the Gazi University Social Studies Ethics Committee (January 25, 2013/No: 66868116-604.01.02-15-1934). Directorate, the institution where the study was conducted, and also from the volunteers who took part in the study.

Results

The average age of participants in the study was $\overline{X}$=46.10±16.21; 76.3% of the participants were female, 76.3% married, 80% had children, and 32.5% were primary school graduates. Half of the caregivers (50%) stated that they lived with the patient, 82.5% gave one to six months of care and nearly half (48.8%) stated that they provided care without any help from others. Fifty-five percent of stroke patients were cared for by their children and 21.3% by their spouse. Regarding caregiving, it was indicated that 36.3% neglected their self-care, 32.5% had problems in interpersonal relations, and 26.2% had economic problems. Additionally, it was identified that the majority of caregivers (73.8%) did not have prior caregiving experience and the great majority of them (86.2%) had poor health. According to the BI score, in terms of the levels of dependence of the patients, 41.3% of the patients were fully dependent and 23.8% of them were severely dependent (Table 1).

When the average scores of the CBS are examined according to the demographic characteristics of caregivers, a statistically significant relationship was not observed between the scores in the CBS and the age, gender, educational status, economic status, or parental status of caregivers, as well as the duration of caregiving. However, a statistically significant relationship was determined between their marital status, their prior caregiving experience, poor health, and their scores on the CBS. In our study it was identified that the CBS score of single caregivers who had prior caregiving experience and poor health was higher than those of caregivers who were married, had no prior caregiving experience, and poor health (Table 1). There was a statistically significant relationship between the levels of dependency of the patients and their average score on the CBS.

In our study, it was determined that the average NIHSS score of stroke patients is 7.86±7.99, average BI scores are 24.55±7.69, average CBS score is 57.52±14.35 and PSQI score is 7.40±3.18. When the NIHSS and BI scores of stroke patients are compared with their total scores on the CBS and PSQI, a significant positive relationship was found (r=0.854, p=0.000; r=0.223, p=0.046) between average BI scores ($\overline{X}$=24.55±7.69) and CBS scores ($\overline{X}$=57.52±14.35), but a significant relationship was not found (r=0.080, p=0.482) between average BI scores ($\overline{X}$=24.55±7.69) and PSQI scores ($\overline{X}$=7.40±3.18). When the relationship between the sub-components of the BI and PSQI are examined, a significant positive relationship was observed (r=0,854, p=0.000; r=0.223, p=0.046) between the sub-component of CBS (57.52±14.35) and sub-component of daytime dysfunction ($\overline{X}$=1.30±1.42). However, a significant relationship was not found (p>0.05) between the NIHSS scores ($\overline{X}$=7.86±7.99) and the average score of PSQI scores ($\overline{X}$=7.40±3.18) and the CBS scores ($\overline{X}$=57.52±14.35) (Table 2).

Discussion

Post-stroke care of patients is provided primarily by family members. Also it was determined in our study that stroke patients are provided care firstly by their children and spouses. In a study conducted by Hung et al. (22) on caregivers of stroke patients, it was indicated that the majority of caregivers are the spouse (44%) and children (33%) of the stroke patient. In another study by Akosile et al. (23), it was found that 55.2% of stroke patients are provided care by their children. In another study conducted in our country, it was found that half of stroke patients are cared for by their children (7). This situation might be their voluntary decision; it may also turn out to be an absolute necessity due to the insufficient number of places in institutions providing care for stroke patients. For our country, providing care to stroke patients within the family is a reflection of our cultural structure.

Stroke caregivers may encounter many emotional, cognitive, economic, and social problems (6). Indeed, the participant caregivers in our study often expressed that they neglected their self-care, their interpersonal relations had deteriorated, and they had economic problems. In addition, it was determined in our study that caregivers with poor health had greater caregiver burden. It is thought that these results are associated with the perceived stress and caregiving burden of the caregivers. In certain studies it was indicated that, associated with caregiver burden and stress, caregivers experienced psychosocial difficulties and their physical and mental health and self-care behaviour was affected (24,25). In another study conducted by Tuna and Olgun (9), more than half of the caregivers stated that their health was adversely affected due to the caregiving process and that they experienced physical and psychological problems. It is thought that these problems have a negative effect on caregivers' quality of life. In studies conducted with the aim of determining the caregiving burden and quality of life of post-stroke caregivers, it was indicated that an increase in care burden decreased quality of life (5,14,22).

It was indicated in the related literature that the increase in the burden of caregivers was caused by the intense stress they

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Table 1: Average caregiver burden scores according to introductory characteristics of caregivers				
Characteristics	**n**	**%**	**$\bar{X}$±SD**	**p**
Age (years)				
20-34	20	25.0	55.65±12.11	p=0.224[a]
35-49	26	32.5	61.00±14.49	
50-64	25	31.3	53.52±16.06	
65 and above	9	11.3	62.77±11.16	
Gender				
Male	61	76.2	57.77±14.91	p=0.756[b]
Female	19	23.8	56.73±12.69	
Marital status				
Married	61	76.2	55.54±14.94	*p=0.025[b]
Single	19	23.8	63.89±10.14	
Parental status				p=0.660[b]
Have children	64	80.0	57.01±14.56	
Do NOT have children	16	20.0	59.56±13.70	
Educational status				
Literate	5	6.3	67.40±14.44	p=0.131[a]
Primary school	26	32.5	51.80±13.37	
Secondary school	10	12.5	58.90±11.76	
High school	21	26.3	60.57±16.02	
University	18	22.5	58.72±13.29	
Economic status				
Good	16	20.0	56.56±13.02	p=0.527[b]
Fair	64	80.0	57.76±14.74	
Degree of caregiver relationship closeness				
Spouse	17	21.3	55.47±17.75	**p=0.005[a]
Child	44	55.0	62.40±12.52	
Attendant	4	5.0	46.00±12.46	
Mother	5	6.3	46.00±6.20	
Other	10	12.5	49.90±10.31	
Living together with the patient				
Living	40	50.0	58.80±16.48	p=0.430[c]
NOT living	40	50.0	56.25±11.92	
Duration of caregiving				
1-6 months	66	82.5	56.72±14.23	p=0.209[b]
7 months and longer	14	17.5	61.28±14.83	
Manner of caregiving				
Without help	39	48.8	57.23±14.76	p=0.859[c]
With help	41	51.3	57.80±14.12	
Prior caregiving experience				
Have	21	26.3	52.09±13.89	*p=0.031[b]
Have NOT	59	73.8	59.45±14.12	
Health problem				
Have	69	86.3	59.18±13.75	*p=0.012[b]
Have NOT	11	13.8	47.09±14.20	
Level of dependence according to Barthel index score* **				
0-20 points	33	41.3	59.45±13.70	**p=0.037
21-60 points	19	23.8	59.21±12.83	
61-90 points	18	22.5	59.00±15.13	
91-100 points	10	12.5	45.30±13.67	

[a]: Kruskal-Wallis test for, [b]: Mann-Whitney U Test was used for, [c]: Student's t test for, SD: Standard deviation, *Mann-Whitney U Test p<0.05, **Kruskal-Wallis test p<0.05, ***Pearson correlation between the average scores of Caregiver Burden scale and Barthel index: R=-0.232, p=0.039

experienced, adversely affecting their physical and emotional health, working and social life, and economic status. In addition, it was also stated that the caregiver experienced difficulties especially regarding his/her mental health and social life and that there was a significant positive relationship between caregiver burden and health-related quality of life (8,26,27). In a study conducted by van den Heuvel et al. (13) to determine the burnout risk factor of caregivers, it was indicated that younger caregivers with poor physical health had higher risk factors for burnout. Rombough et al. (28) indicated a significant positive relationship between the health problems of caregivers and caregiver burdens. Mollaoglu et al. (6) observed that caregivers with health problems had higher scores of caregiver burden.

It is known that caregiver burden is affected by many factors regarding the caregiver and their patient (11). These factors are the caregiver's age, gender, marital status, degree of caregiver's relationship closeness, educational status, economic conditions, and the patient's cognitive and functional inadequacies, presence of caregiving assistance, and the personal characteristics of the patients (7,11,29). In our study, it is indicated that the caregiving burden of single caregivers is greater than those of married ones. A similar result was obtained in a study conducted by Zaybak et al. (30) for the identification of caregiving burden of caregivers of bedridden patients, where it was observed that caregiver burden was greater for single caregivers. The reason for this is that single caregivers receive less support from other people in caregiving activities and that their coping abilities are insufficient. It was also established in our study that caregivers who do not have prior caregiving experience have a greater burden. This is supported by results of other studies (11,31).

In addition to this, a significant negative relationship has been found between the levels of dependence of stroke patients and the CBS score. It was established in some studies that as the level of dependence increases, daily life activities of the patient deteriorate and in further stages there occurs a significant increase in caregiver burden (32-36). Similarly, in a study conducted by Mollaoglu et al. (6) significantly high scale scores were observed on the part of caregivers whose patients are dependent according to the BI and who meet all patients' needs. Parallel to the results of our study, Carod-Artal et al. (37) indicated a negative relationship between the functional status of stroke patient caregivers and caregiver burden.

In our study, a significant positive relationship was found between caregiver burden and daytime dysfunction among the sub-components of the PSQI. Sleep disorder is mentioned in the literature among the most important problems that caregivers suffer (7,35,38,39). Asiret and Kapucu (7) indicated that relatives of patients encounter psycho-social problems, fatigue, and sleeplessness. In a study conducted with caregivers of patients with congestive heart failure, it was indicated that 90% of caregivers suffered from sleep disorders (39).

In a study conducted by Creese et al. (38) with Alzheimer patients, it was indicated that 63% of caregivers had sleep problems. Das et al. (40) determined in their study that caregivers of stroke patients have physical, mental, and economic stress, anxiety and depression (76%), and sleep disorders (43%) associated with increasing burden (70%). The results from these studies show that it is important to know and reveal factors affecting the burden on caregivers of stroke survivors in order to improve the quality of life of patients and their caregivers.

Conclusions

Individuals who care for stroke patients have difficulty in many areas, and this increases the burden of their care. As a result of our study, it is determined that caregivers suffer health problems associated with their caregiving burden and as the functional

Table 2: Comparison of National Institute of Health Stroke Scale, Barthel index, sleep quality, and caregiver burden scale scores of stroke patients

Scales	Average scores
National Institute of Health Stroke Scale	7.86±0.99
Pittsburgh sleep quality index*	7.40±3.18
Self-rated sleep quality	1.16±0.64
Sleep latency	2.68±1.53
Sleep duration	0.81±0.87
Habitual sleeping activity	0.08±0.39
Sleep disorder	1.72±0.67
Use of sleeping pills	0.10±0.37
Daytime dysfunction	1.30±1.42
Caregiver burden scale*	57.52±14.35

*The Pearson correlation between average scores of caregiver burden scale and daytime dysfunction is 0.223, p=0.046<0.05

levels of dependence of patients decline, their caregiving burden increases. In addition, it was observed that daytime dysfunction is more prevalent among sleep disorders associated with the increase of caregiving burden. This descriptive analysis demonstrates the important relationship between level of functional independence of patients, caregiver burden and sleep quality, and can lead to interventions to diagnose and treat sleep disorders and develop strategies to improve the quality of life of caregivers.

In light of these results, it is recommended that care providers' burdens should decrease with cooperation of the family members and should provide all necessary support and assistance, and should direct them to the support groups. In addition, it is advised that the burden of caregivers of stroke patients and the factors affecting it, should be defined and health professionals should include caregivers in the care plan while examining patients because caregivers may experience negative health effects.

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The effects of acupuncture on nausea and vomiting and consumption of propofol in cesarean section performed with spinal anesthesia

Ertugrul Kilic[1]*, Mehmet Levent Uygur[1], Murat Surucu[1], Ferdi Doganay[2], Erhan Hafiz[3]

Abstract

Objective: The incidence of hypotension is 50-60% in obstetric surgeries. The most frequent comorbid clinical case of hypotention is nausea and vomiting. In addition, the probability of vomiting and nausea is very high in the period in which the peritoneum is holden after the birth of newborn. We wanted to observe the effects on nausea and vomiting occuring due to both spinal anesthesia and traction of peritoneum during caesarean section performed under spinal anesthesia by using conventional acupuncture techniques.

Material and Method: The study including 90 patients in the I-II risk groups of American Society of Anesthesiologists who will undergone caesarean section was planned. Acupuncture was performed for group A (n=45) by using acupuncture needles from the P6 acupuncture point. Similar application was performed for group P (n=45) by using acupuncture needles from a point 3 cm proximal to P6 point. In both practice, the needle was applied 20 mm depth of the skin and upholden for 30 minutes in the application area. Formation of nausea, vomiting and amount of propofol used was recorded for each patient.

Results: The observation rate of nausea and vomiting in the group A was significantly lower (5, 33 ($p<0.05$); 2, 5 ($p<0.05$)). Propofol consumption rate was also significantly lower (4.6±11.7, 63.0±9.4 mg ($p<0.05$)).

Conclusion: The acupuncture applied perioperatively on P6 point in order to prevent nausea and vomiting in the cesarean section performed with spinal anesthesia is an effective method and also reduces the amount of propofol which will be used to prevent intraoperative vomiting.

Keywords: Acupuncture, cesarean, nause, vomit, propofol

Introduction

Cesarean section is performed frequently nowadays (1,2). While large studies indicate the incidence of hypotension in spinal anesthesia in non-obstetric operations as 33%, this ratio rises to 50-60% in obstetric surgeries and is more common than postoperative pain (3-5). The most frequent comorbid clinical case of hypotension is nausea and vomiting (6). In addition, the probability of vomiting and nausea is very high in the later phases of operations in the period in which the peritoneum is holding after the birth of newborn and clinical conditions causing by this can lead very serious side effects, including aspiration pneumonia (7-9). In addition, the amount of money spent for nausea and vomiting has been shown to be greater than those expended for postoperative analgesia (10).

Several studies in the literature generally focused on drug applications in order to prevent nausea and vomiting which are expected to be occurred in cesarean sections performed under spinal anesthesia (1,2,7,11). The most preferred method for the prevention of nausea and vomiting occurring during cesarean section is administration of subhypnotic doses (1 mg/kg) of propofol (7,11). However, the side effects that may occur due to the applications of these drugs should also be paid attention. We aim to stay away from these side effects by not using drugs.

Nei Guan (P6) point is located between the two tendons in both hands and inner forearm (flexor carpi radialis and palmaris longus) which is 2 cm away from the wrist (12). The practice of acupuncture for this region is performed for hundreds of years for the prevention of nausea and vomiting, treatment of carpal

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[1]Sehitkamil State Hospital, Clinic of Anesthesiology and Reanimation, Gaziantep-Turkey
[2]Dr. Ersin Arslan State Hospital, Clinic of Anesthesiology and Reanimation, Gaziantep-Turkey
[3]Dr. Ersin Arslan State Hospital, Clinic of Cardiovascular Surgery, Gaziantep-Turkey
*Corresponding Author: Ertugrul Kilic E-mail: drertugrulkilic@yahoo.com Phohe: +90 533 630 48 75

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tunnel syndrome and elimination of headache (12,13). Many studies have focused on the effect of acupuncture done on P6 point on postoperative nausea and vomiting (13-16). Minimal adverse effects of this practice are discussed in very few studies (6,17). These studies are on application of acupuncture with different stimulation methods and the techniques such as laser, electrical and manual applications are focused on (17,18). In addition, the studies are usually on postoperative nausea and vomiting. We wanted to observe the effects on nausea and vomiting occurring due to both spinal anesthesia and traction of peritoneum during caesarean section performed under spinal anesthesia by using conventional acupuncture techniques.

Material and Methods

Our prospective, randomized, double-blind study was approved by the local ethics committee. Then, including 90 patients in the I-II risk groups of American Society of Anesthesiologist (ASA) between the ages of 18-40 who will undergo caesarean section was planned.

Patients were taken to preoperative regional anesthesia room, patients' oxygen saturation (SaO_2), noninvasive mean blood pressure (NIBP), heart rate (HR) and heart rhythm were monitored. Intravenous vascular access was opened with 22 G branul and 0.09% sodium chloride was started as 5 mL/kg/hr. Sedation was not implemented. Acupuncture was performed for group A (n=45) by using acupuncture needles from the P6 acupuncture point. Similar application was performed for group P by using acupuncture needles from a point 3 cm proximal to P6 point where we were sure that no impact will occur for P6 point. In both practice, the needle was applied 20 mm depth of the skin and upholden for 30 minutes in the application area. All acupuncture practice was performed by the same anesthesiologist. The follow up of the patients were done by another anesthesiologist.

As follow standard during the operation, patients' NIBP, HR and saturations were monitored. Thirty % reduction according to baseline NIBP or reduction under 70 and more were considered as hypotension. Thirty % reduction according to baseline HR or reduction under 65 and more were considered as bradycardia.

Formation of nausea and vomiting was recorded for each patient. Especially, the amount of propofol used to prevent vomiting of patients with feeling of nausea observing after clamping the umbilical cord of newborn was recorded by another anesthesiologist.

At the beginning of the study, power analysis was performed. Power application was determined to be 90% and α=0.05. Results were assessed as median, mean (±SD) and the number of patients. The exclusion criteria's of the study are identified as the patient's refusal to participating the study, chronic pain syndrome, hyperemesis gravidarum during pregnancy. Kolmogorov-Smirnov Z test (parametric data) was used for the normalization test. The Student-t test was used to compare parametric variables. Mann-Whitney was used to compare non-parametric variables. $P<0.05$ was considered statistically significant. SPSS 15 (SPSS inc., Chicago, IL, USA) statistical analysis software was used for statistical analysis.

Results

The demographic data of patients, and intervention periods are given in Table 1. There was no statistically significant difference between demographic data of patients and their intervention periods.

Between groups, NIBP and HR monitoring are shown in Figure 1 and 2, respectively. There was no statistically significant difference in NIBP and HR monitoring between groups except the NIBP values 5 minutes after spinal anesthesia application. Considering the average value of the NIBP 5 minutes after the spinal anesthesia, the values were statistically significantly lower in group A (72.6±5.5, 75.26±5.6 ($p<0.05$)). In the same period, the rate of observation of hypotension was observed in 19 patients in group A (53.3%) in 24 patients (42.2%) in group P were observed. When considering all patients, this ratio was observed as 43 patients (47.7%). During hypotension period that occurs after spinal anesthesia, 4 of our patients in group A had sense of nausea and vomiting was observed in only 2 patients. In the same period, sense of nausea was observed in 29 patients of group P, vomiting was observed in 27 patients (Table 2).

Nausea and vomiting observation rates between groups in patients in surgery after clamping the newborn's umbilical cord are given Table 2. The observation rate of nausea and vomiting in the group A was significantly lower (5, 33 ($p<0.05$); 2, 5 ($p<0.05$)). Propofol consumption rate was also significantly lower (4.6±11.7, 63.0±9.4 mg ($p<0.05$)).

