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Bleeding and clotting in hereditary hemorrhagic telangiectasia

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relatively common inherited vascular disorder that was first described in 1864, and is notable for epistaxis, telangiectasia, and arterial venous malformations. While genetic tests are available, the diagnosis remains clinical, and is based on the Curacao criteria. Patients with HHT are at increased risk for both bleeding and clotting events. Because of these competing complications, hematologists are often faced with difficult clinical decisions. While the majority of management decisions revolve around bleeding complications, it is not infrequent for these patients to require anticoagulation for thrombosis. Any anticoagulation recommendations must take into account the bleeding risks associated with HHT. Recent reviews have found that HHT patients can be safely anticoagulated, with the most frequent complication being worsened epistaxis. Large clinical trials have shown that factor IIa and Xa inhibitors have less intracranial bleeding than warfarin, and basic coagulation research has provided a possible mechanism. This article describes the anticoagulation dilemma posed when a 62-year-old female patient with a history of bleeding events associated with HHT was diagnosed with a pulmonary embolism. The subsequent discussion focuses on the approach to anticoagulation in the HHT patient, and addresses the role of the new oral anticoagulants.

Key words: Anticoagulation; Hereditary hemorrhagic telangiectasia; Hemorrhage; Thrombosis; Rivaroxaban; Apixaban; Dabigatran; Warfarin

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Core tip: This article reviews an inherited disorder, hereditary hemorrhagic telangiectasia, in the context of a complicated clinical case. It highlights the problem of balancing the risks of bleeding and thrombosis, and raises the question of whether the new oral anticoagulants might provide safer therapy in such patients who need antithrombotic therapy.

Abstract

Hereditary hemorrhagic telangiectasia (HHT) is a

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CASE PRESENTATION

A 62-year-old female presented to our hematology clinic with previously diagnosed hereditary hemorrhagic telangiectasia (HHT). The patient had lifelong complications associated with this illness, including recurrent epistaxis and pulmonary arteriovenous malformations (AVMs). The patient had received multiple embolization procedures in the past to prevent complications from her pulmonary AVMs. The epistaxis was debilitating, with episodes occurring up to 5 times per day. Further medical history included the presence of a heterozygous prothrombin gene mutation (PT^{A20120G}), discovered from a thrombophilia evaluation for recurrent superficial phlebitis 5 years prior. The patient's more recent medical history included the development of a brain abscess 6 mo prior to presentation, which was treated with surgical evacuation. During her post-operative course, she developed a pulmonary embolism (PE) secondary to a deep venous thrombosis (DVT) in her left lower extremity. Initially, the patient was treated with the insertion of an inferior vena cava (IVC) filter, which was placed because of HHT-related bleeding concerns. The IVC filter ultimately developed extensive thrombosis, and the patient was initiated on warfarin therapy 3 mo prior to presentation. Since warfarin was initiated, she has had an increase in the severity of her epistaxis, but not the frequency. On physical exam, the patient had classic telangiectasia on the tongue and oral mucosa (Figure 1). The clinical question posed to our hematology clinic was how to proceed with anticoagulation for DVT/PE in the setting of a genetic thrombophilia and active bleeding in a patient with HHT.

BACKGROUND

HHT, alternatively known as Osler-Weber-Rendu syndrome, is a relatively common autosomal dominant disorder, with an overall frequency of 1 per 5000 to 10000 individuals^[1]. HHT was first described in 1864, but this account did not note a pattern of inheritance^[2]. Subsequently, multiple case reports specifically included a familial component in their descriptions^[3-5]. In 1909, Frederic Hanes officially used the phrase "hereditary hemorrhagic telangiectasia" for the first time^[6].

As the name suggests, the disease is notable for autosomal dominant inheritance (hereditary), bleeding events (hemorrhagic), and visibly dilated blood vessels (telangiectasia). Additionally, most patients are affected by larger AVMs, commonly found in the pulmonary, hepatic, and cerebral vasculature^[7]. Specific

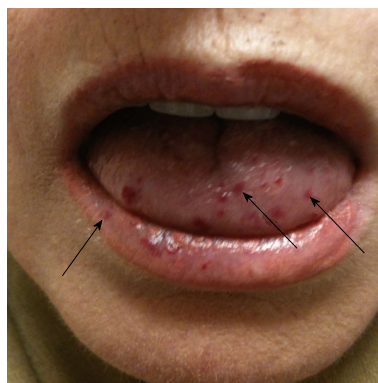


Figure 1 Arrows indicate telangiectatic lesions on tongue and lip of patient.

complications relate to the location of telangiectasia and AVMs, including, but not limited to, epistaxis, gastrointestinal bleeding, visible skin/mucosal manifestations, pulmonary arterial hypertension, pulmonary hemorrhage, and cerebral abscesses. Paradoxically, HHT patients are also burdened by a prothrombotic state due to elevated plasma levels of factor VIII^[8]. The balance between hemorrhage and thrombosis is particularly difficult to manage in these patients, and was exemplified in our patient described above.

The underlying pathology in patients with HHT is a primary defect in the vascular wall. The pathophysiology leading to this defect is complex. Patients inherit a mutation in an autosomal dominant fashion; the penetrance of which is highly variable. The three major genes that have been identified are: *ENG* encoding endoglin (HHT type 1), *ACVRL1* encoding activin receptor-like kinase (ALK-1) (HHT type 2), and *SMAD4* encoding Smad4 (HHT in association with juvenile polyposis, JPHT)^[9-11]. Over 80% of patients with HHT will have mutations in either the *ENG* or *ACVRL1* gene, with the *ENG* gene accounting for the majority^[12]. There is no common mutation in either the *ENG* or *ACVRL1* genes, with over 470 mutations having been described in the *ENG* gene and 375 in the *ACVRL1* gene^[13]. Additionally, researchers have been studying two other gene mutations that can cause HHT: *HHT3* and *HHT4*.