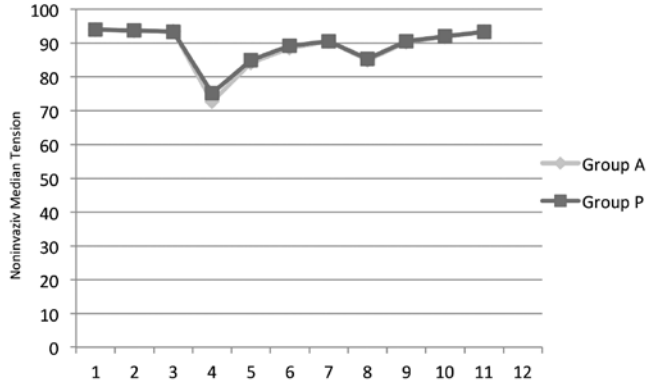

Figure 1. Non-invasive median tension

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Propofol use is given individually for each patient in Figure 3. Propofol was used for 7 patients in group A, propofol was needed for all patients in group P. Maximum 40 mg propofol was used in consumption per person in group A, this amount was observed as 84 mg in group P.

Discussion

We observed in our study that the preoperative P6 acupuncture application in caesarean section performed under spinal anesthesia reduced the nausea and vomiting caused by hypotension due to spinal anesthesia and/or nausea and vomiting occurring during the period of peritoneum clamping and the amount of propofol used in order to prevent nausea and vomiting in the period after the clamping of the umbilical cord of the newborn.

Hypotension observation rates and associated nausea and vomiting are common in cesarean section performed under spinal anesthesia (4,19). In a study conducted by Voigt et al. (20), the incidence of hypotension in cesarean was identified as 46.2%. Intra-operative nausea and vomiting rate was observed as 46.15% in the same study. The most commonly used method for the treatment of nausea and vomiting observed due to hypotension formed by the effects of spinal anesthesia is the use of vasopressor medications, especially the use of ephedrine in order to prevent hypotension (7,19). Considering the side effects of ephedrine used for the treatment of hypotension that occurs after spinal anesthesia in caesarean operations performed under spinal anesthesia, studies have been conducted to identify different doses of ephedrine or new drugs and techniques that can be used instead of ephedrine (4,5,16,21). The positive effects of granisetron on nausea and vomiting were observed in a study conducted by Eldaba and Amr (5). It has been reported in a study conducted by Noroozinia et al. (1) that acupuncture applied on the P6 point had positive effects.

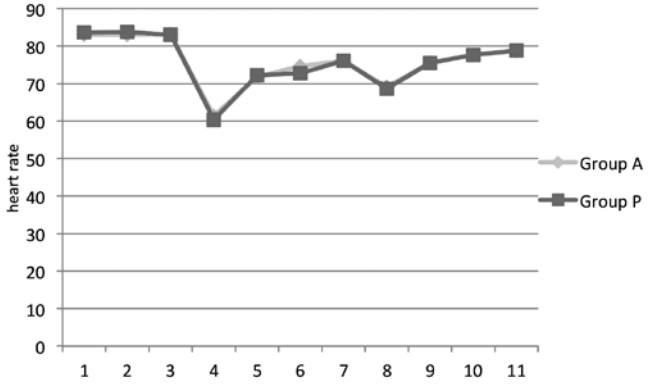

Figure 2. Heart rate between group A and group P

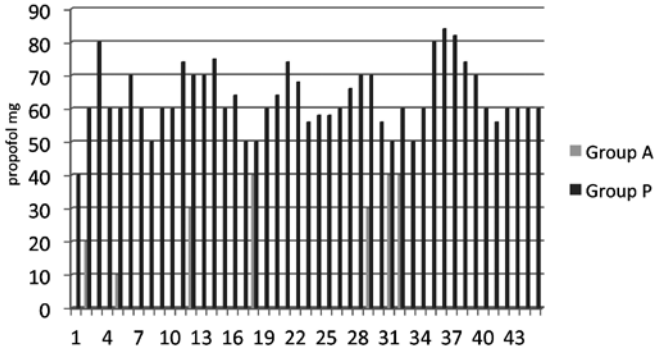

Figure 3. Propofol consumption (mg) per each patient

In our study, the incidence of hypotension after spinal anesthesia was 53.3% in the propofol group and 42.2% in the acupuncture group. Considering the total number, this rate is 47.7%. Despite hypotension was observed more frequently in the acupuncture group, nausea was observed in only 4 (8.8%) patients and vomiting occurred in 2 (4.4%) of them. Considering the same period, the feeling of nausea was observed in 29 (64.4%) patients in the propofol group and vomiting was observed in 27 (60%) of these patients. It was observed that the acupuncture applied on the P6 point had no effect on the occurrence of

Table 1: Comparison of the demographic data of the groups

	Group I (n=45)	Group II (n=45)	p
Age (years)	30.2	30.8	0.5
ASA physical status I/II	28/18	25/20	0.6
Duration of surgery (min)	32.7±2.4	31.4±2.3	0.8

Data means ± standard deviation or number of patient, there are no statistically significant differences between the groups, ASA: American Society of Anesthesiologists

Table 2: Incidence of number of nausea, vomiting and propofol consumption in groups. Data means ± standard deviation or median

	Group A (n=45)	Group P (n=45)	p
Number of nausea post spinal anesthesia 5. min	4	29	0.001
Number of vomiting post spinal anesthesia 5. min	2	27	0.001
Number of nausea after the umbilical cord was clamped	5	33	0.001
Number of vomiting after the umbilical cord was clamped	2	5	0.001
Total propofol consumption (mg)	4.6±11.7	63.0±9.4	0.001

hypotension but was effective in the prevention of nausea and vomiting that can occur during the same period.

It was shown in many studies that the patient's mental status, the formation of hypotension, and traction of visceral peritoneum were effective in the observed occurrence of nausea and vomiting in caesarean section (22-24). It was observed in a study performed by Sane et al. (25) that the mixture of ondansetron and dexamethason administered intravenously 1-2 minutes after the clamping of newborn's umbilical cord was very effective to prevent nausea and vomiting of the mother in surgery that may occur after this period.

In our study, nausea was observed in 5 (11.11%) patients and vomiting occurred in 2 (4.44%) of them in the acupuncture treatment group. Nausea was observed in 33 (7.33%) patients and vomiting occurred in 5 (11.11%) of them in the propofol group. This situation indicates that the sub-hypnotic propofol use is an effective option to prevent vomiting that may occur due to the feeling of nausea especially caused by traction of visceral peritoneum after the clamping of the umbilical cord of newborns. We observed that the implementation of the P6 acupuncture that will be applied preoperatively reduced statistically significantly formation of the feeling of nausea and vomiting.

It has been shown in the study conducted by Numazaki and Fujii (26) that subhypnotic dose of propofol was very effective in preventing vomiting in nausea developing after the fetal umbilical cord clamping in cesarean section performed under spinal anesthesia. Fujii and Numazaki (11) have observed that increasing the dose of propofol did not make a difference in the prevention of vomiting.

Similarly in our study, nausea developed in 33 patients in propofol group, vomiting developed in only 5 of them with implementation of subhypnotic propofol. This shows that vomiting prevented in 84.8% of the patients that nausea developed and these rates are in line with the literature (11,26). The amount of propofol for each patient was 4.6±11.7 mg in the acupuncture group and 63±9.4 mg in the propofol group and this shows that acupuncture application reduces the occurrence of nausea and vomiting and also the amount of propofol used in patients with nausea.

Conclusion

In conclusion, the acupuncture applied preoperatively on P6 point in order to prevent nausea and vomiting in the cesarean section performed with spinal anesthesia is an effective method and also reduces the amount of propofol which will be used to prevent intraoperative vomiting. We believe that our study needs to be confirmed with new studies.

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Assessment of long term patient satisfaction in orthognathic surgery

Ibrahim Tabakan[1], Omer Kokacya[2]*, Erol Kesiktas[3], Cengiz Eser[3], Eyuphan Gencel[3]

Abstract

Objective: Even though there are many reliable sets of data on orthognathic surgery, there is very little information about patients' satisfaction. When evaluating the success of the surgeries, clinicians usually take postoperative occlusion and cephalometric measurements into consideration. However for the patients, aesthetic appearence is just as important as occlusion.

Material and Method: Eighty patients who underwent orthognathic surgery between 2003-2011 in Cukurova University were studied. Patients were interviewed either personally or by phone using a questionnaire reflecting patient satisfaction such as preoperative and postoperative aesthetic facial apperance, change in self confidence, mastication, hypoesthesia and pain in the temporomandibular joint.

Results: 22.5% of the patients stated that there was aesthetic improvement, 8.8% stated only improvement in mastication and 62.5% stated there was improvement in both. A total of 70% (n=56) of the patients pointed out there was significant improvement in their self esteem.

Conclusion: This study suggests that the outcome of surgeries can be evaluated not only by occlusion and cephalometric measurements, but also with subjective complaints and satisfaction of the patients. To achieve long term success in orthognathic surgery, one should know the relationship between function and aesthetic facial appearence and take both of them into consideration equally.

Keywords: Malocclusion, LeFort1 osteotomy, sagittal split ramus osteotomy, patient satisfaction

Introduction

Orthognathic surgery involves surgical manipulation of facial skeleton elements to restore the proper anatomic and functional relationship in patients with dentofacial skeletal anomalies. Skeletal and dental anomalies of the jaws have a broad spectrum including congenital, developmental, and acquired deformities (1,2). Dentofacial anomalies may cause temporomandibular joint (TMJ) dysfunction, imperfect mastication due to irregular teeth, poor oral hygiene and psychological problems accompanied by inappropriate face appereances (3,4). A vast majority of these problems can be solved succesfully with orthodontic treatment that is started at early childhood stages. After the skeletal maturation is completed, following orthodontic treatment surgical procedures may be needed to restore neutral occlusion and appropriate anatomic architecture. The most employed orthognathic surgeries are LeFort1 osteotomy for maxilla and bilateral saggital split ramus osteotomy (BSSRO) for mandible (5-8). Patient's satisfaction after orthognathic surgery is usually high. Because the major complications rate is low and minor complications can be managed succesfully with conservative approaches (9,10).

In this study, long term results and satisfaction status of orthognathic surgery patients have been evaluated.

Material and Methods

In this study, 80 patients underwent LeFort1 osteotomy, BSSRO or both (two-jaw) due to developmental malocclusion between 2003-2011 in Cukurova University Faculty of Medicine, Department of Plastic, Reconstrutive and Aesthetic Surgery with at least 1 year postoperative follow up period were included. Patients with cleft lip and/or palate, congenital syndromes, malocclusion secondary to trauma and the ones in whose surgery

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[1]Erdemli State Hospital, Clinic of Plastic, Reconstrutive and Aesthetic Surgery, Mersin-Turkey
[2]Dr. Ersin Arslan State Hospital, Clinic of Plastic, Reconstrutive and Aesthetic Surgery, Gaziantep-Turkey
[3]Cukurova University Faculty of Medicine, Department of Plastic, Reconstrutive and Aesthetic Surgery, Adana-Turkey
*Corresponding Author: Omer Kokacya E-mail: kokacya@yahoo.com

osteodistraction was performed were excluded. Medical records of 147 patients meeting the criteria of the study were scanned retrospectively and 80 patients we could reach were included.

Patients were divided into 3 groups: Group 1, two-jaw surgery (n=35); group 2, LeFort1 osteotomy (n=24); group 3, BSSRO (n=21).

Patients were interviewed either personally or by phone with using a 13 question questionnaire. Table 1 reflects patients' satisfaction such as preoperative and postoperative aesthetic facial apperance, change in self confidence, mastication, hypoesthesia and pain in TMJ.

Statistical analysis was done using SPSS, version 17.0 (SPSS, S.L. Madrid, Spain). Categorical variables were summerized as numbers or percentages while continuous variables were summerized as means and standard deviations (median and minimum-maximum where necessary). Ki-kare and Fisher tests were used for the comparison of categorical variables. For the comparison of continuous variables, T test and ANOVA were used at normally distributed parameters and Mann Whitney U and Kruscal Wallis test was used at non-normally distributed parameters. Wilcoxson, Friedman and Repeated Measures Analyses were used for preoperative and postoperative assessments. Statistical significance level was taken $p<0.05\%$ for each test.

Table 1: The questionnaire used for interviewing patients

1- What was your prior expectation before the orthodontic treatment?	Aesthetic improvement Improvement of mastication Both None/i don't know
2- What is the most appropriate statement to define your thoughts on the orthodontic treatment and operation?	There is only aesthetic improvement There is improvement only in mastication Both improved No improvement
3- Did the results of surgery meet your expactations? (Rate from 1 to 10)	1-Did not meet my expactations 5-Moderate 10-Meet my expactations totally 1-2-3-4-5-6-7-8-9-10
4- Rate your facial appereance aesthetically before the surgery from 1 to 10.	1-Bad 5-Moderate 10-Very good 1-2-3-4-5-6-7-8-9-10
5- Rate your facial appereance aesthetically after the surgery from 1 to 10.	1-Bad 5-Moderate 10-Very good 1-2-3-4-5-6-7-8-9-10
6- What do your family, relatives and friends think about the results of surgery? (Rate from 1 to 10)	1-Bad 5-Moderate 10-Very good 1-2-3-4-5-6-7-8-9-10
7- Is there an increase in your self confidence following surgery?	Yes No
8- Would you advise this operation to anyone who would need orthognathic operation?	Yes No
9- How was your chewing function before surgery? (Rate from 1 to 10)	1-2-3-4-5-6-7-8-9-10
10- How is your chewing fuction after surgery?	1-2-3-4-5-6-7-8-9-10
11- Currently, can you feel any numbness or tingling around your face, upper/lower lip or gum?	Yes No
12- Did you feel pain while opening and closing your mouth before the surgery?	Yes No
13- Currently, do you feel pain while opening and closing your mouth?	Yes No

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Results

Age and sex distribution of the patients are shown in Table 2.

Results of the answers for question 1 and 2, which reflect the expectations and if the expectations are met, they are summerized in Table 3.

The 3rd question is scrutinizing if the result of the surgery met the expactations yielded the result of 8.4±1.3 (mean ± SD). 17.5% (n=14) of patients answered this question with full score, 10 points.

Results of the 4th and 5th question asking the patients to rate their facial appereance aesthetically from 1 to 10 before and after the surgery are shown in Table 4. Difference between before and after surgery was statistically significant in all groups and in total population (p=0.0001). However, there was no statistical significant difference between the groups (p*=0.056).

The 6th question that scrutinizes thoughts of patient's family, relatives and friends about the result of the surgery yielded the result of 8.5±1.2 (mean ± SD) for group 1, 8.7±1.2 (mean ± SD) for group 2, 8.9±1.0 (mean ± SD) for group 3 and 8.6±1.1 (mean ± SD) for the total population. When we compared the results from question 5 and 6, we did not see any statistical significant difference between the patients self evaluation and opinion of the patient's family, relatives and friends about the result of the surgery.

Results of the 7th question showed that there was an increase in self confidence at 65.7% (n=23) of patients in group 1, 70.8% (n=17) of patients in group 2, 76.2% (n=16) of patients in group 3 and 80% (n=56) of total population.

Outcomes from the 8th question showed that in group 1 68.6% (n=24), in group 2, 83.3% (n=20), in group 3, 81.0% (n=17) and in total population 76.3% (n=61) of the patients would advise this operation to individuals who would need orthognathic operation.

Results from the 9th and 10th question evaluating preoperative and postoperative chewing functions are shown in Table 5.

The 11th question gave the results of 37.1% (n=13) of patients in group 1, 25.0% (n=6) of patients in group 2, 38.1% (n=8) of patients in group 3 and 33.8% (n=27) the total number of patients have reported numbness or tingling around their faces, upper/lower lip or gum.

Outcomes from question 12 and 13 that scrutinize pain in TMJ while opening and closing their mouth before and after surgery show that in group 1 before surgery 25.7% (n=9) and after surgery 31.5% (n=11) feel pain. In group 2, it was 8.3% (n=2) before and again 8.3% (n=2) after surgery. In group 3, it was 14.3% (n=3) before and 38.1% (n=8) after surgery. In the total number of patients, while 17.5% (n=14) of patients used to feel pain in TMJ before surgery, 26.3% (n=21) of patients felt pain after surgery.

Discussion

Dentofacial deformities drastically affect patient's health-related qualities of life. Especially unaesthetic appereances of soft tissue and skeletal architecture in class 3 deformities may cause psychological problems (11). Therefore, the most crucial step of preoperative planning in orthognathic surgery candidates is psychological assessment. Ideally, a psychiatrist or psychologist should undertake this assesment. If this can not be provided, an orthodontist or surgeon should evaluate the patient carefully. Patient's self perception of facial appeareance can differ from physicians perception. Therefore, patient's subjective complaints and expectations should be analized carefully. Physicians should decide whether they can meet these expectations (12).

Studies show that even if there are minor disparities in the results, patients are satisfied with the results of orthognathic surgeries. There are many factors that might cause postoperative dissatisfaction. Most of them are secondary to miscommunication of patient and physician rather than poor postoperative results or lack of surgical skills.

Many measurement indexes are used for assessing the benefits of orthognathic surgery and usually questionnaires are preferred.

Table 2: Age and sex distrubution

	Two-jaw surgery group 1 (n=35)		**LeFort1 osteotomy group 2 (n=24)**		**BSSRO group 3 (n=21)**		**Total (n=80)**		
	Mean ± SD	**Med (min-max)**	**Mean ± SD**	**Med (min-max)**	**Mean ± SD**	**Med (min-max)**	**Mean ± SD**	**Med (min-max)**	**p**
Age	21.9±2.8	22 (18-30)	22.7±3.8	22 (17-32)	22.7±4.0	22 (17-35)	22.4±3.4	22 (17-35)	0.606
Sex	n	%	n	%	n	%	n	%	p
Female	28	80	16	66.7	12	57.1	56	70	0.178
Male	7	20	8	33.3	9	42.9	24	30	

p: Kruskal Wallis Test used for age distrubition, SD: Standard deviation, BSSRO: Bilateral saggital split ramus osteotomy, min: Minimum, max: Maximum

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Orthodontic indexes assess the success of the operation by classifying patients occlusion with numerical values. These indexes are commonly used in Europe.

In 1998, O'Brien et al. (13) studied life quality of orthodonthy patients and they reported that most measurements developed for dentistry should not be used for orthodontic patients, because most of the orthodontic anomalies are asymptomatic and most of the orthodontic anomalies are related with aesthetic apperreance rather than symptoms like pain.

In 1999, Bennett and Phillips reported that there are significant differences between physicians' results and patients' subjective assesment (14).

These studies directed the physicians to make patient-centered treatment plans and Ortognathic Quality of Life Questionnaire to be formed. This questionnaire is easily and quickly applicable and economic, however, it should be kept in mind that it is subjective because replies can be effected by patients' moods at the time of quastionnaire.

Table 3: Results of the answers for question 1 and 2

	Group 1 (n=35)		**Group 2 (n=24)**		**Group 3 (n=21)**		**Total (n=80)**		
Question 1 -What was your prior expectation before the orthodontic treatment?	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p**
Aesthetic improvement	14	40	6	25.0	4	19	24	30	0.439
Improvement of mastication	4	11.4	5	20.8	6	28.6	15	18.8	
Both	16	45.7	13	54.2	11	52.4	40	50	
None/i don't know	1	2.9	0	0.0	0	0.0	1	1.3	
Question 2 -What is the most appropriate statement to define your thoughts on the orthodontic treatment and operation?	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p**
There is only aesthetic improvement	9	25.7	4	16.7	5	23.8	18	22.5	0.988
There is improvement only in mastication	3	8.6	2	8.3	2	9.5	7	8.8	
Both improved	21	60.0	16	66.7	13	61.9	50	62.5	
No improvement	2	5.7	2	8.3	1	4.8	5	6.3	

Table 4: Self evaluation of facial appereance before and after surgery

	Before surgery		**After surgery**			
	Mean ± SD	**Med (min-max)**	**Mean ± SD**	**Med (min-max)**	**p**	**p***
Total	5.1±1.0	5 (3-7)	8.4±1.3	9 (5-10)	0.0001	
Group 1	5.4±0.9	5 (3-7)	8.2±1.3	9 (5-10)	0.0001	0.056
Group 2	5.1±1.0	5 (3-7)	8.4±1.4	9 (5-10)	0.0001	
Group 3	4.6±1.1	5 (3-7)	8.7±1.2	9 (6-10)	0.0001	

p: Friedman test and Wilcoxson test, p*: Repeated measure analysis-Greenhouse Geisser test, SD: Standard deviation, min: Minimum, max: Maximum

Table 5: Evaluation of mastication before and after surgery

	Before surgery		**After surgery**			
	Mean ± SD	**Med (min-max)**	**Mean ± SD**	**Med (min-max)**	**p**	**p***
Group 1	5.7±1.0	6 (3-8)	7.6±1.3	7 (4-10)	0.0001	0.001
Group 2	4.4±1.1	4 (3-7)	8.2±1.6	9 (5-10)	0.0001	
Group 3	4.2±1.2	4 (2-6)	8.0±1.5	8 (5-10)	0.0001	
Total	4.9±1.3	5 (2-8)	7.9±1.5	8 (4-10)	0.0001	

p: Friedman test and Wilcoxson test, p*: Repeated measure analysis-Greenhouse Geisser test, SD: Standard deviation

Young male patients expect functional improvements primarily, while young female patients prior expectations are aesthetical improvements and therefore increase in self confidence (15). Nicodema et al. (16) reported remission in depression symptoms together with increase in self confidence following surgery at elderly female class 3 malocclusion patients while there was no change in male patients.

Rustmeyer et al.'s (17) study included patients with class 3 occlusion at the age of 23 in average and they reported that there was no significant difference between genders from a satisfaction point of view. The same study showed significant improvements in patients who had TMJ problems (pain, limitations in mouth opening) before surgery. A few patients that came along with TMJ problems after surgery were followed with splint and physiotherapy.

In our study, there is no significant difference between genders in the "satisfaction" context like Rustmeyer et al.'s (17) study, but our TMJ results are different. Before surgery, 17.5% (n=14) patients had TMJ pain and after surgery it was 26.3% (n=21) patients. While 14 patients suffering from pain did not recover; 7 patients started to feel pain after surgery. In our opinion, this is an exaggerated result because some patients stated that pain relieved spontaneously when they went back to their social life.

One of the most frequent consequences following BSSRO are sensation changes at mentum, lips, and gum as a result of inferior alveolar nerve (IAN) injury. It is believed 85-100% of the patients at the early postoperative period and by decreasing over time, full recovery expected (18-20). Raveh et al. (21) reported 97% neurosensational loss after BSSRO at the early postoperative period. Studies with more than 500 patients showed that permanent nerve injury at long term period is between 32-39% (8,22). High rates of IAN injury even after 1 year postoperative period is one of the disadvantages of BSSRO (23,24).

Westermark et al.'s (25) study, which is the biggest series with 496 BSSRO patients, reported 66% hypoesthesia due to varying degrees of nerve injury. They indicated that nerve injury is more frequent in elderly patients and they emphasized the importance of the surgical experience.

In our study, the IAN injury rate after BSSRO is 38.1% (n=8) and after two-jaw surgery 37.1% (n=13). In order to obtain clearer results about the IAN injury, peroperative and postoperative two point discrimination, light touch, needle pricking and cold-hot discrimination tests as performed in the study of Ylikontiola et al. (26) should have been employed.

Overall, our patients found the surgeries successful. Only 6.3% of our patients think that there is neither aesthetical nor functional improvement. Opinions patient's familiy, relatives and friends are similar. There were significant differences between preoperative and postoperative self assessment of facial aesthetic aperreance in all groups (p=0.0001). Percent of 70 (n=56) patients found increase in their self confidence and 76.3% (n=61) would advise the operation to other candidates. The rate of positive advise was lower in group 1 (two-jaw) compared to the rest of the groups. This might be due to more powerful postoperative pain and swelling as the operation is more complicated.

Van de Perre et al.'s (27) retrospective study with 2.049 patients communicates that the most common complication of maxillary orthognathic surgery is severe bleeding, but in Kramer et al.'s (28) study with 1000 LeFort1 osteotomies only 1.1% (n=11) patients had blood transfusion and in only in 1 patient external carotid artery ligation was performed.

Panula et al. (8) reported 1% transfusion rate in BSSRO patients and 17% in LeFort1 osteotomy patients. Transfusion need is lower in mandibular osteotomies than maxillary osteotomies. Retromandibular vein, internal maxillary artery, facial artery and inferior alveolar artery are the most commonly injured vessels (8). Cautious subperiosteal dissection and ecartation of vessels decreases bleeding.

Compression during the operation can stop the bleeding. Topical hemostatic agents and fibrin including hemostatic filling materials can be used. In case of persistant or recurrent bleeding ligation or embolisation ef external carotid artery can be necessary (8).

One of the worst complications of LeFort1 osteotomy is aseptic necrosis. This complication is very rare because of extensive vascularization of maxilla. However, tension of the palatal vascular pedicle, seperation of maxillary segments, injury of descendant palatine artery, injury of palatal mucosa, overdissection of maxilla and accompanying hypotension may result in aseptic ischemic necrosis (29). After the LeFort1 osteotomy was completed, maxillary vascularization is ensured by branches of descendant palatine artery, branches of posterior superior alveolar artery to soft tissue, palatal branch of ascendent pharangeal artery and palatal branch of facial artery (29-30).

Skeletal relapse is the most common complication of orthognathic surgery (31). Bone fixation is mandatory for preventing skeletal relapse. Stability is closely related with the direction and amount of movement, type of fixation, surgical technique and vascularity of bone segments (31,32). When we consider the direction of movement from the aspect of stabilization, the most stable technique is upper movement of maxilla and advancement of mandible. The least stable technique is the down movement of maxilla and maxillary expansion (32).

According to the description of rigid fixation techniques, it has an increased stability, but rigid fixation can not guarentee stability in every patient. Hoffman and Brennan (33) reported 10% relapse in maxillary advancement patients in whose operation rigid fixation was used.

Relapse is related with upper movement of mandible by mastication muscles and thereby pushing of maxilla upwards by mandible. Research studies report up to 48% relapse rates (34). When maxillary bone grafting is used with rigid fixation, relapse rates can decrease to 4% (35).

In our study, we did not see any major complications. Minor complications experiences have been summerized below.

A patient who had two-jaw surgery operation were reoperated at the postoperative 25th day because of nonunion and bone gap in the mandiblular osteotomy line was repaired with bone graft.

Another two-jaw patient was reoperated due to unnoticed hematome. The operation was completed with compression after applying the hemostatic material. Same patient was operated 2 months later due to lateralization. There was malunion at mandibular osteotomy line and a new fixation was made.

A patient who underwent BSSRO was reaoperated after 6 hours because of malocclusion and rigid fixation was renewed.

A patient whose mandibular bone segment was exposed through mucosa was reoperated in order to excise exposed bone segment.

One LeFort1 and 2 two-jaw patients were reoperated in late postoperative period in order to remove exposed titanium plates.

One LeFort1 osteotomy patient underwent seprorhinoplasty operation at the late postoperative period because of nasal septum deviation.

Conclusion

This study suggests that outcomes of the surgeries can be evaluated not only by occlusion and cephalometric measurements, but also with subjective complaints and satisfaction of the patients. To achieve long term success in orthognatic surgery, one should know the relationship between function and aesthetic facial appearence and take both of them into consideration equally.

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Prevalence of pulmonary hypertension in patients with early stages of chronic renal disease

Ezgi Coskun Yenigun[1]*, Sevket Balli[2], Didem Turgut[1], Sukran Gurses[3], Ramazan Ozturk[4], Eyup Koc[5], Fatih Dede[1]

Abstract

Objective: Pulmonary hypertension (PHT) has recently been described as a cardiovascular complication of chronic kidney disease (CKD). There are many studies on the prevalence of PHT in patients undergoing hemodialysis (HD); however, there are no data on the presence or prevalence of PHT in patients with early-stage kidney disease.

Material and Method: The demographic and laboratory findings for 172 adult patients with stage 1-5 CKD, as well as Doppler echocardiographic findings were evaluated. Systolic pulmonary arterial pressure (sPAP) was compared according to CKD stage, and also between the patients in stages 1-4 and those in stage 5 with and without AVF.

Results: Mean age of the patients was 55.4±15.2 years. Mean sPAP in the entire study group was 34.5±5.7 mmHg and PHT was noted in 90 (52.3%) patients. Mean sPAP and the prevalence of PHT were similar in the stage 1-4 patients and stage 5 patients, regardless of HD (p=0.86). The serum calcium level was significantly lower and the serum intact parathyroid hormone level was significantly higher in patients with PHT than in those without PHT (p=0.02, and p=0.03).

Conclusion: The present findings show that the prevalence of PHT in patients with early stage CKD was similar to those with stage 5 CKD. Due to the high morbidity and mortality rates associated with PHT, follow-up of sPAP via Doppler echocardiography might be indicated in all patients with CKD.

Keywords: Chronic kidney disease, pulmonary hypertension, prevalence

Introduction

Pulmonary hypertension (PHT) is a serious cause of morbidity and mortality, regardless of its etiology. Elevated pulmonary arterial pressure (PAP) can be observed secondary to heart, lung, or systemic disorders (1). PHT, defined as systolic pulmonary artery pressure (sPAP) ≥35 mmHg at rest as estimated via Doppler echocardiography, has been reported with variable prevalence's in patients with chronic kidney disease (CKD), both predialysis and during hemodialysis (HD) (2). According to Dana Point classification, CKD combined with dialysis is causes of PHT not clear (3).

PHT was first described in a group of HD patients in 1996, after that time many studies have investigated the prevalence of PHT in CKD patients. The prevalence of PHT ranges from 9-39% in cases of non-dialysis-dependent CKD stage 5 patients, 18.8-68.8% in regular HD patients, and 0-42% in peritoneal dialysis patients, but there are no data on the prevalence of PHT in patients with stage 1-4 CKD (4). As such, the present study aimed to determine the prevalence of PHT via Doppler echocardiography in patients with early-stage (stage 1-4) CKD and the factors associated with PHT.

Material and Methods

Patient selection

The study included 172 stage 1-5 CKD patients that regularly received treatment between January 2013 and January 2014 at Balikesir Ataturk State Hospital, Clinic of Nephrology, Balikesir, Turkey. CKD was defined as kidney damage or a glomerular filtration rate (GFR) <60 mL min^{-1} 1.73 m^{-2} for ≤3

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[1]Ankara Numune Education and Research Hospital, Clinic of Nephrology, Ankara-Turkey
[2]Balikesir Ataturk State Hospital, Clinic of Pediatric Cardiology, Balikesir-Turkey
[3]Balikesir Ataturk State Hospital, Clinic of Nephrology, Balikesir-Turkey
[4]Kırıkkale State Hospital, Department of Nephrology, Kirikkale-Turkey
[5]Kırıkkale University Faculty of Medicine, Department of Nephrology, Kirikkale-Turkey
*Corresponding Author: Ezgi Coskun Yenigun E-mail: drezgi_76@hotmail.com Phone: +90 312 508 45 52

months, irrespective of cause (5). GFR was calculated according to the 4-variable Modification of Diet in Renal Disease (MDRD) (6), and the patients were considered stage 1-5 based to their GFR according to Kidney Disease Outcomes Quality Initiative guidelines (5,6). Stage 5 CKD patients were divided into 2 subgroups based on the presence or absence of an arteriovenous fistula (AVF). All patients with an AVF were undergoing HD. The Ankara Numune Education and Research Hospital Ethics Committee approved the study protocol (625/2013) and written informed consent was obtained from all participants.

Clinical and laboratory investigations

Patient's data, including age, gender, comorbidities, etiology of renal disease, and the presence of an AVF, were obtained from the patients and their records. Laboratory investigations, including serum urea, creatinine, serum calcium (Ca), phosphorus, hemoglobin, hematocrit, and intact parathyroid hormone (iPTH), were analyzed the same day that echocardiographic evaluation was performed. All patients underwent a complete clinical evaluation, and those with an sPAP >35 mmHg underwent chest radiography, pulmonary function tests, and standard 12-lead electrocardiography to exclude pulmonary diseases. All echocardiographic examinations were performed by the same experienced technician using a Philips HDHXS. Two-dimensional and M-mode Doppler echocardiographic images were obtained from apical or parasternal windows while patients were in the left lateral recumbent position.

Patients with chronic obstructive pulmonary disease, chest wall and parenchymal lung disease, abnormal pulmonary function tests results (forced vital capacity/forced expiratory volume in 1 s <0.7), and a left ventricular ejection fraction <50%, mitral or aortic regurgitation grade ≥2, significant valvular stenosis, and an E/E' ratio >15 via echocardiogram were excluded. The modified Bernoulli equation was used to estimate sPAP: (sPAP (mmHg)=4 v^2+right atrial pressure) (7). PHT was diagnosed based on sPAP ≥35 mmHg (8). sPAP was compared according to stage 1-5 CKD, was compared according to stage 1-4 and stage 5 CKD, and according to the presence or absence of an AVF, so to determine the effect of an AVF on sPAP.

Statistical analysis

Statistical analysis was performed using SPSS v.21.0 for Windows (IBM Corp., Armonk, NY). Data were expressed as mean±SD or as median (range), as appropriate. Differences in numeric variables between two independent groups were evaluated using the parametric t-test or the non-parametric Mann-Whitney U test, whereas the Kruskal-Wallis test was used to compare >2 groups. Categorical variables were analyzed using the chi-square test. The level of statistical significance was set at $p<0.05$.

Results

The study included 172 CKD patients. Mean age of the patients was 55.4±15.2 years, and 78 (45.3%) were female and 94 (54.7%) were male. In all, 36 (21%) patients were stage 1 and 2, 44 (26%) were stage 3, 38 (22%) were stage 4, and 54 (31%) were stage 5. Among the stage 5 patients, 30 were undergoing HD and 24 were not. Patient clinical characteristics and laboratory findings are summarized in Table 1. The patients' primary renal diseases varied; 42 (25%) had hypertensive glomerulosclerosis, 34 (20%) had diabetic nephropathy, 28 (16%) had autosomal dominant polycystic kidney disease, 20 (12%) had tubulointerstitial nephritis, 12 (7%) had glomerulonephritis/nephrotic syndrome, 12 (7%) had undergone renal transplantation, and 24 (14%) had an unknown etiology. Mean sPAP in the entire study population was 34.5±5.7 mmHg.

sPAP and the prevalence of PHT did not differ significantly according to disease stage ($p>0.05$). In addition, sPAP and the prevalence of PHT did not differ between the stage 1-4 patients and stage 5 patients (34.2±6 mmHg and 35.2±4.8 mm Hg, respectively, and 50.8% and 55.6%, respectively; $p>0.05$). To estimate the effect of an AVF on PHT, stage 5 CKD patients with and without an AVF were compared. All patients with an AVF were undergoing HD. PHT was diagnosed in 16 (53.3%) patients with stage 5 CKD that were undergoing HD and in 14 (58.3%) stage 5 CKD patients not undergoing HD ($p>0.05$); mean sPAP did not differ significantly between these 2 patient subgroups (34.5±5.3 mmHg vs. 36±6.3 mmHg respectively, $p>0.05$) (Table 2).

In total, PHT was diagnosed in 90 (52.3%) patients via echocardiography. There weren't any significant differences in age, gender, systolic and diastolic blood pressure, or the hemoglobin concentration between the patients with and without PHT. The serum Ca level was significantly lower and the serum iPTH level was significantly higher in the patients with PHT than in those without PHT (8.8±1 mg dL^{-1} vs. 9.3±0.6 mg dL^{-1} ($p=0.02$), and 133.5 pg mL^{-1} vs. 79.6 pg mL^{-1} ($p=0.03$), respectively). On the other hand, the prevalence of hypertension was significantly lower in the patients with PHT than in those without PHT ($p=0.03$). PHT-related data are shown in Table 3. There wasn't an association between the prevalence of PHT and the etiology of the primary renal disease.

Discussion

To the best of our knowledge, the present study is the first to determine the prevalence of PHT in patients with early-stage CKD. The present findings show that 52.3% of the patients with stage 1-5 CKD and 50.8% of patients with stage 1-4 CKD had PHT. Additionally, the prevalence of PHT in the stage 1-4 CKD patients and stage 5 patients was similar. Studies on

non-dialysis-dependent stage 5 CKD patients reported that the prevalence of PHT ranges from 9-39% and that the prevalence of PHT is higher in patients undergoing dialysis than in non-dialysis patients (9-12). In the present study the prevalence of PHT in patients with stage 5 CKD not undergoing HD was 58.3%, which is higher than reported earlier (9,11,13,14). In addition, there weren't any significant differences in sPAP or the prevalence of PHT between the patients undergoing and not undergoing HD.

The prevalence of PHT in the present study's stage 1-4 patients was 50.8%- the most noteworthy of the present study's findings. Accordingly, we think in addition to CKD patients undergoing HD early-stage CKD patients should also be considered high risk patients. In most studies on patients with CKD, sPAP has been estimated as Doppler-derived sPAP and various sPAP cut offs have been used, ranging from 25 to ≥45 mmHg (9,11,13-15). In the present study sPAP ≥35 mmHg based on Doppler echocardiography was considered diagnostic for PHT and the high prevalence of PHT in this study may be explained due to the lack of uniformity in diagnostic criteria and sPAP cutoffs in the literature. Right-sided cardiac catheterization is the gold standard for the diagnosis of PHT, but Doppler echocardiography measurement of sPAP was also correlated with measurement obtained via catheterization, without the risks associated with an invasive test procedure (15). The present study and most other studies on CKD and PHT used Doppler echocardiography-derived PAP measurements.