Animal models have shed light on how these mutations lead to vascular wall abnormalities. The mutated *HHT* genes described above encode proteins that alter signaling by the transforming growth factor- β superfamily^[7]. It is suggested that endoglin, ALK-1, and Smad4 are all part of a common signaling pathway that is altered in HHT. Additionally, studies have shown that vascular endothelial growth factor is increased in HHT patients^[14]. In the setting of HHT and an angiogenic stimulus, there is increased proliferation of endothelial cells, excessive vessel branching, and decreased recruitment of mural cells^[7]. Ultimately, this process leads to the formation of telangiectases,

Table 1 The Curacao criteria for the diagnosis of hereditary hemorrhagic telangiectasia

Criteria	Description	Percent manifestation
1 Epistaxis	Spontaneous, recurrent	90
2 Telangiectases	Multiple, at characteristic sites: Lips Oral cavity Finger tips Nose	80
3 Visceral lesions	Gastrointestinal telangiectasia	15-30
	Pulmonary AVMs	50
	Hepatic AVMs	30-70
	Cerebral AVMs	10-20
	Spinal AVMs	< 1
4 Family history	Affected first degree relative	
Diagnosis of HHT:		
Definite: 3-4 criteria	Possible: 2 criteria	Unlikely: 0-1 criterion

HHT: Hereditary hemorrhagic telangiectasia; AVMs: Arteriovenous malformations.

which are focal dilatations of postcapillary venules. Once fully developed, these malformed vessels are dilated, convoluted, extend through the dermis, and have excessive layers of smooth muscle without elastic fibers^[15,16]. These vessels lack capillaries and connect directly to dilated arterioles. AVMs are similar to telangiectases but have a direct connection between veins and arteries, and are thus much larger. These abnormal HHT blood vessels are prone to bleeding because of their inherently abnormal wall structure, as well as the presence of high perfusion pressures^[7].

CLINICAL MANIFESTATIONS

Clinical diagnosis

The diagnosis of HHT remains clinical, although genetic testing has been increasingly utilized. The classic triad of epistaxis, telangiectases, and family history lacks sensitivity and specificity, thus diagnostic criteria were formally created, which are generally referred to as the Curacao criteria (Table 1)^[17]. These criteria were recently validated in 263 patients who were screened for HHT and had first degree relatives available for genetic testing^[18]. This analysis found that the positive predictive value for a definite clinical diagnosis was 100%, and a negative predictive value for an unlikely clinical diagnosis was 97.7%. Fifty-two study participants had a possible clinical diagnosis, of which 17 (32.7%) had an HHT-causing mutation. Therefore, the utility of genetic testing is most apparent in those with a possible clinical diagnosis. This lends itself to the application of a diagnostic algorithm that can be used to combine the clinical criteria with genetic testing (Figure 2).

Bleeding in HHT

Patients with HHT are at increased risk for both bleeding and thrombosis. Bleeding complications can arise from

any location where telangiectases and AVMs are found. The most prevalent form of bleeding in HHT patients is epistaxis, which can be severe and recurrent. Mucosal telangiectases are very common, but their presence is mostly a cosmetic concern. Telangiectases in the gastrointestinal tract are an important source of chronic bleeding, and contribute to the common diagnosis of iron-deficiency anemia found in HHT patients. Perhaps the most important lesions in terms of both morbidity and mortality are pulmonary AVMs. These are present in roughly 50% of HHT patients, although the majority are asymptomatic^[7]. The clinical implications of pulmonary AVMs can be divided into two categories: (1) Right-to-left shunting; and (2) Hemorrhage. Right-to-left shunting can result in severe complications, such as brain abscesses and ischemic strokes, as well as less dramatic events such as migraines and dyspnea^[19]. Hemorrhagic complications from pulmonary AVMs can include hemoptysis as well as hemothorax. The consequences of pulmonary AVMs can be so severe that current recommendations include screening asymptomatic HHT patients with transthoracic contrast echocardiography (TTCE), or chest computed tomography if TTCE is not available^[20]. Cerebral vascular malformations are less common than pulmonary AVMs, but can have devastating effects. Perhaps the most feared complication of HHT is intracranial hemorrhage (ICH), which is most commonly seen with cerebral arteriovenous fistulae (AVF). As vascular lesions in the brain decrease in size, ICH becomes less common. Therefore, AVFs have the greatest risk of ICH, AVMs have intermediate risk, and telangiectasia have the lowest risk. Current guidelines recommend screening for cerebral AVMs with magnetic resonance imaging^[20]. One of the more prevalent, but usually asymptomatic, aspects of HHT is hepatic vascular malformations^[21]. These can occur as hepatic AVMs (hepatic artery to hepatic vein), hepato-portal VMs (hepatic artery to portal vein), and porto-venous VMs (portal vein to hepatic vein). Lastly, patients rarely may have spinal AVMs that can lead to hemorrhage and subsequent paraplegia.

Thrombosis in HHT

Despite the presence of an overwhelming bleeding propensity, HHT patients also suffer from thrombotic complications. First, they may develop paradoxical thromboembolic stroke from pulmonary AVMs as described above. Second, it seems these patients may also possess an inherent prothrombotic state relating to disturbances in the regulation of coagulation at the endothelial surface. A recent study compared the presence of plasma proteins in HHT-affected adults without a history of thrombosis with non-HHT controls^[8]. The researchers found statistically significant elevations in von Willebrand Factor and Factor VIII (FVIII) in HHT-affected adults. The researchers then evaluated the presence of elevated FVIII levels in the general HHT population and found that 87 of