Table 1: Clinical and laboratory characteristics of the study groups

Variables	**Mean ± SD**
Age (year)	55.4±15.2
Sex	
Male (n, %)	94 (54.7)
Female (n, %)	78 (45.3)
Stage (n, %)	
1-2	36 (21)
3	44 (25)
4	38 (22)
5	54 (32)
Etiology (n, %)	
HT	42 (25)
DM	34 (20)
PKD	28 (16)
Transplant	12 (7)
Glomerulonephritis	12 (7)
TIN	20 (12)
Unknown	24 (14)
Laboratory variables	
Urea (mg/dL)	88.2±49
Creatinine (mg/dL)	3.5±3.1
Na	137.9±3.6
K	4.6±0.7
Ca (mg/dL)	9±0.9
P (mg/dL)	4±1.1
PTH (pg/mL)	191.5±230.1
Hemoglobin (g/dL)	12.5±2.8
sPAP (mmHg)	34.5±5.7

HT: Hypertension, DM: Diabetes mellitus, PKD: Polycystic kidney disease, TIN: Tubulointerstitial nephritis, PTH: Parathyroid hormone, sPAP: Systolic pulmonary arterial pressure, Ca: Calcium, SD: Standard deviation

Frucher et al. studied 191 CKD patients and reported that HD was the third most common cause of PHT, accounting for 13% of cases of PHT (16). Uremia (leading to pulmonary arterial vasoconstriction), the presence of an AVF, low bioavailability of nitric oxide (17), an elevated endothelin level (18,19), vascular calcification, hypervolemia, exposure to dialysis membranes, endothelial dysfunction, and anemia (20,21) are the reported pathogenetic mechanisms for the development of PHT in patients with CKD. Patients with an AVF had a high incidence of PHT due to increased cardiac output and it has been reported that the incidence of PHT in stage 5 CKD patients with an AVF was 40-50% (12,22). Although Havlucu et al. (11) showed that the presence of PHT in patients with an AVF was significantly higher than that in patients without an AVF, Yigla et al. (9) reported that mean sPAP significantly decreased after successful renal transplantation in CKD patients, while their AVF was intact. It was reported that compression of AVF can decrease cardiac output and sPAP, and that an AVF increases sPAP via elevation of cardiac output (23). In the present study the prevalence of PHT in stage 5 CKD patients with and without an AVF was similar (53.3% vs. 58.3%, respectively) and, as previously reported, there wasn't an association between the presence of an AVF and PHT (24,25). Anemia can also contribute to the development of PHT by increasing cardiac output and exacerbating hypoxia (26). In the present study there wasn't a significant difference in the hemoglobin level between the patients with and without PHT, as reported earlier (27,28).

Vascular calcification is a common and important risk factor for cardiovascular death in patients with CKD. Impaired Ca-phosphorus balance and secondary hyperparathyroidism play an important role in the pathogenesis of vascular calcification (29). Although researches has shown that there isn't an association between pulmonary calcification and the PTH level (30,31), it was also reported that in dogs with experimentally induced CKD

an elevated PTH level might induce right ventricular pressure, right ventricular hypertrophy, and pulmonary resistance without pulmonary calcification (32). Secondary hyperparathyroidism and an elevated PTH level in a uremic environment have been implicated in many cases of vascular calcification. The present study did not evaluate pulmonary calcification formation, but in this study, as in Havlucu et al. (11) and Kumbar et al. (33), the serum PTH level was significantly higher and the serum Ca level was significantly lower in the patients with PHT ($p<0.05$); however, Amin et al. (30) and Unal et al. (25,27) reported that there wasn't a significant difference in PTH between CKD patients with and without PHT. They also reported that there wasn't a correlation between the Ca level and PHT.

Endothelial dysfunction, a common finding in CKD patients, and such comorbid conditions as hypertension, diabetes mellitus, and diastolic dysfunction have also been suggested to contribute to PHT (31). Although the prevalence of hypertension was significantly lower in the present study's CKD patients with PHT than in those without PHT, blood pressure was similar and there were no diastolic dysfunction on echocardiographic measurement between patients with PHT and without PHT. Although hypertension and diabetes mellitus were the most common primary diseases in the present study, there wasn't an association between the prevalence of PHT and primary renal disease. The present findings support the notion that hormonal-metabolic factors play a role in the development of PHT. The prevalence of PHT was similar in the stage 1-4 CKD patients and stage 5 patients, there wasn't an association between PHT, and an AVF or HD, and the PTH level in the CKD patients with PHT was higher than in those without PHT.

The present study has several limitations. The sample was small and sPAP was noninvasively measured via Doppler echocardiography. Unfortunately, the mechanisms of PHT were not investigated. To the best of out knowledge the present study

Table 2: sPAP and prevalence of parathyroid hormone in each stages of chronic kidney disease

	sPAP (mmHg)	PHT (n, %)	p
Stages			
1	34.8±5.8	16 (57.1)	0.32
2	28.3±2.5	-	
3	34.5±4.7	24 (54.5)	
4	34.7±7.5	20 (52.6)	
5	35.2±4.8	30 (55.6)	
Stage 1-4	34.2±6.0	60 (50.8)	0.86
Stage 5	35.2±4.8	30 (55.6)	
Stage 5 with AVF	34.5±5.3	16 (53.3)	
Stage 5 without AVF	36±6.3	14 (58.3)	0.47

AVF: Arteriovenous fistula, sPAP: Systolic pulmonary arterial pressure, PHT: Pulmonary hypertension

Table 3: Comparison of parametres in patients with and without pulmonary hypertension

	Patients without PHT (n=82)	Patients with PHT (n=90)	p
Age (year)	55.2±15.1	55.6±15.5	0.91
Gender (n)			
Male	38	56	0.20
Female	44	34	
Systolic blood pressure (mmHg)	131.2±21.5	128.0±29.8	0.570
Diastolic blood pressure (mmHg)	76.8±14.4	76.9±14.6	0.985
LVEDD (cm)	4.2±0.4	4.3±0.3	0.34
Ca (mg/dL)	9.3±0.6	8.8±1	0.026
p (mg/dL)	3.8±1	4.1±1.2	0.289
Hb (g/dL)	12.4±1.8	12.5±3.5	0.795
PTH (pg/mL)	79.6 (5.4-1420)	133.5 (9.6-697)	0.032
HT (n, %)	60 (73.2)	44 (48.9)	0.038

LVEDD: Left ventricular end-diastolic diameter, Hb: Hemoglobin, PHT: Pulmonary hypertension, HT: Hypertension, Ca: Calcium

is the first to assess the prevalence of PHT in early stages of CKD patients and, based on the present findings, we think additional larger scale studies are needed to more clearly understand the long-term effects of PHT in CKD patients.

Conclusion

As the presence of PHT is prognostically important in patients with end-stage renal disease, the present study investigated PHT in early-stage CKD patients. The present findings show that the prevalence of PHT in all stages of CKD was high. Renal disease itself, rather than an AVF, appeared to be the primary risk factor for PHT. Due to the high morbidity and mortality rates associated with PHT, systematic screening using Doppler echocardiography might be indicated in all CKD patients for early recognition.

Conflict of Interest Statement

The authors declare there are no conflicts of interest-financial or otherwise-related to the materials presented herein.

Authorship Contributions

Idea/Hypothesis: Ezgi Coskun Yenigun, Design: Ezgi Coskun Yenigun, Sevket Balli, Data Collection: Sukran Gurses, Data Analysis/Interpretation: Ramazan Ozturk, Ezgi Coskun Yenigun, Literature Review: Didem Turgut, Critical Review: Eyup Koc, Fatih Dede

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Investigation of Gremlin 1, COL15A1 immunoreactivity and the relationship between microvessel density and Gremlin 1 in papillary renal cell carcinoma and chromophobe renal cell carcinoma

Sevgul Kara*, Metin Karakok

Abstract

Objective: The current study aimed to investigate expressions of Gremlin 1 (GREM1) (a bone morphogenetic protein antagonist and a proangiogenic factor) and COL15A1 (Collagen type XV alpha-1, encodes the proteoglycans located in various human tissues and particularly in the basement membrane) immunohistochemically in papillary renal cell carcinoma (PRCC) and chromophobe renal cell carcinoma (CRCC) in order to assess the relationship between these markers and said tumors and also explore associations of GREM1 with angiogenesis, tumor necrosis and tumor diameter by looking at the microvascular density (MVD) through the expression of COL15A1 in vascular endothelium.

Material and Method: GREM1 and COL15A1 expressions were investigated in 20 PRCC and 39 CRCC patients. Cytoplasmic staining with GREM1 and COL15A1 was examined. Microvascular structures stained with COL15A1 were examined in order to evaluate angiogenic profile.

Results: In CRCC, GREM1 staining was statistically significant in tumor tissues compared to intact tissues (p=0.006). The relationship between MVD and GREM1 staining was statistically significant in PRCC (p=0.007). Cytoplasmic staining with COL15A1 observed in PRCC was statistically significant (p=0.005).

Conclusion: Positive GREM1 staining observed in both tumor groups and much higher expression of this marker particularly in the tubular epithelium of the neighboring normal tissue supports our argument that this gene might be a tumor suppressor gene.

Keywords: Chromophobe renal cell carcinoma, papillary renal cell carcinoma, Gremlin 1, collagen type XV alpha-1, angiogenesis

Introduction

Gremlin 1 (GREM1) is a bone morphogenetic protein (BMP) antagonist and a novel proangiogenic factor (1). GREM1 suppresses transforming growth factor-beta (TGF-ß) signaling by binding to BMP-2, BMP-4 and BMP-7 and blocking the interaction of these ligands with their receptors. BMP family is largest subfamily of TGF-ß superfamily of growth factors which are involved in several functions including angiogenesis, proliferation, apoptosis, differentiation, chemotaxis and production of extracellular matrix in many cells (2). BMP and BMP antagonists like GREM1 have been demonstrated in the pathogenesis of nephropathy and regulation of kidney development. GREM1 directly interacts with cancer cells in a BMP-independent manner and modulates angiogenesis. Although the role of GREM1 in the pathogenesis and underlying mechanism of renal (kidney) cancer has been shown through GREM1 gene expression, its other actions have not been clearly elucidated (1).

Epigenetic mechanisms may play a key role in the regulation of GREM1 expression. Recent studies have indicated that methylation of GREM1 promoter region is strongly associated with the development of certain types of cancer (1).

Collagen type XV alpha-1 (COL15A1) is a large proteoglycan that has been demonstrated in all human tissues. By light microscopy, it was localized to most epithelial and all nerve, muscle and endothelial basement membrane zones except for the glomerular capillaries or hepatic/splenic sinusoids (3).

COL15A1 gene encodes the proteoglycans located in various human tissues and particularly in the basement membrane and

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Gaziantep University Faculty of Medicine, Department of Pathology, Gaziantep-Turkey
*Corresponding Author: Sevgul Kara E-mail: drsevgulkara@gmail.com

it is believed to have a major role in signaling pathways (3). Hypermethylation of the promoter region of the COL15A1 gene was reported in patients with clear cell renal cell carcinoma (CCRCC) (4) but COL15A1 gene has not been previously studied in patients with papillary renal cell carcinoma (PRCC) and chromophobe renal cell carcinoma (CRCC).

Kidney cancer is the thirteenth most common cancer worldwide and tenth most common cancer in Europe. According to the World Health Organization data, 271,000 new cases were identified globally in 2008. Although the incidence of kidney cancer stabilized in recent years and even declined in some European countries, metastasis occurs in 20% to 30% of diagnosed patients. Kidney cancers remain life-threatening since patients with kidney cancers experience relapse and metastasis following nephrectomy. Genetic and molecular studies contribute to the understanding of tumor pathogenesis and may also be used for determination of the tumor type. Additionally, such studies would serve as a guide for developing individualized and targeted therapies. Renal cell carcinoma (RCC) is the most common malignant kidney tumor and has 3 major subtypes including CCRCC which has the highest incidence and PRCC and CRCC. These subtypes differ in their histological, morphological and genetic characteristics ally as well as clinical course (5).

In one study, it was concluded that hypermethylation of the promoter region of GREM1 gene as shown in patients with CCRCC may have an impact on the development of this type of cancer and angiogenesis (1). Another study has also demonstrated deoxyribonucleic acid (DNA) hypermethylation in PRCC (6). However, no study was identified in literature on GREM1 in PRCC and CRCC. Hypermethylation of the promoter region of the COL15A1 gene was reported in patients with CCRCC (4) but COL15A1 gene has not been previously studied in patients with PRCC and CRCC.

In the present study, we aimed to investigate GREM1 and COL15A1 expressions in PRCC and CRCC immunohistochemically in order to assess the relationship between these markers and studied tumors and explore the association of GREM1 with angiogenesis, age, tumor necrosis and tumor diameter by looking at the microvascular density (MVD) through the expression of COL15A1 in the vascular endothelium.

Material and Methods

Digital archives of Gaziantep University Faculty of Medicine, Department of Pathology were screened and 59 cases of neprectomy were identified in patients diagnosed with CRCC and PRCC between 2002 and 2011. Paraffin-embedded blocks were retrieved from the block archive in order to prepare 4 micron thick sections of tissue (one from tumor tissue and one from normal kidney parenchyma) for each patient and GREM1 and COL15A1 antibodies were studied using an immunohistochemical method.

Gremlin 1 (GREM1 polyclonal antibody PAB 14845, Abnova Corp.) and COL15A1 (polyclonal antibody NBP1-91087, Novus Biologicals) antibodies were studied with Leica Bond Max (Leica Biosystems) using a Bond Polymer Refine Detection kit. Preparations obtained were examined by 2 pathologists under light microscope. Normal tissue staining pattern was compared with tumor tissue staining pattern.

Gremlin 1 staining and its interpretation

Areas of cytoplasmic staining with GREM1 were examined both in the tumor tissue and normal kidney tissue of each patient under light microscope. Cytoplasmic staining observed in the renal tubular epithelium of the normal tissue was considered positive. Based on the pattern of staining, no staining was assigned a score of 0, weak and diffuse staining was assigned score 1 positive and diffuse and strong staining was assigned score 2 positive. For convenience in statistical analysis, score 1 and 2 were combined in a single parameter to indicate “staining present (positive)” and score 0 indicated “staining absent (negative)”.

Collagen type XV alpha-1 staining and its interpretation

Areas of cytoplasmic staining with COL15A1 in tumor cells were examined in tumor tissues. Based on the pattern of staining, no staining was assigned a score of 0, weak and diffuse staining was assigned score 1 positive and diffuse and strong staining was assigned score 2 positive. For convenience in statistical analysis, score 1 and 2 were combined in a single parameter to indicate “staining present (positive)” and score 0 indicated “staining absent (negative)”.

Microvascular density

Considering that COL15A1 also serves as an endothelial marker, microvessels stained with COL15A1 were counted under light microscopy at a magnification of x 400 in 5 fields with a clear view of the lumen in randomly selected tumor tissues and normal tissues (7).

Statistical analysis

For statistical analyses, Fischer exact test and Mann-Whitney U test were used to conduct appropriate comparisons between tumor groups. SPSS for Windows software was used for statistical analyses. For comparisons, a p value less than 0.05 was considered statistically significant.

General findings

RCC cases included 20 PRCC and 39 CRCC cases. The mean age was 56.5 years in PRCC patients and 54.15 years in CRCC

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patients. The mean tumor size was 6.34 cm for PRCC and 8.24 for CRCC.

Immunohistochemical findings

GREM1 and COL15A1 markers were studied in 59 RCC patients using immunohistochemical methodology. Associations of these markers with the type and diameter of tumor, age, sex, MVD and tumor necrosis were evaluated.

Cytoplasmic staining of tumor tissues with GREM1 was assessed in the two tumor groups separately (Figure 1). Staining was negative in 80% (score 0) and positive in 20% of PRCC cases (Images 1, 2).

Among CRCC cases, staining was absent in 20.5% and positive staining was found in 69.2% (score 1) and 10.3% (score 2) (Table 1 and Images 3, 4).

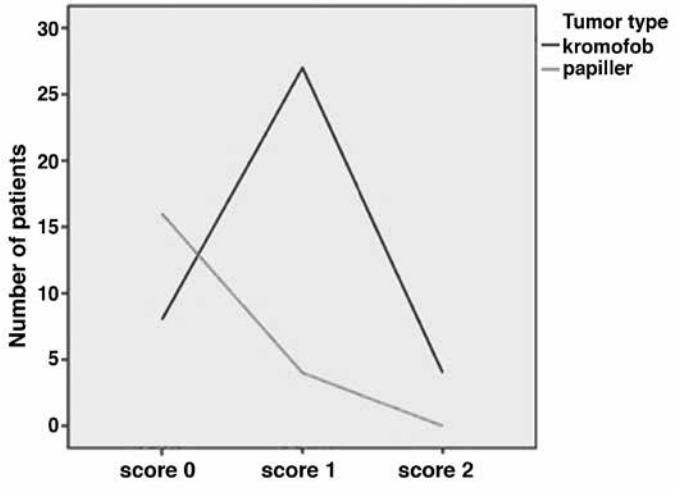

Figure 1. The degree of Gremlin 1 staining in tumor tissues as shown by the number of chromophobe renal cell carcinoma and papillary renal cell carcinoma patients

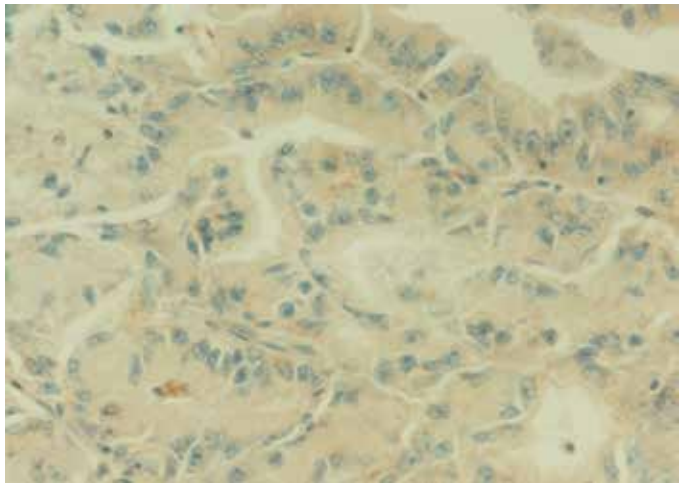

Image 1. Gremlin 1 expression in papillary renal cell carcinoma (score 0), x400

When cytoplasmic GREM1 staining of the tubular epithelial cytoplasm was evaluated separately in the healthy kidney tissues of the two tumor groups, no staining was detected in 35% of PRCC patients and positive staining was found in 60% (score 1) and 5% (score 2). For CRCC patients, staining was absent in 7.7% and positive staining was observed in 79.5% (score 1) and 12.8% (score 2) (Image 5, Table 2).

In PRCC, cytoplasmic GREM1 staining was statistically non-significant between tumor tissue versus normal tissue (p=0.249).

In CRCC, cytoplasmic positive staining with GREM1 was statistically significant for tumor tissue in comparison to normal tissue (p=0.006).

Analysis of the relationship between GREM1 expression and sex did not reveal a statistically significant difference between

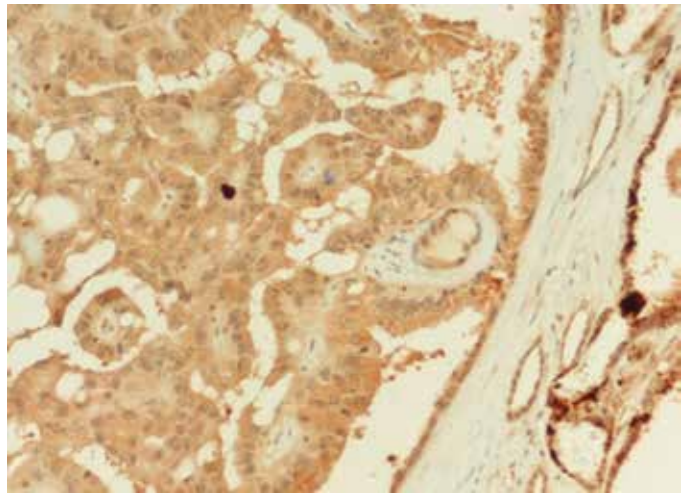

Image 2. Cytoplasmic expression of Gremlin 1 in papillary renal cell carcinoma (score 1) x200

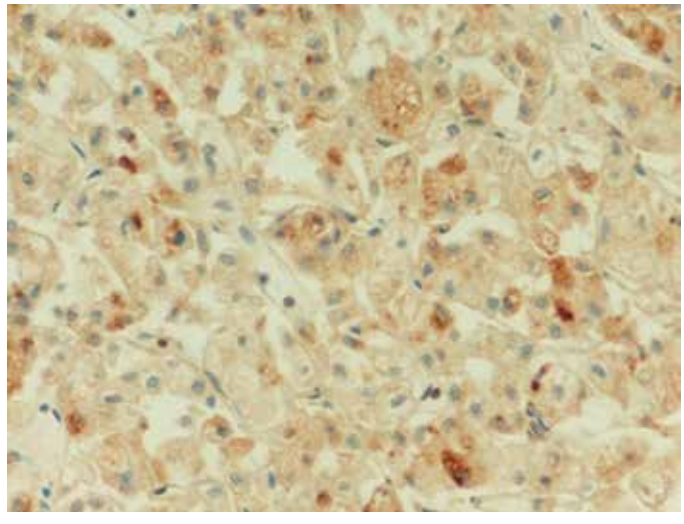

Image 3. Cytoplasmic expression of Gremlin 1 in chromophobe renal cell carcinoma (score 1) x400

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males (n=6) and females (n=13) among CRCC patients. GREM1 expression did not differ statistically significantly with respect to necrosis in CRCC patients (necrosis present: 13 patients, necrosis absent: 13 patients). Tumor diameter did not show a statistically significant association with GREM1 expression among CRCC patients (Table 3).

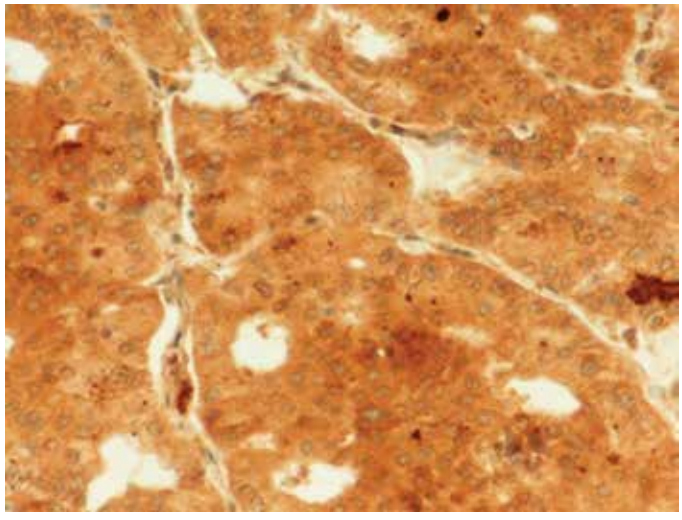

Image 4. Cytoplasmic expression of Gremlin 1 in chromophobe renal cell carcinoma (score 2) x400

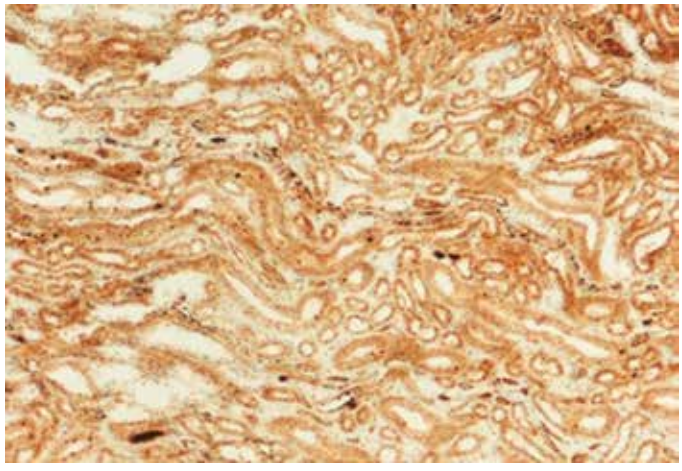

Image 5. Gremlin 1 expression in the renal tubules of healthy kidney tissue in a chromophobe renal cell carcinoma patient (score 2) x100

Evaluation of the cytoplasmic staining with COL15A1 in the tumor tissues of two tumor groups separately showed negative staining in 70% of PRCC patients and score 1 positive staining in 30% of patients (Images 6, 7). Negative staining with COL15A1 was observed in 97.4% of CRCC patients and positive staining in 2.6% (Image 8). Higher rate of staining observed in PRCC was statistically significant (p=0.0059) (Table 4).

No significant association was found between COL15A1 expression and age, sex, presence of tumor necrosis or tumor diameter in PRCC patients (Table 5).

Analysis of the association of tumor COL15A1 expression and sex did not show a statistically significant difference between males (n=15) and females (n=5) among PRCC patients. Tumor

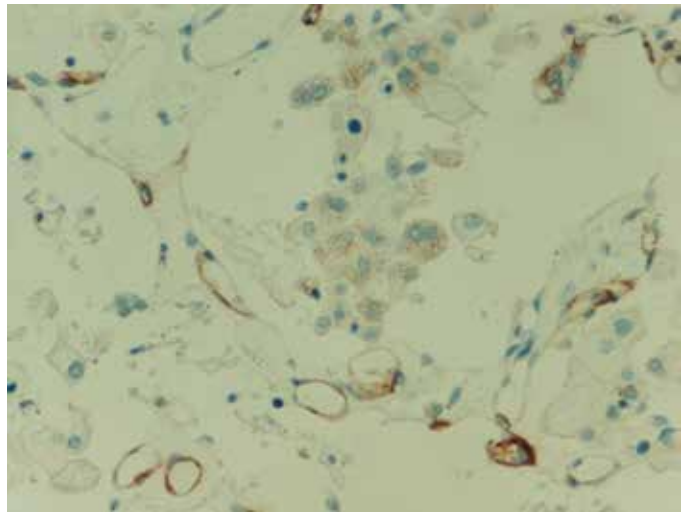

Image 6. Cytoplasmic granular collagen type XV alpha-1-positive tumor cells (score 1) and microvascular structures in a chromophobe renal cell carcinoma patient (x400)

Table 1: Rates of cytoplasmic staining for Gremlin 1

Diagnosis	Score 0	Score 1	Score 2	Total
PRCC	16 (80.0%)	4 (20.0%)	0 (0.0%)	20 (100%)
CRCC	8 (20.5%)	27 (69.2%)	4 (10.3%)	39 (100%)

PRCC: Papillary renal cell carcinoma, CRCC: Chromophobe renal cell carcinoma

Table 2: Rates of cytoplasmic Gremlin 1 staining in normal kidney tissues of both tumor groups

Diagnosis	Score 0	Score 1	Score 2	Total
Normal tubular epithelial tissue in PRCC patients	7 (35.0%)	12 (60.0%)	1 (5.0%)	20 (100%)
Normal tubular epithelial tissue in CRCC	3 (7.7%)	31 (79.5%)	5 (12.8%)	39 (100%)

PRCC: Papillary renal cell carcinoma, CRCC: Chromophobe renal cell carcinoma

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COL15A1 expression did not differ statistically significantly with respect to necrosis in PRCC patients (necrosis present: 9 patients, necrosis absent: 11 patients). Tumor diameter did not show a statistically significant relationship with COL15A1 expression among CRCC patients.

Taking into account the fact that COL15A1 serves as an endothelial marker, the relationship between numerical values of microvascular structures (MVD) stained with COL15A1 and the pattern of cytoplasmic staining with GREM1 was compared between two tumor groups and found significant for PRCC (p=0.007) but non-significant for CRCC (p=0.147). Based on these results, a positive significant correlation was found between GREM1 and angiogenesis in PRCC but not in CRCC (Image 9).

Tumor necrosis was observed microscopically in 45% in PRCC patients and in 33% of CRCC patients. Combined analysis of both tumor groups with respect to the tumor diameter and

Table 3: Relationship between tumor diameter and Gremlin 1 expression in CRCC

CRCC		**Cytoplasmic staining of tumor with Gremlin 1**		**Total**
		0	**1**	
Tumor Diameter	0-4 cm	0	5	5
		0.0%	100.0%	100.0%
	4.1-7 cm	3	11	14
		21.4%	78.6%	100.0%
	7.1-10 cm	3	8	11
		27.3%	72.7%	100.0%
	>10 cm	2	7	9
		22.2%	77.8%	100.0%
Total		8	31	39
		20.5%	79.5%	100.0%

CRCC: Chromophobe renal cell carcinoma

Table 4: Cytoplasmic staining with COL15A in tumor tissues of both tumor groups

Diagnosis	**Score 0**	**Score 1**	**Total**
PRCC	14 (70%)	6 (30%)	20 (100%)
CRCC	38 (97.4%)	1 (2.6%)	39 (100%)

PRCC: Papillary renal cell carcinoma, CRCC: Chromophobe renal cell carcinoma

Table 5: Relationship between tumor diameter and collagen type XV alpha-1 expression in papillary renal cell carcinoma

PRCC		**COL15A1 tumor expression**		**Total**
		Negative	**Positive**	
Tumor Diameter	0-4 cm	4	3	7
		57.1%	42.9%	100.0%
	4.1-7cm	5	2	7
		71.4%	28.6%	100.0%
	7.1-10 cm	3	0	3
		100.0%	0.0%	100.0%
	>10 cm	2	1	3
		66.7%	33.3%	100.0%
Total		14	6	20
		100.0%	30,0%	100.0%

PRCC: Papillary renal cell carcinoma, COL15A1: Collagen type XV alpha-1

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necrosis of the tumor tissue showed that necrosis was more likely to be found as tumor diameter increased and their association was statistically significant (p=0.035).

Discussion

Approximately 271,000 cases of kidney cancer were identified worldwide in 2008 with 116.000 people dying as a result of kidney cancer. RCC originating from renal parenchyma accounts for the majority of kidney cancers. Kidney cancers represent 2% of all adult malignancies. Among patients with kidney cancers, males are more commonly affected than females with a male to female ratio of 3:2 (8). In our study, the percentage of male patients was higher with a male to female ratio of 2.28.

The incidence of RCC peaks in the sixth decade of life and 80% of cases occur between the ages of 40 and 69 (9). Consistent with literature, the mean age of our patients was 54.9 years.

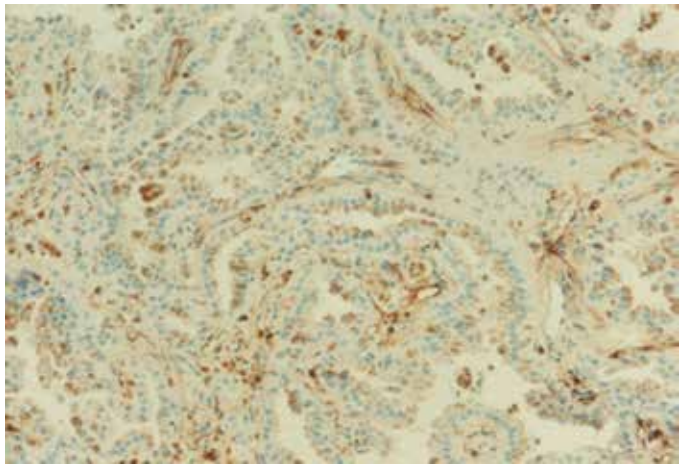

Image 7. Cytoplasmic granular collagen type XV alpha-1-positive tumor cells in a papillary renal cell carcinoma patient (x200)

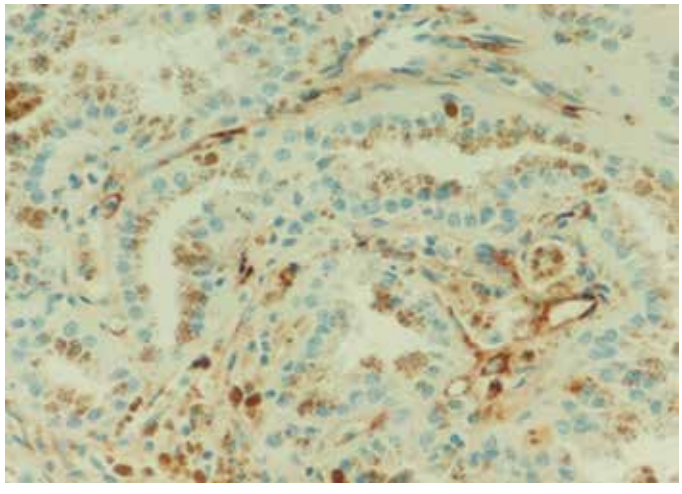

Image 8. Cytoplasmic granular collagen type XV alpha-1-positive tumor cells in a papillary renal cell carcinoma patient (score 2) (x400)

The mean tumor diameter is 6.4 cm in PRCC patients (10). In our study, the mean tumor diameter was 6.34 cm in PRCC patients, which was consistent with literature.

Intratumoral necrosis may be found in 32-75% of RCC patients (10). Tumor necrosis was observed microscopically in 45% of PRCC patients in our study.

The mean tumor diameter is 9 cm in CRCC patients (10). Our PRCC patients had a mean tumor diameter of 8.2 cm. Tumor necrosis is found in one-third of CRCC patients (10). Tumor necrosis was observed microscopically in 33% of CRCC patients in our study.

Both genetic and epigenetic factors are known to play a role in renal carcinogenesis. Epigenetics are defined as changes in a gene's function that are inherited by meiotic or mitotic division without alterations in the DNA sequence (11).

Recent studies have demonstrated upregulation of GREM 1 in a variety of human cancers (12-15). In the present study, GREM1 expression did not differ statistically significantly between tumor tissue and neighboring intact tissue in PRCC patients but tumor tissue showed significantly higher GREM1 expression in CRCC patients (p=0.006). The percentage of tumor staining was 20% in PRCC patients versus 79.5% in CRCC patients. These findings suggest that GREM1 may have a prominent role as a tumor suppressor gene in the development of CRCC. Detailed genetic studies are needed to draw more definite conclusions on the putative role of GREM1 in CRCC tumorigenesis. We suggest that differential results obtained from the two tumor types examined in the present study might be explained by different genetic pathways involved in the development of these tumors.

In our study, COL15A1 expression was observed in the vascular structures and basement membranes of tumor tissues and

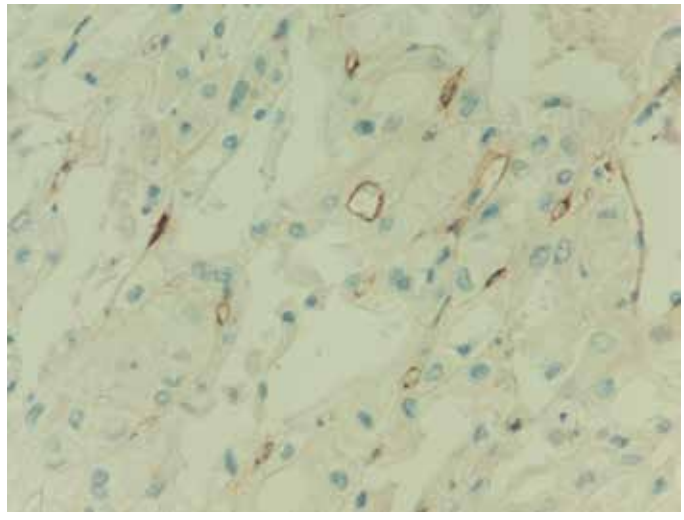

Image 9. Microvascular structures stained with collagen type XV alpha-1 in chromophobe renal cell carcinoma (x400)

neighboring intact tissues in both tumor groups. Additionally, cytoplasmic staining of tumor zones was detected in 30% of PRCC patients and 2.6% of CRCC patients. This percentage was statistically significant in PRCC (p=0.0059). Since hypermethylation of the promoter region of the COL15A1 gene was previously reported in CCRCC patients (4,5) concurrent genetic studies have to be conducted in order to determine whether cytoplasmic staining is related to hypermethylation. To our best knowledge, there are no immunohistochemical studies in literature that examined COL15A1 in any tumor tissue. Thus, our study is the first to report relevant findings on this issue.

GREM1 is a novel proangiogenic factor as demonstrated by several studies (2,7). In a study by Chen et al. (7) on tumor-related angiogenesis, expression of GREM1 was shown to be correlated with increased angiogenesis in patients with pancreatic neuroendocrine tumors. In a study by Chen et al. (7) it was argued that GREM1 might be used as a prognostic marker in pancreatic neuroendocrine tumors which was based on the positive correlation observed between increased MVD and GREM1 expression. On the other hand, Van Vlodrop et al. (1) reported that methylation of the promoter region of Gremlin was associated with higher tumor grade, higher tumor stage, reduced MVD and shorter survival time in patients with CCRCC. Karagiannis et al. (16) showed that GREM1 promotes the loss of cancer cell differentiation at the cancer invasion front, a mechanism that may facilitate tumor progression. Yan et al. (17) reported that Gremlin1-overexpressing cells display increased growth and tumor formation abilities. In our study, the association between GREM1 expression and angiogenesis was examined in tumor tissues using numerical values of microvascular structures (MVD) stained with COL15A1 taking into account the fact that COL15A1 serves as an endothelial marker. In PRCC patients, the number of microvascular structures showed a positive, significant association with GREM1 expression in the tumor tissue (p=0.007). Increased number of microvascular structures associated with GREM1 expression as observed in the current study suggested that GREM1 might be involved in increased angiogenesis in PRCC. For CRCC, a statistically significant association was not found between aforementioned parameters.

Increased angiogenesis is a characteristic feature of CCRCC. These tumors have the worst prognosis among all RCC cases. Given the fact that PRCC tumors are associated with a worse prognosis than CRCC tumors, it was suggested that a marker associated with increased angiogenesis in PRCC might serve as an indicator of poor prognosis. The association of GREM1 and COL15A1 markers with poor prognosis in RCC should be explored in future studies.

Conclusion

Cytoplasmic staining with GREM1 detected in both tumor groups, albeit at different rates, and much higher expression of this marker particularly in the tubular epithelium of the neighboring intact tissue support the hypothesis that GREM1 might be a tumor suppressor gene as suggested by literature data.