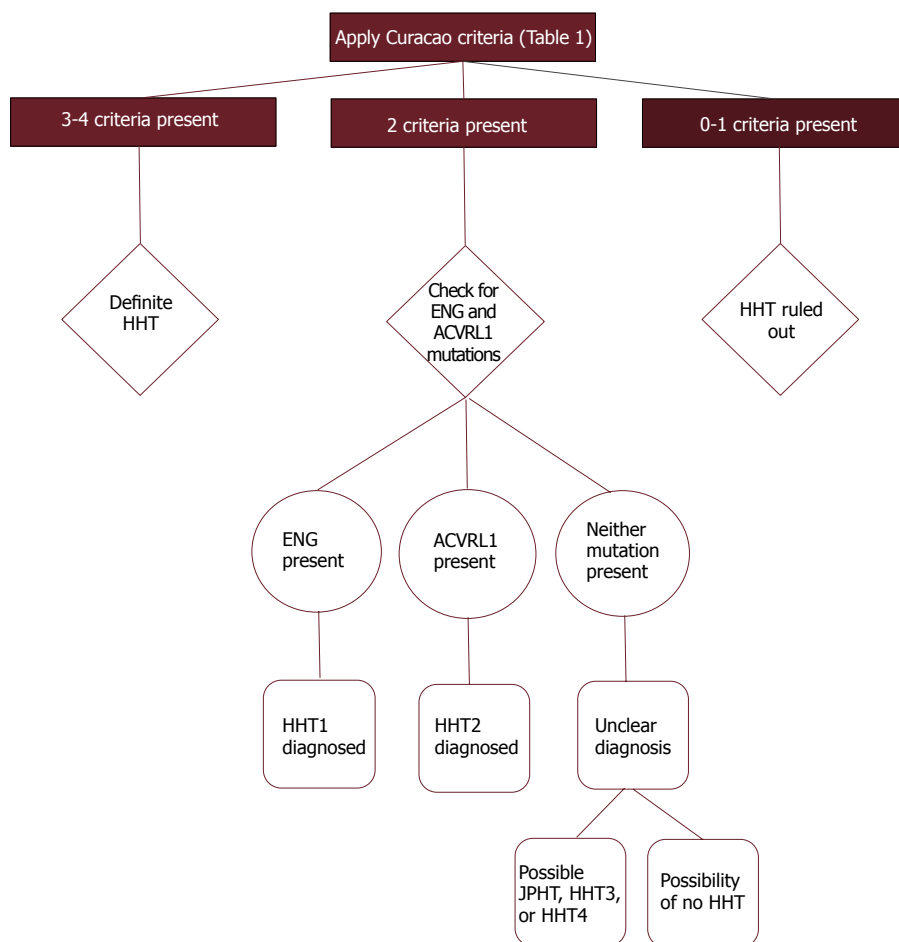


Figure 2 Diagnostic algorithm incorporating the Curacao criteria and genetic testing. HHT: Hereditary hemorrhagic telangiectasia.

125 (70%) individuals had measurements exceeding the upper limit of normal. An inverse correlation was also described between FVIII level and activated partial thromboplastin time. Furthermore, when compared to HHT individuals with no history of thrombus, HHT individuals who ultimately developed a thrombotic event were more likely to have an elevated FVIII level when it was initially measured at least 10 mo prior. To summarize the findings of this study, individuals with HHT have higher levels of FVIII than non-HHT controls, and the degree of FVIII elevation correlates with future thrombotic risk.

MANAGING THROMBOSIS IN HHT

Traditionally, physicians have been reluctant to treat HHT patients with either antiplatelet or anticoagulant therapy even if otherwise indicated. A recent survey found that 153 of 379 (40.4%) patients with HHT who received antiplatelet or anticoagulant therapy reported no change in epistaxis^[22]. Furthermore, 86.9% of patients reported no hemorrhagic events other than epistaxis associated with antiplatelet and anticoagulant use. This survey supports the reasoning that HHT patients who have a strong indication for antiplatelet or anticoagulant use, should not have these

agents withheld. Another study examining the use of antithrombotic agents in HHT patients arrived at a similar conclusion^[23]. As in the Devlin study, this study found worsening of epistaxis to be the most common complication. There were no new or progressive cases of pulmonary or cerebral hemorrhage, likely because all patients in this study were pre-screened. These data again support the notion that anticoagulation should not be withheld from HHT patients with strong indications for its use. Although bleeding is the major complication associated with all anticoagulant medications, the rate of bleeding varies between agents, and may be of clinical importance in HHT patients.

Choice of anticoagulant agent

For the prior half century, warfarin has been the gold standard of oral anticoagulation. Within the past decade, new oral anticoagulants have been developed and evaluated in clinical trials. Specifically, these agents include the direct thrombin (factor IIa) inhibitor, dabigatran, and the factor Xa inhibitors, rivaroxaban and apixaban (Figure 3). Indications vary by agent, but all have been studied for stroke prevention in non-valvular atrial fibrillation and prevention and treatment of venous thromboembolism (VTE). Interestingly, dabigatran, as well as the factor Xa inhibitors, have

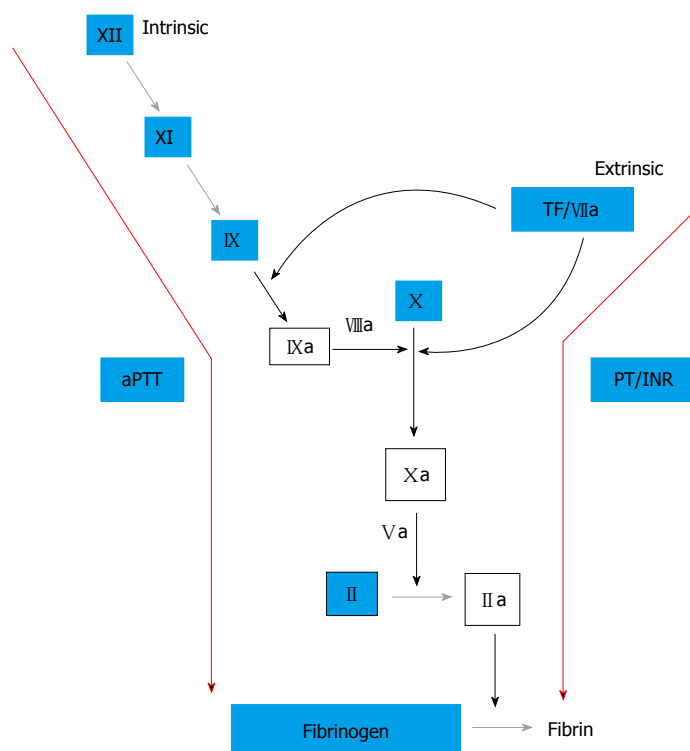


Figure 3 Coagulation cascade. Factors Xa and IIa (thrombin) are the principal targets for the new oral anticoagulants, while factors II, VII, IX, X, and protein C and S are decreased by the vitamin K antagonist, warfarin. Warfarin's effect on the factor VIIa/TF complex is a possible cause of the increased intracranial bleeding seen in warfarin compared to the newer targeted agents.

been associated with reduced intracranial hemorrhage compared to warfarin in patients with non-valvular atrial fibrillation^[24-26]. In studies examining the treatment of acute VTE, dabigatran and rivaroxaban had similar bleeding rates compared to warfarin, while apixaban had decreased bleeding relative to warfarin^[27-30].