Significant relationship between the microvascular distribution pattern and GREM1 observed in PRCC patients suggest that GREM1 implicated in tumor angiogenesis might act as a proangiogenic factor in these tumors as well, in parallel with literature data.

We believe that the significant pattern of cytoplasmic staining in tumor tissues observed with COL15A1 particularly in PRCC cases in our study is of interest and this finding should be confirmed with additional studies.

It is our belief that genetic studies simultaneously conducted with immunohistochemical studies would provide more definite results on tumorigenesis in PRCC and CRCC and eventually contribute to the development of new diagnostic and therapeutic approaches by elucidating the underlying mechanism of these tumors.

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Conflict of Interest

The authors declare that there is no conflict of interest arising out of this manuscript.

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Aqueous garlic extract protects against sepsis-induced toxicity in pulmonary and ileal tissues

Sevil Ozkan[1]*, Tugba Tunali Akbay[2], Selin Sakarcan[3], Emre Gunay[4], Goksel Sener[5]

Abstract

Objective: Based on the potent antioxidant effects of aqueous garlic extract (AGE), the present study was designed to characterize the potential of AGE to modify blood coagulation parameters as well as and pulmonary and ileal injury in septic rats. Sepsis was induced using the caecal ligation and perforation (CLP) method.

Material and Method: Twenty-four hours after sepsisinduction, rats were decapitated and trunk blood was collected for the measurement of platelet counts, fibrinogen, prothrombin time, activated partial thromboplastin time (APTT) and d-dimer levels. Then, pulmonary and ileal tissue samples were immediately obtained and stored at-70 °C for malondialdehyde (MDA), glutathione (GSH), myeloperoxidase (MPO) and superoxide dismutase (SOD) activity assays.

Results: Sepsis was associated with a decrease in platelet count and fibrinogen and an increase in APTT and International normalized ratio. It also caused a significant decrease in GSH levels and SOD activity in both pulmonary and ileal tissue samples. On the other hand, AGE treatment in rats with CLP caused significantly augmented the level of these antioxidants. As a result of CLP induction increased MPO activity and MDA levels and decreased thromboplastic activity were reversed with AGE treatment.

Conclusion: AGE treatment, through its antioxidant effects, protects against oxidative pulmonary and ileal injury and normalizes the impaired coagulation in sepsis.

Keywords: Oxidative stress, thromboplastic activity, septic, rat, pulmonary injury, ileal injury

Introduction

Septic shock is an infectious complication in which toxins initiate an inflammatory response involving all systems. Therefore, it is defined as an excessive and irregular systemic inflammatory response to an infectious state, involving various organ systems, that leads to hemodynamic changes, and ultimately results in shock, organ failure or even death. Excessive production of reactive oxygen species (ROS) by activated immune cells causes oxidative damage, which is thought to play a significant role in the pathogenesis of sepsis induced organ damage (1,2). These radicals lead to lipid peroxidation, impair cell membranes, and give rise to oxidative damage in deoxyribonucleic acid and proteins (3). Several experimental and clinical studies have shown beneficial effects of antioxidants in preventing organ failure and decreasing mortality in sepsis (4,5).

Garlic Allium sativum 'A. sativum' has been widely used as a foodstuff and also a traditional medicine for many centuries throughout the world (6). The antibacterial effects of garlic against a wide range of bacteria (7) and the intrinsic antioxidant activity of garlic, garlic extracts and some garlic constituents (8-10) have been widely documented in vivo (11,12) and in vitro (8,13). Furthermore, garlic acts as an enhancer of cellular antioxidant enzymes; superoxide dismutase (SOD), catalase, and glutathione (GSH) peroxidase, in addition to increasing cellular GSH levels (14-16). These properties of garlic increase the antioxidant capacity of the body and provide effective scavenging of free radicals, thereby improving immunity (17,18).

Based on the potent antibacterial and antioxidant effects of garlic, we investigated the putative protective role of aqueous

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[1]Haydarpasa Numune Education and Research Hospital, Clinic of Internal Medicine, Istanbul-Turkey
[2]Marmara University Faculty of Medicine, Department of Medical Biochemistry, Istanbul-Turkey
[3]Temple University Faculty of Medicine, Department of Microbiology, Pennsylvania-USA
[4]Haydarpasa Numune Education and Research Hospital, Clinic of General Surgery, Istanbul-Turkey
[5]Marmara University Faculty of Pharmacy, Department of Pharmacology, Istanbul-Turkey
*Corresponding Author: Sevil Ozkan E-mail: sevilozkan@hotmail.com

garlic extract (AGE) against sepsis-induced oxidative damage in pulmonary and ileal tissues as well as its effects on certain coagulation parameters.

Material and Methods

Animals

Wistar albino rats of either sex, weighing 200 to 250 g, were kept in a room at a constant temperature (22±2 °C) with 12-h light and dark cycles and were fed a standard rat chow. Rats were fasted for 12 h before experiments, but were allowed free access to water. Experimental protocol was approved by the Marmara University Animal Care and Ethics Committee.

Preparation of garlic extract

Garlic, from which the study preparations were derived, was harvested in August from Kastamonu region of Turkey and was kept in dry storage conditions protected from light. Peeled garlic (30 g) was crushed with distilled water in a mortar. The crushed material was carefully decanted by pressing, and 60 mL of aqueous extract was extracted. One milliliter of aqueous extract contained material from 500 mg of garlic (19,20). The aqueous extract was stored at 4 °C.

Experimental protocol and induction of sepsis

Rats were divided into four groups, 2 control and 2 sepsis groups, with 8 animals in each. Rats were supplemented with either saline or AGE (250 mg/kg/day orally) for 15 days prior to sham operation or caecal ligation and perforation (CLP), and also immediately postoperatively.

In the sham operated control groups, after laparotomy, the cecum was manipulated but left intact (without ligation or perforation). In the sepsis groups rats underwent CLP technique according to the method described by Fujimura et al. (21). Briefly, under ether anesthesia, a midline laparotomy was made using minimal dissection and the cecum was ligated just below the ileocaecal valve with 3-0 silk ligatures so that intestinal continuity was maintained. On the antimesentric surface of the cecum, using an 18-gauge needle, the cecum was perforated at two locations 1 cm apart and the cecum was gently compressed until the feces were extruded. The bowel was then returned to the abdomen and the incision was closed. At the end of the operation, all rats were resuscitated with saline (3 mL/100 g body weight) administered subcutaneously.

Twenty-four hours after the sepsis-induction, rats were decapitated and trunk blood was collected for the measurement of platelet counts, fibrinogen, International normalized ratio (INR) and activated partial thromboplastin time (APTT) levels. Furthermore lung and ileum tissue samples were immediately taken and stored at -70 °C to analyze SOD, myeloperoxidase (MPO), and thromboplastic activities, as well as malondialdehyde (MDA) and GSH levels.

Determination of coagulation parameters in blood

Trunk blood was collected into plastic syringes containing one-tenth in a volume of 3·8% (w/v) trisodium citrate or into plastic syringes containing sodium ethylenediaminetetraacetic acid (EDTA). Blood samples taken into 3·8 % (w/v) trisodium citrate were centrifuged at 2000 g for 10 min for the measurement of prothrombin time (prothrombin time, INR) (Cat. no. 52601003, Agappe, Switzerland), APTT (Cat. no. 52602001, Agappe, Switzerland), fibrinogen (Cat. no. 840155, Pacific Hemostasis, UK), and d-dimer (Cat. no. D2050-000, Teco, Germany). In d-dimer test, agglutination occurs within 180-200 seconds for samples containing more than 250 ng/mL. If agglutination is observed within 180-200 seconds a pathological condition probably exists. Platelet count was determined in the whole blood samples drawn into sodium EDTA by using an automated analyzer (KT 6200 VET, Genius, China).

Measurement of tissue superoxide dismutase activity

SOD activity in the lung and ileum tissue samples was measured in accordance with a previously described method (22). Briefly, measurements were performed in cuvettes containing 2.8 mL 50 mM potassium phosphate (pH=7.8) with 0.1 mM EDTA, 0.1 mM 0.39 mM riboflavin in 10 mM potassium phosphate (pH=7.5), 0.1 mL of 6 mM O-dianisidin.2 HCl in deionized water, and tissue extract (50, 100 mL). Cuvettes with all their components were illuminated with 20-W Sylvania Grow Lux fluorescent tubes that were placed 5 cm above and to one side of cuvettes maintaining a temperature of 37 °C. Absorbance were measured at 460 nm with a Shimadzu UV-02 model spectrophotometer. A standard curve was prepared routinely with bovine SOD (Sigma Chemical Co, ST-2515-3000 U) as reference. Absorbance readings were taken at 0 and 8 min of illumination and the net absorbance were calculated.

Measurement of tissue myeloperoxidase activity

MPO activity was measured in tissues in a procedure similar to that documented by Hillegass et al. (23). Tissue samples were homogenized in 50 mM potassium phosphate buffer (PB, pH=6.0), and centrifuged at 41,400 g (10 min); pellets were suspended in 50 mM PB containing 0.5% hexadecyltrimethylammonium bromide. After three freeze and thaw cycles, with sonication between cycles, the samples were centrifuged at 41,400 g for 10 min. Aliquots (0.3 mL) were added to 2.3 mL of reaction mixture containing 50 mM PB, O-dianisidine, and 20 mM H_2O_2 solution. One unit of enzyme activity was defined as the amount of MPO present that caused a change in absorbance measured at 460 nm for 3 min. MPO activity was expressed as U/g tissue.

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Measurement of tissue thromboplastic activity

Thromboplastic activity of lung and ileum tissues was evaluated according to Quick's onestage method using normal plasma (24). This was performed by mixing 0.1 mL tissue homogenate with 0.1 mL 0.02 M $CaCl_2$; the clotting reaction was started upon the addition of 0.1 mL plasma. All reagents were brought to the reaction temperature (37 °C) before mixing. Thromboplastic activity was expressed as seconds. The lengthening of the clotting time is an indication of decreased tissue factor (TF) activity.

Measurement of tissue malondialdehyde and glutathione levels

Lung and ileum tissue samples were homogenized with ice-cold 150 mM chloride for the determination of MDA and GSH levels. MDA levels were assayed for products of lipid peroxidation by monitoring thiobarbituric acid reactive substance formation as described previously (25). Lipid peroxidation was expressed in terms of MDA equivalents using an extinction coefficient of $1.56x10^5$ M^{-1} cm^{-1} and results are expressed as nmol MDA/g tissue. GSH measurements were performed using a modification of the Ellman procedure (26). Briefly, after centrifugation at 3000 rev/min for 10 min, 0.5 mL of supernatant was added to 2 mL of 0.3 mol/l $Na_2HPO_4.2H_2O$ solution. A 0.2 mL solution of dithiobisnitrobenzoate (0.4 mg/mL 1% sodium citrate) was added and the absorbance at 412 nm was measured immediately after mixing. GSH levels were calculated using an extinction coefficient of 1.36x104 M^{-1} cm^{-1}. Results are expressed in µmol GSH/g tissue.

Statistical analysis

Statistical analysis was carried out using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA) and all data were expressed as means ± standard error of mean. Groups of data were compared with an analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. A p value of less than 0.05 was considered significant.

Results

As shown in Table 1 sepsis was associated with reduced platelet and fibrinogen, and increased APTT and INR levels. D-dimer levels also increased after sepsis induction (Table 2). On the other hand AGE treatment did not have a significant effect on these parameters except for d-dimer, which was significantly reduced by AGE treatment (Table 2).

Sepsis induced significant decrease in GSH and SOD in both lung ($p<0.001$, Figure 1) and ileum ($p<0.01$, Figure 2) tissue samples, while AGE treatment in rats with CLP gave rise to significant increases in both of these antioxidants ($p<0.5$).

As a result of CLP induction, MPO activity and MDA levels were found to increase in both lung and ileum tissues ($p<0.001$, Figure 3 and Figure 4, respectively). On the other hand, AGE treatment in the CLP group caused a decline in these values ($p<0.005$-0.001) restoring baseline levels.

Since the clotting time is inversely proportional to the TF activity, prolonged clotting time is indicative of decreased TF activity. Accordingly, CLP caused decrease in TF activity of lung and ileum tissues ($p<0.001$, Figure 3c, 4c). On the other hand AGE treatment in CLP rats caused an increase in TF activity in both lung ($p<0.05$) and ileum ($p<0.001$) tissues.

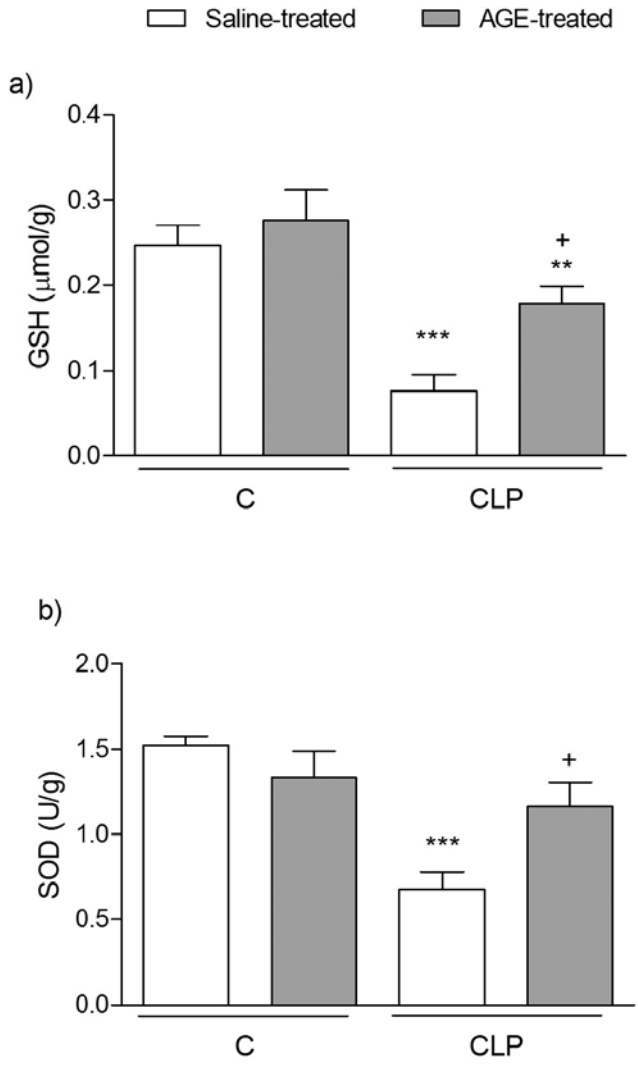

Figure 1. Glutathione levels and b) Superoxide dismutase activities in the lung tissue samples of saline-and aqueous garlic extract-treated control and sepsis groups, **p<0.01, ***p<0.001 versus saline-treated control group, $^{+}$p<0.05 versus saline treated-sepsis group, for each group n=8, GSH: Glutathione, SOD: Superoxide dismutase, CLP: Caecal ligation and perforation, AGE: Aqueous garlic extract

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Discussion

Being one of the most popular herbal remedies, garlic has been widely used for the treatment of diseases since ancient times, despite the scarcity of data in the current literature on the effects of AGE on pulmonary and ileal tissues in sepsis. In the present study, pulmonary and ileal pathologic changes induced by oxidative damage due to experimentally-induced sepsis and the potential protective effects of AGE against this damage were investigated. Our results showed an alleviation of sepsis-induced oxidative damage in the lung and intestinal tissues by AGE, as suggested by significantly reduced MDA and MPO levels and increased GSH and SOD. Furthermore, thromboplastic activity, which decreased due to sepsis, was augmented by AGE

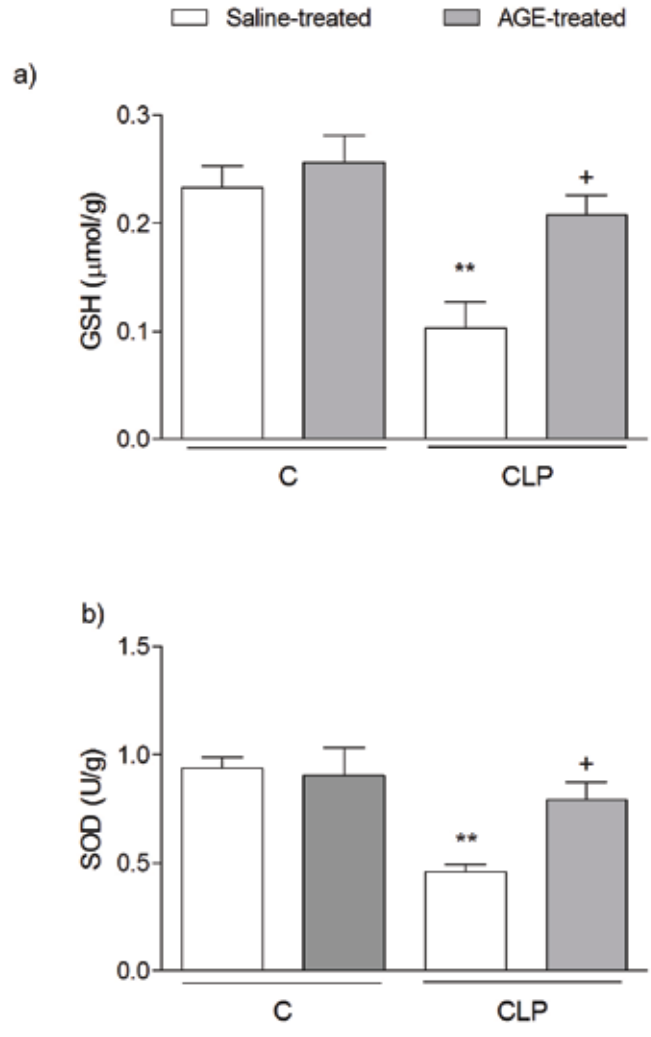

Figure 2. Glutathione levels and b) Superoxide dismutase activities in the ileal tissue samples of saline-and aqueous garlic extract-treated control and sepsis groups, **p<0.01 versus saline-treated control group, $^{+}$p<0.05 versus saline treated-sepsis group, for each group n=8, GSH: Glutathione, SOD: Superoxide dismutase, CLP: Caecal ligation and perforation, AGE: Aqueous garlic extract