The mechanism by which these new agents lead to similar or improved efficacy in relation to warfarin, while achieving less intracranial hemorrhage, has been evaluated. A recent study compared peak thrombin generation in the presence of both warfarin and dabigatran^[31]. This study found that, while the mean lag times were equally prolonged in each group, the peak thrombin level was significantly decreased in the warfarin group. Furthermore, the authors found that in the presence of tissue factor (TF), the peak thrombin level increases. Lastly, it was shown that warfarin has a greater inhibitory effect on peak thrombin level in the presence of TF than dabigatran. When the mechanism of action of warfarin and dabigatran are compared, it is notable that one major difference is the suppressive effect warfarin has on formation of the TF-factor VIIa complex which initiates coagulation (Figure 3). Dabigatran, as well as the factor Xa inhibitors, lack this inhibitory effect since these agents blockade the coagulation cascade further downstream. The brain, in particular, has a rich endowment of tissue factor, thus the effect of warfarin is enhanced in the brain relative to dabigatran, which may explain the increased intracranial hemorrhage seen in patient's taking warfarin vs the newer target-specific oral anticoagulants. Additionally, there is evidence that some of this effect may be due to reduced drug entry through the blood-brain barrier relative to warfarin^[32].

Multiple studies have examined the efficacy of antithrombotic agents in the prevention of recurrent VTE after an initial course of anticoagulation. Both low-dose warfarin and low-dose aspirin have been shown to effectively reduce the risk of recurrent VTE, when compared to placebo, without increasing the risk of bleeding complications^[33,34]. As for the new oral anticoagulants, dabigatran and rivaroxaban have been shown to effectively decrease the risk of recurrent VTE, but both increased the risk of clinically relevant bleeding when compared to placebo^[35,36]. Notably, dabigatran had a lower risk of major or clinically relevant bleeding when compared to regular-dose warfarin (INR 2-3). Apixaban has been shown to have similar bleeding risk to aspirin when evaluated for stroke prevention in nonvalvular atrial fibrillation^[37]. More recently, apixaban was compared at two doses (2.5 mg and 5 mg, twice daily) vs placebo in the extended treatment of VTE^[38]. In this study, each dose was effective in reducing the risk for recurrent VTE relative to placebo. There was no increased risk of major or clinically relevant bleeding in either dose of apixaban vs placebo, or between the two doses.

Due to the inherent bleeding risk in HHT patients, any approach to anticoagulation that may decrease the risk of bleeding would be prudent. Through the use of either a factor IIa or Xa inhibitor, as opposed to warfarin for the acute treatment of VTE, the TF-VIIa interaction can be preserved, which may lead to decreased bleeding events, particularly in the brain. Based on the studies reviewed above, it would be reasonable to use either low-dose aspirin, low-dose warfarin, or apixaban to prevent recurrent VTE in a patient at risk for bleeding. Further research is

necessary to fully describe these important differences between anticoagulant agents.

CONCLUSION

The patient presented with a difficult clinical scenario: new venous thromboembolism in the setting of a prothrombin gene mutation and bleeding complications secondary to HHT. The physicians who initially cared for our patient understood this dilemma and opted to place an IVC filter. Unfortunately, this filter thrombosed and the patient was initiated on warfarin. While on warfarin, the patient, like most patients studied, complained of worsening epistaxis, but no major bleeding events.

Our initial approach was to ensure she had been adequately screened for AVMs (pulmonary and cerebral) that could cause severe harm to our patient prior to the initiation of anticoagulation. The next management decision was to address the anticoagulation needs of our patient. Despite her bleeding risk, she had a strong indication for anticoagulation given progressive DVT and PE despite the presence of an IVC filter, as well as a prothrombotic state related to heterozygosity for the prothrombin gene mutation, immobilization, and recent surgery. Our primary options included: continuing warfarin (normal or low-dose); changing to low-dose aspirin; changing to a new oral anticoagulant, such as dabigatran, rivaroxaban, or apixaban; or discontinuing all anticoagulation. At the time of her appointment she had received 3 mo of anticoagulation with warfarin. Despite the role her recent surgery played in provoking the VTE, the presence of a thrombosed IVC filter and heterozygosity for prothrombin gene mutation indicated that she should receive long-term treatment. After 6 mo of anticoagulation, her IVC filter was retrieved as her thrombus burden had declined significantly in her IVC and lower extremities. We hoped retrieval would decrease her risk for recurrent VTE and allow us to eventually discontinue warfarin. Because her epistaxis was more symptomatic on therapeutic anticoagulation, we reduced her INR target range to 1.5-2. After 3 mo of warfarin therapy at a lower target INR, we discontinued anticoagulation completely. Unfortunately, 6 mo after her filter retrieval she developed recurrent right leg pain and a new iliofemoral DVT was identified. Subsequently, a new Celect IVC filter was placed. While recovering from this procedure, the patient developed abdominal pain and was ultimately found to have extensive thrombosis of the portal, superior and inferior mesenteric veins. Therapeutic anticoagulation with warfarin was resumed, and, after six months, her epistaxis became more severe, so her INR range was again reduced to 1.5-2. She has now been on low-dose warfarin for eighteen months and remains free of recurrent VTE or severe epistaxis. If a change to her anticoagulant regimen is warranted in the future, other options include low-dose aspirin and apixaban to prevent recurrent VTE, while minimizing the risk of bleeding.