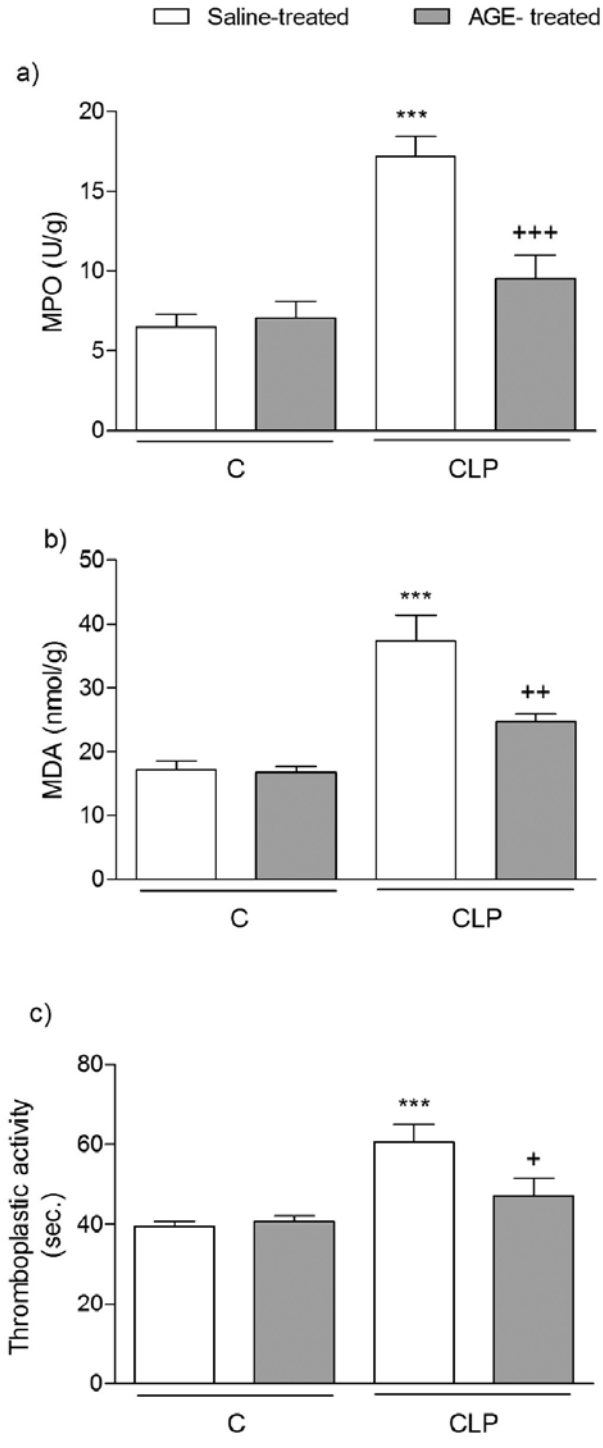

Figure 3. Myeloperoxidase activities, b) Malondialdehyde levels and c) Thromboplastic activities in the lung tissues of saline- and aqueous garlic extract-treated control and sepsis groups, ***p<0.001 versus saline-treated control group, $^{+}$p<0.05, $^{++}$p<0.01, $^{+++}$p<0.001 versus saline treated-sepsis group, for each group n=8, MPO: Myeloperoxidase, MDA: Malondialdehyde, CLP: Caecal ligation and perforation, AGE: Aqueous garlic extract

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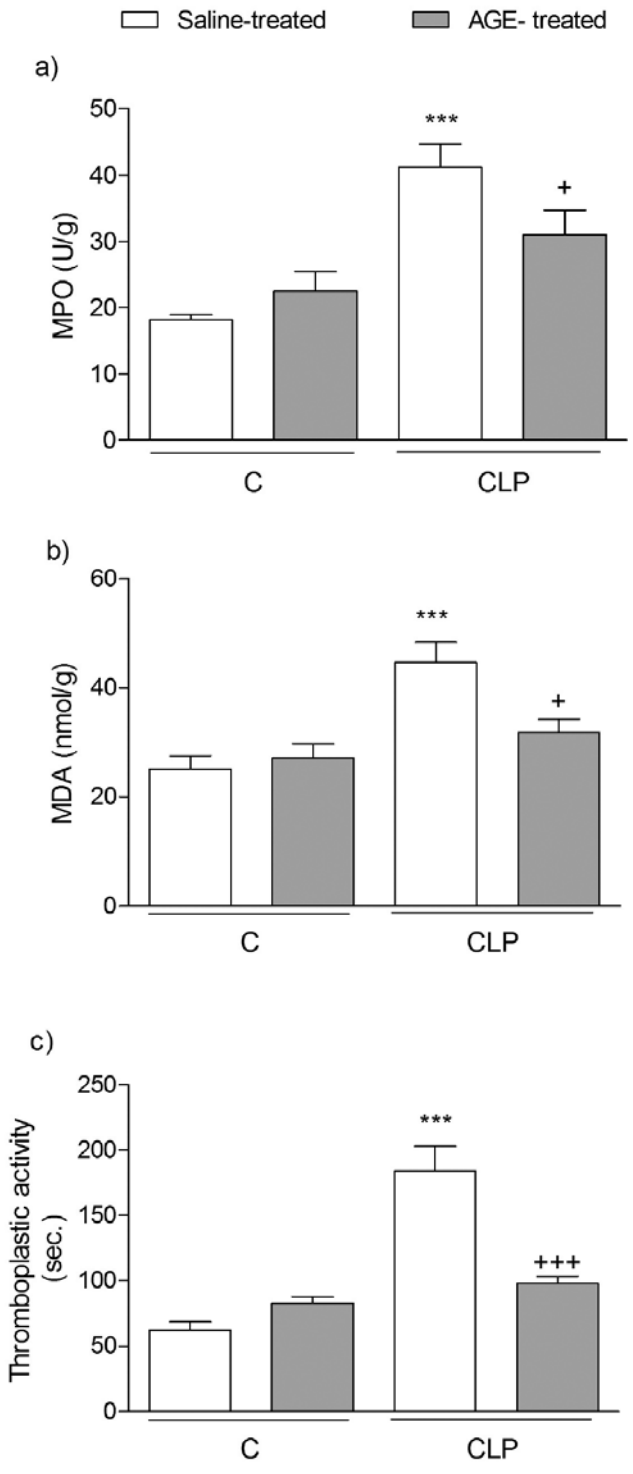

Figure 4. Myeloperoxidase activities, b) Malondialdehyde levels and c) Thromboplastic activities in the ileal tissues of saline- and aqueous garlic extract-treated control and sepsis groups, ***p<0.001 versus saline-treated control group, $^{+}$p<0.05, $^{+++}$p<0.001 versus saline treated-sepsis group, for each group n=8, MPO: Myeloperoxidase, MDA: Malondialdehyde, CLP: Caecal ligation and perforation, AGE: Aqueous garlic extract

treatment and the sepsis-induced reduction in platelet count was partially reversed. On the other hand, INR and APTT, which were elevated in septic rats, were significantly decreased by AGE treatment. AGE treatment did not affect fibrinogen and d-dimer levels, which were decreased and elevated, respectively, during sepsis. Garlic containing preparations have recently been shown to exert beneficial effects against tumor promotion (27), in cardiovascular disorders, in hepatic damage (28) and in the process of aging (29) and these effects were mostly attributed to its anti-oxidant properties. Preventive or therapeutic strategies that incorporate the use of AGE might arguably be developed in this condition, considering the fact that sepsis is associated with oxidative damage in various organs (30) and that garlic is known to have antioxidant properties.

Sepsis is a generalized inflammatory response, involving various organ systems and causing disturbance of homeostasis through a currently uncontrollable cascade of excessive inflammation and coagulation with impaired fibrinolysis that contributes to an inflammatory response, microvascular hypoperfusion, organ dysfunction, and increased mortality. The magnitude of disruption in homeostasis is influenced by the virulence of the causative pathogens and the host's response to the infection (31-33). In this regard, the results of the present study are consistent with the above-mentioned hemostatic disturbance in sepsis. On the other hand, although garlic has been shown to have antithrombotic and antiplatelet properties (34,35), in the present study AGE decreased the platelet count only in the control group without an antithrombotic effect. However reversal of the sepsis-induced changes in platelet count, INR, APTT and d-dimer level by AGE treatment suggests that these effects of AGE in sepsis may not be directly linked with its antithrombotic and antiplatelet effects, and rather may stem from its antioxidant and antibacterial effects.

The CLP are widely used for the induction of sepsis in models of sepsis based on its clinical resemblance to sepsis in humans. Recent studies have shown that sepsis is associated with the enhanced generation of reactive oxygen metabolites (ROMs), leading to multiple organ dysfunction (36,37), most marked in lungs, liver, kidneys, heart, and intestines. These pathological changes are known to result from bacterial invasion, direct effects of bacterial toxins and enzymes, effects of mediators, impaired perfusion, and disseminated intravascular coagulation (38). Pulmonary involvement occurs early in sepsis and pulmonary complications are major factor contributing to poor prognosis. After pulmonary involvement, other common pathological conditions include the acute ischemic colitis in the intestines and zonal necrosis of the liver (39,40).

Lipids are a major target of free oxygen radicals, which initiate lipid peroxidation by receiving a hydrogen atom from

polyunsaturated fatty acids, giving rise to the formation of hydrogen peroxide. The result of this process is the disrupted cell membrane fluidity followed by cell death (41). In the present study, the levels of MDA, an end-product of lipid peroxidation, were significantly increased in pulmonary and ileal tissues, in line with the previous studies, in which elevated levels of lipid peroxidation products were increased from 40% to 80% above basal values as a result of oxidative stress (30,42,43). On the other hand, AGE treatment inhibited MDA elevations and restored the control levels suggesting that AGE might be protective against organ damage by maintaining cellular integrity.

There are enzymatic and non-enzymatic antioxidant mechanisms involved the removal of free radicals and for damage repair. Among enzymatic antioxidants, SOD is particularly important for intracellular killing of phagocytized bacteria and for granulocyte function (44). It catalyzes the conversion of superoxide to hydrogen peroxide and is primarily protective against oxyradicals. GSH, on the other hand, a non-enzymatic antioxidant, is an important constituent of intracellular protective mechanisms against various noxious stimuli including oxidative stress (45). In a previous study by our team, CLP was shown to cause significant decrease in GSH levels, which was reversed by the powerful antioxidant melatonin (46). Furthermore we also demonstrated that following a variety of various oxidative insults resulting in depletion of GSH, repletion could be accomplished by AGE (19,47). Similarly, Kilikdar et al. (28) demonstrated that AGE treatment provided an elevation in SOD activity in lead -induced hepatic injury in rats. In our study, pulmonary and ileal tissue GSH levels and SOD activities were lower in the sepsis group as compared to the control group, while AGE was effective in replenishing these antioxidants.

Studies have demonstrated that neutrophils are one of the major sources of ROMs (48). The heme enzyme MPO, found in neutrophils, uses a superoxide anion to produce hypochlorous acid, which is the major oxidant for its immune function. However, these MPO-derived oxidants also cause tissue and cellular damage (49). Thus, the tissue-associated MPO activity is considered to indicate the severity of inflammatory damage. Kettle and Winterbourn (50) suggested that inhibition of the enzyme activity could modulate the oxidant production and ultimately, tissue damage. In our study, increased MPO activity in both tissues suggests that neutrophil accumulation contributes to the sepsis-induced oxidative injury. Previously, in ischemia/reperfusion-or naphthalene-induced oxidative stress models (51), increased MPO activities have been reported to decrease with AGE treatment. Similarly in our study, pulmonary and ileal tissue MPO activities were significantly higher in sepsis group as compared to the control group, while a significant decrease occurred in the sepsis group treated with AGE, suggesting an anti-inflammatory effect for AGE.

Thromboplastin (TF, factor III), the primary cellular initiator of blood coagulation, is a transmembrane receptor that is expressed in a tissue-specific manner (52). Moreover, various tissues and body fluids are known to harbor thromboplastic activity (53,54). In the present study, although a significant decrease in the thromboplastic activity occurred in in the lung and pulmonary tissues in association with sepsis, AGE treatment resulted in a significant increase in thromboplastic activity in both tissues. Normalization of thromboplastic activity with AGE may also help eliminate the increased risk of bleeding due to the decreased thromboplastic activity in pulmonary and ileal tissues in sepsis.

Table 1: Platelet count, fibrinogen, International normalized ratio and activated partial thromboplastin time levels in plasma

	C		CLP	
	Saline-treated	**AGE-treated**	**Saline-treated**	**AGE-treated**
Platelet count (x10^3/mm^3)	493±17.1	420±23.3*	205±10.4***	280±21.7***, $^{+}$
Fibrinogen (mg/dL)	428±5.4	389±31.9	296±22.8**	355±30.1
INR	1.06±0.04	1.11±0.07	1.84±0.13***	1.40±0.06^{+}
APTT (sec.)	29.5±2.4	35.7±3.0	70.2±2.5***	54.4±1.3***, $^{+++}$

n=8 per group, *p<0.05, **p<0.01, ***p<0.001 vs. control group, $^{+}$p<0.05, $^{+++}$p<0.001 vs. saline-treated sepsis group, CLP: Caecal ligation and perforation, AGE: Aqueous garlic extract, INR: International normalized ratio, APTT: Activated partial thromboplastin time

Table 2: Changes in d-dimer for all groups

	C		CLP	
	Saline-treated	**AGE-treated**	**Saline-treated**	**AGE-treated**
D-dimer (ng/mL)	<250	<250	>16000***	500-1000*

<250 ng/mL: There is no agglutination in undiluted and serial dilutions until 1:64 dilutions 500-1000 ng/mL: There is agglutination in 1:2 dilutions and there is no agglutination in serial dilutions until 1:64 dilutions n=8 per group, *p<0.05, ***p<0.001 vs. control group, CLP: Caecal ligation and perforation, AGE: Aqueous garlic extract

Conclusion

In conclusion, the results of our study showed antioxidant and anti-inflammatory effects of AGE against tissue damage caused by free oxygen radicals and lipid peroxidation resulting from sepsis in an experimental rat model. However, further studies are warranted to better define the mechanisms of pulmonary and intestinal injury due to sepsis as well as the mechanisms of the benefit observed in AGE treatment.

Conflict of Interest: The authors declare that there is no conflict of interest arising out of this manuscript.

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Ecthyma gangrenosum in a pediatric patient and review of the literature

Sevgi Buyukbese Sarsu[1]*, Mehmet Ergun Parmaksiz[1], Ayhan Yaman[2]

Abstract

Ecthyma gangrenosum (EG), is an infective lesion of skin, and mucous membranes typically occurring in patients with chronic disease or immunocompromised patients. It is a very rarely seen vasculitis with a potentially progressive and fatal course. An 8-year-old pediatric patient was referred to an external medical center with complaints of fever, abdominal pain, and skin rashes starting 2 days previously, and upon deterioration of his general health state, he was admitted into a surgical intensive care unit with manifestations of septic shock. In the treatment, all necrotic tissues including skin, and subcutaneous tissue were excised down to a healthy tissue after excision of all necrotic tissue. Vacuum assisted closure was applied on this area for drainage. Herein, we aimed to indicate that definitive treatment of a neutropenic child with EG is surgery excision, and also emphasize critical importance of re-excision of newly developed necrotic tissue at an early stage, and close monitorization of the patient.

Keywords: Ecthyma gangrenosum, abdomen, neutropenic child

Introduction

Ecthyma gangrenosum (EG) is an infective lesion characterized by direct involvement of the skin, and mucous membranes by pathogens or hematogenous spread typically seen in patients with chronic or immunosuppressive diseases (1,2). In this very rarely encountered form of vasculitis bacterial dissemination affects adventitia, and media of venous blood vessels of the skin, while intima, and intimal layer, and lumina of these vessels remain intact.

These lesions which are generally seen on the gluteal, and lumbar regions, manifest themselves firstly as painless, red colored macules, and enlarge gradually. They develop into papules, then hemorrhagic bullae, and finally rupture. Gray-black eschar lesion is surrounded by an erythematous halo. EG is very rarely seen in healthy individuals without any risk factor, however, rarely nonbacteremic EG has been also reported (3). Most cases may be associated with septisemia that can increase mortality rate. Herein, we reported the importance of surgical excision as a definitive treatment in a male child with EG.

Case

An 8-year-old male patient was brought to an external center with complaints of fever, abdominal pain, and rashes persisting for the previous 2 days. Upon deterioration of his health state, he was admitted into intensive care unit with the diagnosis of severe sepsis. Some of his physical examination findings were as follows: body temperature, 390C; heart rate, 150 bpm; ABP 70/35 mmHg, and respiratory rate, 44/min. An ulcerated necrotic lesion with regular contours, and dimensions of 10x12 cm extending from the right side of the umbilicus on the anterior abdominal wall was seen. This pink colored lesion converted to a black colored eschar with time (Figure 1). Some laboratory parameters of the patient with a history of pneumonia, and recurrent episodes of dental abscess were as follows: white blood cell, 1.270/mm^3 UL (4.5-11), neutrophil counts: 260/mm^3, hemoglobin 10.8 g/dL (14-18), hematocrit 33.2 (42-52), platelet 806 103 (130-400), alanine aminotransferase 158 U/L (8-60), aspartate aminotransferase 66 U/L (5-45), creatinine kinase: 4800 ng/mL (55-170), C-reactive protein 27 ng/mL (0-0.6), mass creatine kinase-MB 101.26 ng/mL (0-5), troponin I 5.191 ng/mL (0-0.06), and lactate dehydrogenase 399 U/L (110-295). On abdominal tomograms a widespread area of necrosis with a diameter of 12 cm which penetrated deeply into peritoneum was detected (Figure 2). The patient in septic shock was given clindamycin, vancomycin, meropenem, metronidazole, fluconazole, and trimethoprim-sulfametoxazole in addition to inotropic agents. Immunologic tests were

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[1]Cengiz Gokcek Obstetrics and Children's Hospital, Clinic of Pediatric Surgery, Gaziantep-Turkey
[2]Cengiz Gokcek Obstetrics and Children's Hospital, Clinic of Pediatric Intensive Care Unit, Gaziantep-Turkey
*Corresponding Author: Sevgi Buyukbese Sarsu E-mail: sarsusevgi@yahoo.com.tr

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requested. Bacterial growth was not detected on blood, and biopsy specimen cultures Neutrophenic patient received granulocyte-colony stimulating factor, and intravenous immune globulin. Treatment: All necrotic tissue under the skin and subcutaneous tissue were excised down to healthy tissue. Then drainage was achieved using vacuum assisted closure (Figure 3). Histopathological evaluation revealed hemorrhagic necrosis,

Figure 1. An ulcerated, necrotic lesion measuring 10x12 cm on the anterior abdominal wall

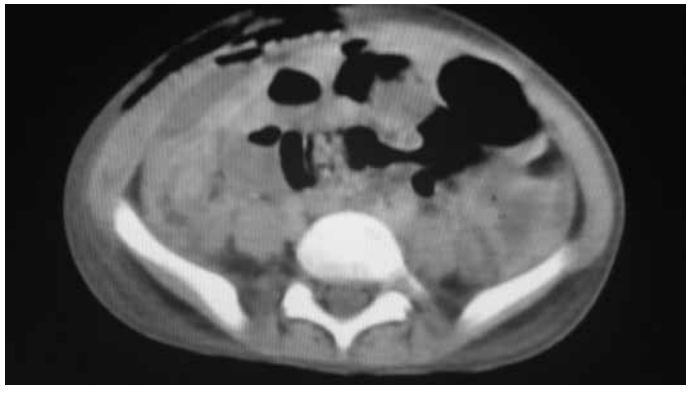

Figure 2. A widespread necrotic lesion with an approximate diameter of 12 cm penetrating deeply into the peritoneum is observed on abdominal computerized tomography scan

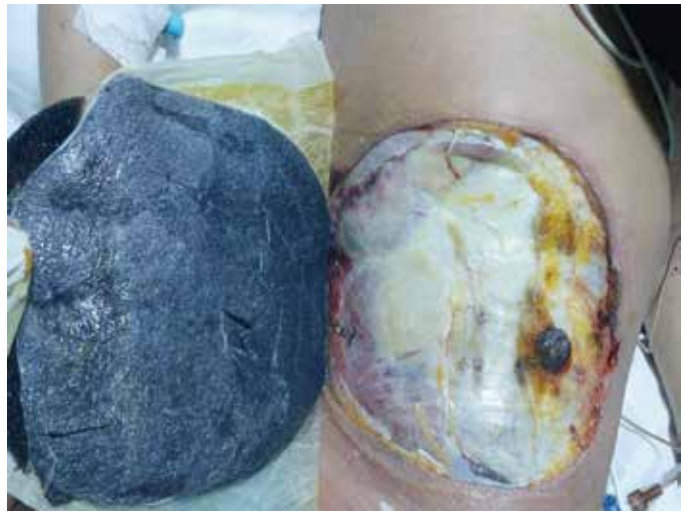

Figure 3. Application of vacuum assisted closure

thrombus formation, inflammatory cell infiltration involving vascular walls, and perivascular space. Newly formed 2x2 cm necrotic tissues 12 hours later lateral to the excised area were immediately excised. However during follow-up period he had not experienced disease progression or recurrence.