HHT patients present hematologists with difficult clinical decisions due to the inherent bleeding and thrombotic complications associated with the disease. The majority of management decisions revolve around bleeding complications. When a thrombotic complication arises, anticoagulation recommendations must take into account the bleeding risks associated with HHT. Recent reviews have found that HHT patients can be safely anticoagulated, with the most frequent complication being worsened epistaxis. Patients should be aggressively screened for pulmonary and cerebral AVMs prior to initiating any anticoagulant. Large clinical trials have shown that factor IIa and Xa inhibitors have less intracranial bleeding than warfarin, and basic coagulation research has provided a possible mechanism. In light of this, there is an important role for the use of factor IIa and Xa inhibitors in HHT patients requiring acute anticoagulation. For long-term anticoagulation to prevent VTE recurrence, the agents associated with the lowest risk of bleeding relative to placebo are low-dose warfarin, low-dose aspirin, and apixaban. These agents will have an important role in the long-term prevention of VTE recurrence in patients with HHT.

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Review of health risks of low testosterone and testosterone administration

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replacement therapy (TRT) for older hypogonadal men is a promising therapy. However, a number of important clinical concerns over TRT safety remain unsolved due to a lack of large-scale randomized clinical trials directly comparing the health risks of untreated hypogonadism vs long-term use of TRT. Meta-analyses of clinical trials of TRT as of 2010 have identified three major adverse events resulting from TRT: polycythemia, an increase in prostate-related events, and a slight reduction in serum high-density lipoprotein cholesterol. There are other purported health risks but their incidence can be neither confirmed nor denied based on the small number of subjects that have been studied to date. Furthermore, subsequent literature is equivocal with regard to the safety and utility of TRT and this topic has been subject to contentious debate. Since January 2014, the United States Food and Drug Administration has released two official announcements regarding the safety of TRT and clinical monitoring the risks in TRT users. Additionally, the health risks related to the clinical presentation of low or declining testosterone levels not been resolved in the current literature. Because TRT is prescribed in the context of putative risks resulting from reduced testosterone levels, we reviewed the epidemiology and reported risks of low testosterone levels. We also highlight the current information about TRT utilization, the risks most often claimed to be associated with TRT, and current or emerging alternatives to TRT.

Key words: Hypogonadism; Epidemiology; Aging; Low testosterone; Testosterone replacement therapy

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Core tip: The topic of testosterone replacement therapy which has seen two official announcements for the United States Food and Drug Administration in 2014, is the subject of several large studies both prospective and retrospective, and there is unsettled debate about the safety and efficacy of this treatment. Readers should become familiar with this topic and be aware that further

Abstract

Hypogonadism is prevalent in older men and testosterone

publications and announcements are likely in the near future.

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LOW TESTOSTERONE EPIDEMIOLOGY AND RISKS

Production of testosterone (T) and serum T concentrations decline as men age. Hypogonadism may be defined either as serum concentration of T (either total T, bioavailable T or free T) or as low T plus symptoms of hypogonadism. The Baltimore Longitudinal Study on Aging reported the incidence of total serum T < 325 ng/dL to be 20% for men in their 60s, 30% for men in their 70s and 50% for men over 80^[1]. In an authoritative review by Kaufman and Vermeulen^[2] in 2005, similar rates and trends in the reduction of total serum T level were reported. The Massachusetts Aging Male Study reported that 12.3% of men aged 40 to 70 had a total serum T of < 200 ng/dL with 3 or more symptoms of hypogonadism^[3]. The Boston Area Community Health Study reported that 5.6% of men aged 30 to 70 were hypogonadal, as defined by total serum T < 300 ng/dL; or, free serum T < 5 ng/dL plus 3 or more symptoms of hypogonadism^[4].

Hypogonadism causes a wide range of signs and symptoms including loss of libido, erectile dysfunction, diminished cognitive function, depression, lethargy, osteoporosis, loss of muscle mass and strength^[5]. In a literature review on the burden of hypogonadism in adult men, Maggi *et al.*^[6] demonstrated strong evidence associating hypogonadism with sexual dysfunction and cognitive impairment; and, less compelling evidence associating hypogonadism with depressive symptoms, fractures, and mortality. Several recent studies also reported the health risks associated with untreated hypogonadism, including increased all-cause mortality^[7,8], coronary artery disease^[9], and stroke^[10].

Unfortunately, studying the health risks associated with untreated hypogonadism is often limited by the lack of universally accepted diagnostic criteria, and by study design variations^[6].

Hypogonadism does not appear to be identical across racial and ethnic boundaries. In a health screening project among 819 men in Taiwan, the prevalence of hypogonadism (total serum T < 300 ng/dL) ranged from 16.5% for men in their 40s, 23.0% for men in their 50s, 28.9% for men in their 60s, and 37.2% for men older than 70 years of age^[11]. The prevalence of hypogonadism among men in Taiwan is higher than the prevalence reported in the Massachusetts Male Aging

Study^[3], for a similar age group. There are no definitive biological explanations for differences in the epidemiology of hypogonadism. Candidate reasons are related to various lifestyle factors as well as genetic reasons, including the CAG repeat sequence, within the androgen receptor (AR). Rajender *et al.*^[12] reviewed over 30 studies on the AR trinucleotide repeat and infertility. Overall, for European populations, no significant distinctions were drawn, based on the CAG repeat. However, in Asian populations, four studies indicated a longer repeat was associated with infertility, two indicated no difference was present, and one study reported a shorter length (samples were all oligozoospermic for this subgroup). While there is a suggestion that CAG repeat length may determine androgen responsiveness, this issue is not clearly settled.

Nevertheless, a strong inference remains that race and ethnicity play a role in both the genotype and phenotype as they relate to the epidemiology of hypogonadism.

In summary, the reported prevalence of low T in older men range from 5.6% to 50%, depending upon study design, level of T blood concentration used, and study subjects' age. Combining serum T measurement with signs and symptoms most commonly seen with androgen deficiency are recommended in order to confirm the diagnosis of hypogonadism.

Hypogonadism comes with economic burden as well. An analysis of 8538 men, between the ages of 34 and 65, found direct and indirect cost differences associated with hypogonadism^[13]. This study examined an administrative database spanning four years and three months. Men with at least two diagnoses for hypogonadism, or, at least one prescription for testosterone therapy with at least one diagnosis for hypogonadism were considered hypogonadal in the analysis. They were matched against those not satisfying either of the two criteria. Those in the hypogonadal group ($n = 4269$) had direct health care costs, that exceeded the eugonadal group ($n = 4269$) by an average of \$7100 over the course of the observation window. Due to the expense of treatment for HIV/AIDS, those affected individuals were excluded in another analysis to avoid skewing the difference. The difference in direct costs was then \$5579, meaning that the hypogonadal group incurred an additional cost of just over \$109 per person per month. Indirect costs went up a little more than \$30 per person per month. Examples of mean disease-specific costs for hypogonadal vs eugonadal were as follows (these numbers do not exclude those with HIV/AIDS): Cardiovascular and metabolic health: \$1453 vs \$757; Pain: \$980 vs \$365; Mental health: \$558 vs \$176. The hypogonadal group had a higher Charlson's Co-morbidity Index at baseline, with a mean of 0.95, as compared to the eugonadal group at 0.28. In risk-adjusted analyses of costs, the difference in health care costs (both direct and indirect) was \$4869, or just over \$94 per person per month on average.

This investigation plainly demonstrated higher economic burden and presence of co-morbidities for

hypogonadism. Additionally, it highlighted a potentially serious threat to the interpretation of all observational studies in the testosterone replacement therapy (TRT) field-compliance. Over 31% of individuals in the hypogonadal did not receive TRT during the observation period. Similarly, within the hypogonadal group receiving therapy the proportion of days covered under TRT therapy was only 38% based on medical claims data. These study findings demonstrate that the economic burden for the hypogonadal group is higher than the eugonadal group even when 2/3 of the hypogonadal group did receive the TRT. However, because at least 31% of the hypogonadal group did not receive testosterone replacement, and those that did receive testosterone replacement were covered less than 40% of the time, it's not possible to infer whether or not TRT was mitigating the additional burden. The socioeconomic burden of hypogonadism should be addressed in detail in future observational and clinical trials, to provide robust metrics on the risks, benefits, and costs of TRT.

TRT

An increased awareness of the health risks associated with untreated hypogonadism has caused a substantial increase in TRT utilization in men^[14]. The efficacy of TRT has been demonstrated in several randomized clinical trials^[15-17] and has shown minor to moderate improvements in lean mass and muscle strength^[18,19], increased bone mineral density (BMD)^[18,20], modest enhancement in sexual function^[21-23], reduced adiposity^[18] and lessening of depressive symptoms^[24]. In 2011, the estimated sales for TRT were 1.6 billion dollars in the United States^[25]. However, significant questions remain regarding the safety of TRT because no large-scale randomized clinical trials have directly compared the health risks of untreated hypogonadism vs long-term TRT use^[25].

Enthusiasm for TRT utilization has been tempered by concerns regarding the health risks of this therapy. Meta-analyses of clinical TRT trials as of 2010 have identified three major adverse events resulting from TRT: (1) polycythemia; (2) an increase in prostate-related events; and (3) and a slight reduction in serum high-density lipoprotein (HDL) cholesterol^[26-28]. Clinical concern over the health risks of TRT was heightened in mid-2013 when a meta-analysis reported increased cardiovascular (CV) risk in men receiving TRT^[29]. Similarly, a recent retrospective study reported increased risk of stroke, myocardial infarction, and all-cause mortality in hypogonadal men receiving TRT after angiography^[30].

CARDIOVASCULAR AND CEREbroVASCULAR RISKS OF TRT

Two widely established health risks associated with TRT are polycythemia (> 3.5-fold increase in risk)^[26,27] and

reduced HDL cholesterol^[27]. These risk factors represent increased risk for CV and cerebrovascular events. Serious concern regarding the safety of TRT was raised in 2010 when the data and safety monitoring board (DSMB) of a double-blind randomized clinical trial recommended discontinuation of the trial because elderly hypogonadal men (with a high prevalence of chronic disease) experienced an increased incidence of CV events after receiving TRT^[31]. This randomized clinical trial was discontinued because 23 participants in the TRT group (approximately 22% of all TRT participants) vs 5 participants in the placebo group (approximately 5% of all placebo participants) experienced adverse CV-related events within the first 6 mo. Adverse events ranged from chest pain ($n = 1$) to myocardial infarction (MI) ($n = 3$ with one death suspected from MI), with peripheral edema being the most commonly reported side-effect ($n = 5$).

A large meta-analysis evaluating CV risks associated with TRT (including 27 RCTs and 2994 older men) also reported that TRT increased risk for CV-related events by 1.54 times (odds ratio = 1.54) in comparison to placebo treatment^[29]. In a similar but more recent and larger meta-analysis of 75 RCTs on CV risks and TRT, no significant association between CV events (both single and composite events) and TRT was established^[32]. However a retrospective study reported that men receiving TRT after angiography ($n = 1223$) experienced a 29% greater hazard ratio-adjusted rate of MI, stroke, and all-cause mortality (95%CI: 1.04-1.58) at 3 years post angiography vs men with untreated hypogonadism ($n = 7486$)^[30]. Finkle *et al.*^[33] evaluated 55000 patients and reported a more than 2-fold greater risk of MI in men who had received a TRT prescription. These results differ from several smaller analyses reporting heightened CV risk and all-cause mortality in men with untreated hypogonadism^[26,28]. This is especially important given that the TRT literature has thus far been equivocal and/or underpowered, despite large, coordinated efforts such as the forthcoming series of trials from Snyder *et al.*^[34].