Discussion

EG is an aggressive cutaneous disease seen mostly in cases with pseudomonas sepsis, and it is characterized by a wide spectrum of skin lesions ranging from maculopapular lesions, hemorrhagic bullae, necrotic tissue to ulcerations (4-7). Lesions can mature within a short time (12 hr) or turn into ulceration with a necrotic center, and manifest different stages of evolution. As was learnt from the anamnesis of our patient, his lesions also followed up the typical stages of development. Lesions generally develop both in cases with or without sepsis This evolution from macule to eschar occurs over a period of approximately 12-24 hours (4). The lesions reportedly are localized on gluteal, and perineal regions, extremities, neck, trunk, and face (8). Mortality rates for EG range from 15% to as high as 77% based on reports in the literature (9). Currently, a large local excision, and antibiotherapy are recommended as soon as the diagnosis is established. In the literature, the critical importance of surgeon during the process of definitive diagnosis, and treatment has been emphasized (10). In a neutropenic child with EG should be closely monitored for a possible early intervention in consideration of potential development of new necrotic tissues. Lesions of EG should be rapidly diagnosed by their characteristic morphology so as to avoid complications (11).

Conclusion

In the definitive treatment of EG timely performed surgical excision has a crucial importance regarding prevention of mortality.

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A child with Hallermann-Streiff syndrome; as an infrequent cause of hypotrichosis and cataract

Sultan Kaba*, Murat Dogan, Nesrin Ceylan, Keziban Bulan, Nihat Demir, Sekibe Zehra Dogan, Selami Kocaman

Abstract

In present case report, four-months-old boy who referred to our pediatric endocrinology outpatient clinic from department of ophthalmology due to evaluation of endocrine and metabolic disorders for cataract was discussed. The characterized features of patient were hypotrichosis, microphthalmia, nystagmus, strabismus, congenital cataract, beaked nose, micrognathia, scaphocephaly, frontal and parietal bossing. The case has typical dysmorphic physical examination findings that appropriate diagnostic features to rare Hallermann-Streiff syndrome.

Keywords: Hallermann-Streiff syndrome, congenital cataract, microphthalmia, hypotrichosis

Introduction

Hallermann-Streiff syndrome (HSS) is characterized by a typical skull shape (brachycephaly with frontal bossing), hypotrichosis, microphthalmia, cataracts, beaked nose, micrognathia, skin atrophy, dental anomalies, and proportionate short stature (1,2).

The pathogenesis of the HSS is uncertain but it is thought to be a developmental abnormality occurring at 5-7 weeks gestation. The inheritance mode has not fully understood. Although familial cases have been reported, the disease is seen mostly sporadically. Reports of patients of consanguineous or affected siblings and the recurrent abortions of the mother in cases may suggest an autosomal recessive nature in HSS. An autosomal dominant (AD) inheritance with variable expression or new mutation has also been mentioned.

Case

A four-months-old-boy was brought with the complaint of cataract. He is the first child of an un-consanguineous marriage which the father was 25 years old and the mother was 28 years old. No problem had been observed during pregnancy and he was born with normal weight and height. It was learned that hypotrichosis and strabismus had been recognized by parent recently. The parents were healthy and they did not have any eye disorder. On physical examination, height, weight and head circumference were determined as 60.8 cm (10 percentile), 6.3 kg (10-25 percentile) and 42 cm (50-75 percentile), respectively. All of these measurements were within the normal ranges. The patient had also brachycephaly with frontal bossing, markedly hypotrichosis on scalp (like alopecia subtotalis), sparse eyebrows and eyelashes, small face, beaked nose, micrognathia, microphthalmia, bilateral cataract, strabismus and nystagmus (Figure 1, 2). The patient's interest, eye contact, response to stimuli and muscle tone was normal. Other system examinations were normal. On laboratory analyses, hemoglobin, hematocrit, platelet and white blood cell count were normal. Additionally, liver and kidney function tests, serum electrolytes, insulin like growth factor I, insulin like growth factor binding protein 3 levels were also normal. He was euthyroid, and tandem mass spectrophotometer for inborn error of metabolism (especially galactosemia, biotinidase deficiency) was found to be normal. While no abnormality was detected on whole body X-ray bone examination, magnetic resonance imaging, urinary ultrasonography, and echocardiographic examinations were also revealed normal findings. Peripheral blood karyotype analysis revealed 46, XY karyotype without any abnormality.

Informed consent for participation in the study was obtained from the parents of the subject according to the guidelines of the institutional review boards for human subjects at the participating study centers.

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Yuzuncu Yıl University Faculty of Medicine, Department of Pediatrics, Van-Turkey
*Corresponding Author: Sultan Kaba E-mail: sultan33kaba@hotmail.com

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Discussion

HSS was described firstly by Hallermann and following Streiff as presence of dyscephalia, bird-like face, congenital cataracts and microphthalmia togetherness (1,2). After them, Francoiss was reported a case with HSS who had skin atrophy, hypotrichosis, dental anomalies and short stature in addition to the characterized findings (3). Then, another case report was published by Steele and Bass (4) at 1970 about a HSS case associated with hypoplasia of costae and clavicle, absence of mandibular angle. But, all of these reports, it was emphasized that the diagnosis of HSS met with skepticism in the absence microphthalmia and cataract (5).

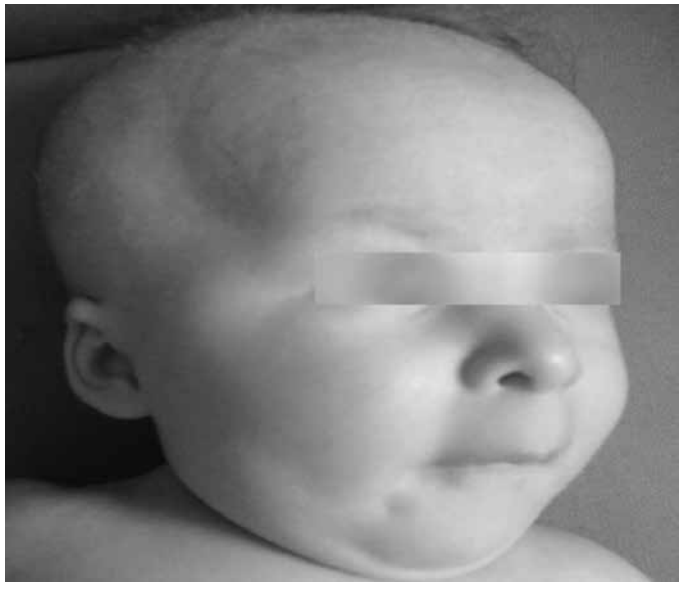

Figure 1. Brachycephaly with frontal bossing, markedly hypotrichosis on scalp, sparse eyebrows and eyelashes, small face, beaked nose, micrognathia, microphthalmia

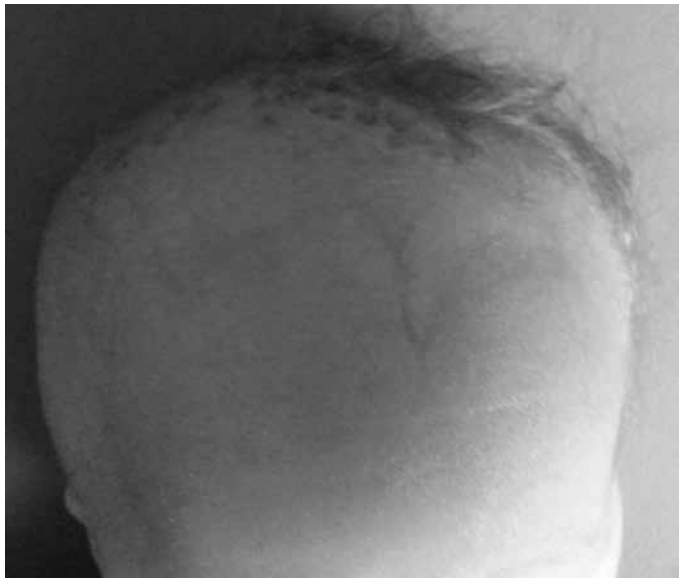

Figure 2. Markedly hypotrichosis on scalp

In present case, we did not speculate any dental anomalies due to younger age of our patient. Skin atrophy, short stature and bone abnormality was not detected. But the patient had brachycephaly with frontal bossing, markedly hypotrichosis on scalp, eyebrows and eyelashes, small face, beaked nose, micrognathia, microphthalmia, bilateral cataract, strabismus and nystagmus. These features were also the characterized findings of HSS. In the literature there are a lot of report with HSS without skin atrophy, bone abnormality and short stature in the literature (6).

Newborns and infants with HSS are generally suffered from upper respiratory tract obstruction and recurrent infection (7,8). Association of congenital heart disease, choanal atresia, small cerebellum, very low insulin-like growth factor I level, hypothyroidism, generalized organic aciduria, has also rarely been reported in HSS (9). Mental retardation was observed to be present only in a minority of cases (4), and some authors even postulated that the absence of the neuropsychological deficit distinguished this condition from other related conditions (10). Mental and motor developments in our case were consistent with his age.

As HSS and oculodentodigital dysplasia (ODDD) share several phenotypic characteristic. Although HSS and ODDD resemble to each other in terms of typical facial appearance, dyscephaly, congenital cataract and microphthalmia which are known to be characteristic features of HSS, have been rarely reported and aren't typical in ODDD. Congenital cataract, microphthalmia, nystagmus and strabismus are the features reported in HSS while microphthalmia, microcornea and glaucoma are the most common ocular findings in ODDD. However, hypotrichosis is one of the characteristic features of HSS while it has been rarely reported in ODDD. The findings that association of dyscephaly, cataract and hypotrichosis and lack of finger anomaly as well as being a sporadic case with normal karyotype analysis decrease the likelihood ODDD in our case.

The case whose typical dysmorphic physical examinations findings appropriate diagnostic features of HSS was presented due to rarely causes of hypotrichosis and cataract.

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Triple-X syndrome accompanied by Chilaiditi syndrome in preterm infant: A case report

Yusuf Kale*, Dilek Ulubas Isik, Istemi Han Celik, Ahmet Yagmur Bas, Nihal Demirel

Abstract

Chilaiditi syndrome (CS) is a variant of the rotation of the colon that gives rise to the interposition of the colon between the right diaphragm and the liver intermittently or constantly. Also, Necrotizing enterocolitis (NEC) is typically seen in premature infants. In this report, we presented a female case report accompanied with a 47,XXX karyotype and CS and NEC. This association was not reported in any case study. Our findings suggest that abnormalities of X chromosome may be associated with other anomalies.

Keywords: Triple X, Chilaiditi syndrome, preterm newborn

Introduction

The triple-X syndrome is one of the most frequent aneuploid variations in female infants and the incidence of this syndrome is approximately 1/1000 in population (1). A mistake in cell division called non-disjunction can result additional chromosomes in reproductive cells (2). The prevalence, like other chromosomal abnormalities increases with maternal age (3). Chilaiditi syndrome (CS) is a variant of the rotation of the colon that gives rise to the interposition of the colon between the right diaphragm and the liver intermittently or constantly. This condition occurs in 0.14% to 0.28% (4). Necrotizing enterocolitis (NEC) is typically seen in premature infants, and the timing of its onset is generally inversely proportional to the gestational age of the baby at birth (5). Here, we report an preterm infant with triple X accompanying CS. To our knowledge, this is the first report of an association of these conditions.

Case

A 1.540-g female infant was born at 33 weeks gestation to a 43-year-old multigravida by cesarean delivery. Apgar scores were 7 and 8 at 1 and 5 minutes respectively. She was transferred to the neonatal intensive care unit for preterm care. Case mother had an uneventful pregnancy. There was no consanguinity between case parents. Fetal ultrasonography of case was normal. Karyotype analysis of the amniotic fluid was performed due to advanced maternal age and the triple-X syndrome was diagnosed. Prenatal diagnosis was confirmed by postnatal karyotype analysis (Figure 1). No dysmorphic features were evident at birth, and the clinical examination was normal except for mild respiratory distress. The chest X-ray revealed an elevation of the right hemi-diaphragm caused by the presence of the dilated colonic loop below (Figure 2). Chest X-ray posteroanterior view and abdomen standing reveal free gas under right dome of diaphragm. At serial interval x-rays were taken. All of them reveal free gas under right side of diaphragm only. X-rays showed a hepatodiaphragmatic interposition of the colon, leading to the diagnosis of CS. Cardiac examination revealed a grade I/VI systolic murmur and echocardiographic examination showed patent foramen ovale.

She initially made good progress and enteral feeding with breast milk was increased up to 140 mL/kg on day 6. On postnatal day 7, there was an acute clinical deterioration with marked abdominal distension, vomiting and bloody stools. Oral feeding was stopped. Laboratory investigation revealed thrombocytopenia (90.000/mm^3) and elevated C-reactive protein level. The abdomen was mildly distended without hepatosplenomegaly. Stool cultures, clostridium difficile toxin, adenovirus, norovirus and rotavirus polymerase chain reaction examinations were all negative. Stage IIB NEC was diagnosed and she was treated with intravenous fluids, antibiotics, a nasogastric tube on free drainage and bowel rest. Repeated abdominal X-ray showed intramural gas and thickened bowel walls. There was evidence of pneumoperitoneum on the X-ray

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Etlik Zubeyde Hanim Women's Health Teaching and Research Hospital, Clinic of Neonatal Intensive Care Unit, Ankara-Turkey
*Corresponding Author: Yusuf Kale E-mail: yusufkl06@yahoo.com

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films. A possibility of intestinal perforation was considered and surgical opinion was sought. Primary peritoneal drainage (PPD) as the initial surgical intervention for NEC was done on the 9th day. Response to PPD was monitored by serial abdominal examinations and radiographic studies. After the return of bowel function enteral feeding was started on the 19th day and gradually increased. She made an uncomplicated recovery and was transferred back to the referring hospital on postnatal day 45th.

Discussion

Trisomy X occurs from a nondisjunction event, in which the X chromosomes fail to properly separate during cell division (6). The first published report of a woman with a trisomy X was written by Jacobs et al. (7) in 1959. Approximately 1 of every 1.000 newborn girls carries a 47,XXX karyotype (8). Most individuals with 47,XXX are diagnosed incidentally prenatal genetic screening (9). The karyotype is usually not associated with a characteristic physical phenotype. However, minor physical findings can be present in some individuals including epicanthal folds, hypertelorism, up-slanting palpebral fissures, clinodactyly, overlapping digits, pes planus, and pectus excavatum. Hypotonia and joint hyper-extensibility may also be present (10). Our patient had none of these physical findings. The major medical problem doesn't see in most of the cases.

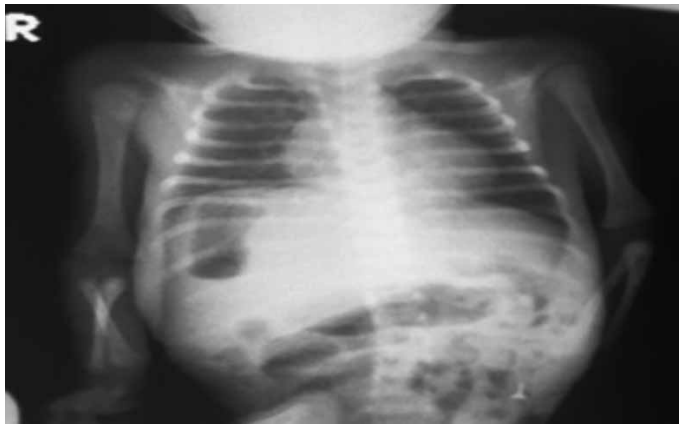

Figure 1. X-ray of the chest demonstrating elevation of the right hemi-diaphragm caused by the presence of the dilated colonic loop and gas accumulation

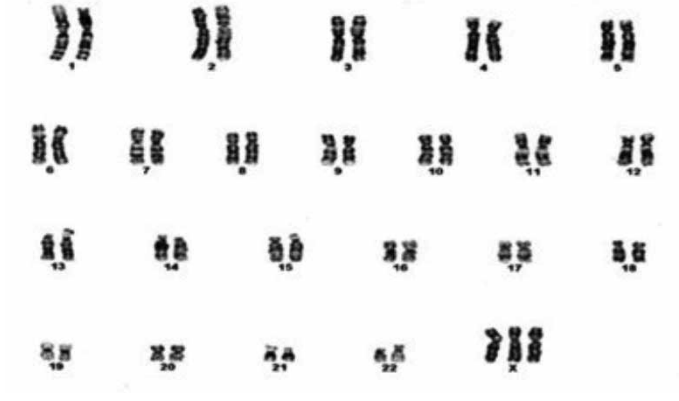

Figure 2. Patient's karyotype showing the presence of the triple X as the single chromosomal aberration

Most of the previously reported cases showed an association of triple-X syndrome with urogenital malformations, ranging from unilateral kidney and renal dysplasia to ovarian malformations, and gastrointestinal abnormalities including esophageal atresia, imperforate anus, cloacal exstrophy, omphalocele and jejunal atresia (11-13). Our patient had only CS as congenital abnormality (13).

CS is a rare disorder diagnosed in childhood. This syndrome incidence increases with advancing age. Although CS is usually asymptomatic, it can lead to many several complications such as vomiting, diarrhea, volvulus, perforation, bowel obstruction, respiratory distress or cardiac arrhythmias (14). In infants, CS may be interfered with gastrointestinal abnormalities such as NEC.

In this report, we presented a female with a 47,XXX karyotype and CS and NEC. This association was not described previously. Our findings suggest that abnormalities of X chromosome may be associated with other anomalies.

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Conflict of Interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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