As a response to the above study reports, the United States Food and Drug Administration (FDA)^[35] the Endocrine Society^[36] and the United States Veteran's Administration^[37] have called for monitoring and reassessing the health risks associated with TRT, respectively. Since these advisory announcements, a number of literature reports have critiqued the TRT literature, particularly the studies by Vigen and Finkle, for issues associated with the study design, statistical methods, and interpretation of findings^[38-40].

Notwithstanding several letters to the editor, and several recent TRT articles showing no increased cardiovascular risk, the United States FDA Joint Advisory Panel voted to change the labeling on testosterone replacement medication until larger studies demonstrate a clinical benefit and account for patient safety^[41].

PROSTATE RELATED RISKS OF TRT

Another well-established health risk of TRT is increased incidence of prostate/lower urinary tract-related events (*i.e.*, combined incidence of prostate-biopsy, prostate enlargement, elevated PSA, and prostate cancer)^[26]. Several coauthors of this commentary recently conducted a double-blind randomized clinical trial (NCT00475501) and observed that TRT produced a 40% prostate enlargement in older hypogonadal male Veterans over 12 mo^[42]. These increased prostate-related risks have raised concern that TRT may increase prostate cancer risk or hasten the development of undiagnosed prostate cancer.

However, no published analysis has reported measurable increases in prostate cancer risk or Gleason score in men undergoing TRT, or in hypogonadal men with a history of prostate cancer undergoing TRT^[26,27,43]. Despite this, Calof *et al.*^[26] estimated that an evaluation of 85862 participants is necessary to detect a hypothetical 20% increase in prostate cancer resulting from TRT. The largest meta-analysis evaluating prostate cancer risk associated with TRT included only 1700 men (*i.e.*, < 2% of the necessary population size)^[43].

OTHER PUTATIVE HEALTH RISKS ASSOCIATED WITH TRT

A number of putative health risks have been reported with TRT, including fluid retention^[31], gynecomastia^[44], liver disorders, and worsening of sleep apnea^[45]. These adverse outcomes are worrisome because they represent risks for several serious life-threatening adverse events and for other potentially serious clinical conditions. However, current meta-analyses have not established a definite relationship between TRT and these potential health risks, likely because they lack the statistical power. Additionally, the mechanisms through which T incites the above mentioned health risks are not completely understood, but may result in part from tissue-specific 5 α -reduction of T to dihydrotestosterone (DHT)^[46] or from the aromatization of T to estradiol. This is especially true in the prostate which highly expresses the type II 5 α -reductase enzyme. Inhibition of this enzyme via finasteride (a type II 5 α -reductase inhibitor) or dutasteride (a dual type I and II 5 α -reductase inhibitor) reduces circulating DHT 50%-75% and > 90%, respectively^[47], and reduces prostate mass^[48] and prostate cancer risk^[49]. Our team^[42] and others^[15] have demonstrated that finasteride also prevents prostate enlargement resulting from high-dose TRT without inhibiting the beneficial musculoskeletal or lipolytic effects of T, indicating the clinical viability of this combination pharmacologic therapy. It is unknown whether other potentially life-threatening health risks and other adverse events discussed above are mediated by the 5 α -reduction or aromatization of T.

ALTERNATIVES TO TRT

Given that there is currently no global consensus on the medical approach to testosterone deficiency, it is not surprising that alternative approaches to rectifying low T-levels are great in number, yet also lacking widespread agreement^[50]. Several decades of research have been completed evaluating the field of selective estrogen receptor modulators and selective androgen receptor modulators (SARMs). Clomiphene Citrate (CC) is an estrogen receptor modulator that is used in the treatment of male hypogonadism in an off-label capacity. Normally estradiol partially regulates testosterone levels, at the hypothalamus, blunting LH and FSH release from the pituitary. As a selective estrogen receptor modulator, CC interrupts this pathway, and consequently there is a greater stimulation for the production of testosterone in Leydig cells^[51].

A cohort of 1150 hypogonadal men were evaluated, and matched to produce a final sample of 93 in three groups: CC, Testosterone Injections (TI), or Testosterone Gel (TG)^[52]. Each group consisted of 31 individuals. The research team evaluated changes in serum testosterone and patient satisfaction. All treatment modes were effective at raising T-levels. Changes in T-levels (ng/dL) from pre- treatment to post-treatment were as follows: CC = 247-504, TI = 224-1104, TG = 230-412. Patient satisfaction was equal among groups, though the responses in T-levels were not equivalent. The noted difference was in libido, where injection produced the greatest index of libido on the qADAM questionnaire (4 v. 3 for each comparison of injection v. CC, injection v. TG). CC appears to be a suitable alternative to testosterone supplementation. However, larger randomized clinical trials are needed to determine its proper use, potential safety, and whether this agent effectively mitigates the known side-effects of hypogonadism. Similarly, as reported by Taylor *et al.*^[51], 104 men received either CC or T-Gel (CC = 65, T-Gel = 39). The CC group had higher post-treatment T-levels, 573 ng/dL v. 553 ng/dL. The monthly cost of T-Gel medication is over three times that of CC (Testim 1%, 5 gm daily = \$270/mo, Androgel 1%, 5 gm daily = \$265/mo, CC 50 mg every two days = \$83/mo). Thus, in terms of cost-effectiveness, CC would appear to be advantageous. However, more research is needed to determine its proper use.

SARMs

The combined research and clinical goals of SARMs are the reductions in catabolic actions initiated by hypogonadism and/or aging in order to preserve skeletal muscle and bone allowing for the individual to maintain functional activities of daily living, reduce fall and fracture risk, and consequent disability. SARMs are of particular interest because of recent guidance documentation^[41] on the restriction of exogenous testosterone administration warranted by observational studies indicating an

increased risk of cardiovascular events^[30,53]. In light of the recently cited effects on the cardiovascular disease system, SARMS are the most likely candidates to improve skeletal muscle mass in hypogonadal individuals. SARMS are engineered to bind to the androgen receptor without inducing other known side effects (e.g., prostate related events and polycythemia) of TRT. Several SARMS, including JNJ-28330835^[54], BMS-564929^[55], MK-0773^[56], and others have shown a positive levator ani/bulbocavernosus muscle complex/prostate ratio in pre-clinical rodent models, demonstrating an improved anabolic/androgenic ratio is associated with these drugs^[57]. The anabolic to androgenic ratio with limited side effects is the therapeutic target of SARMS research.

CONCLUSION

In summary, circulating testosterone concentrations decline throughout the aging process in males^[2]. The prevalence of low circulating testosterone (i.e., hypogonadism) is approximately 20% in men between 60-70 years of age and increases to roughly 50% of men over 80 years of age^[2]. The use of TRT has increased substantially among men in recent years^[14] because of an increased awareness of the risks associated with male hypogonadism (e.g., muscle and bone loss, and increased frailty)^[58,59]. However, TRT safety remains of primary concern, as do the potential health risks of untreated hypogonadism. To date, the largest prospective clinical trials that have been conducted on TRT involved only several hundred individuals; as such, they were dramatically underpowered to assess many of the more rare, yet severe health risks that are putatively associated with TRT. Unfortunately, even the largest meta-analyses on adverse events associated with TRT lack sufficient power to detect these and other potentially life-threatening health risks. Additionally, these clinical trials and meta-analyses have only assessed health risks during relatively short-term TRT or for only a very brief follow-up period after the cessation of TRT, which is concerning because once TRT is initiated it is typically continued throughout the lifespan. TRT studies should address additional external factors that may contribute to the reported risks and benefits currently associated with TRT including: diet, exercise, nutraceutical supplementation, sleep, and obesity.

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Atherosclerosis and the role of immune cells

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cells in the atherosclerosis.

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Core tip: Activated endothelium to adhere to the endothelium and move into the intima with the expression of adhesion molecules appears to be an early event in atherosclerosis, which allows mononuclear leukocytes such as monocytes and T-cells. This inflammatory mechanism must be explained before determining a new therapy.

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INTRODUCTION

Atherosclerosis is one of the leading causes of morbidity and mortality arising from coronary artery disease, stroke, and peripheral vascular disease. The pathophysiology of atherosclerosis is best characterized with hyperlipidemia and inflammation^[1,2].

For a long time after recognition, atherosclerosis was associated with passive lipid accumulation in the vessel wall. Nowadays we know that atherosclerosis is a chronic inflammatory disorder caused by lipids, particularly low-density lipoproteins (LDLs), and leukocytes^[3]. Atherosclerosis is likely to be initiated by the activation of endothelium with the expression of adhesion molecules, and this in turn enables the adhesion of mononuclear leukocytes, such as monocytes and T-cells, to the endothelium and also their transmigration into the intima. At this point, the lesions may be present with rare cells such as dendritic cells (DCs), few neutrophils and

Abstract

Atherosclerosis is a chronic inflammatory disease arising from lipids, specifically low-density lipoproteins, and leukocytes. Following the activation of endothelium with the expression of adhesion molecules and monocytes, inflammatory cytokines from macrophages, and plasmacytoid dendritic cells, high levels of interferon (IFN)- α and β are generated upon the activation of toll-like receptor-9, and T-cells, especially the ones with Th1 profile, produce pro-inflammatory mediators such as IFN- γ and upregulate macrophages to adhere to the endothelium and migrate into the intima. This review presents an exhaustive account for the role of immune

B-cells, and also with smooth muscle cells (SMC), which transform phenotype into synthetic SMC and move into the intima from the media^[4].

Polymorphonuclears (PMNs) are recruited and adhered to the endothelium upon the subsequent expression of adhesion molecules, such as E-selectin, P-selectin and intercellular adhesion molecule 1 (ICAM-1)^[5]. The endothelial cell expression of selectins and vascular cell adhesion molecule 1 (VCAM-1) is further increased by pro-inflammatory cytokines and mmLDL, and this facilitates the infiltration of the monocytes into the intima^[6]. As a result of intimal lipid accumulation, disturbed blood flow, low shear stress, and other stimuli, the transition of monocytes, which are major precursors of macrophages, through the endothelium is allowed by endothelial cells^[3]. Endothelial cells and SMCs are triggered by oxidized LDL (OxLDL), and this leads to the secretion of monocytic maturation factors such as monocyte-colony stimulating factor (M-CSF). Monocytes are transformed to macrophages and phagocytose modified lipoproteins, mainly due to the scavenger receptors AI and CD36^[7], and then become foam cells^[8]. Macrophages may be activated by PMNs following the secretion of tumor necrosis factor (TNF)- α , interleukin (IL)-8, and interferon (IFN)- γ . In addition, the release of myeloperoxidase from granules can stimulate the formation of reactive oxygen species (ROS), as well as the secretion of other pro-inflammatory cytokines, including TNF- α , IL-1, IL-6, IL-8 and granulocyte macrophage colony stimulating factor (GM-CSF) from macrophages. In response, ROS transform the extravasated LDL into OxLDL, consequently forming the foam cell development^[9].

Monocyte recruitment and the size of atherosclerotic lesion are bound to decrease if a failure is experienced in adhesion molecules, such as P-selectin, ICAM-1 and VCAM-1, or their interactions with their respective ligands are constrained^[10,11].

MONOCYTES AND MACROPHAGES

After the migration from the circulation into the intima of the arterial wall, monocytes are converted to macrophages and DCs. These cells then transform into foam cells by taking up modified lipoproteins^[12]. There are three major monocyte subsets in humans^[13,14]: the classical CD14⁺⁺CD16⁻ subset is similar to the mouse Ly6C high inflammatory subset and also presents a high expression of CCR2, and the non-classical CD14⁺CD16⁺⁺ monocytes are considered to match the Ly6C cells in mice, which express high levels of CX3CR1 and CCR5 but low levels of CCR2^[15]. The third subset, however, is known as the intermediate CD14⁺⁺CD16⁺CCR2⁺ subset^[16]. Of these, the classical subset includes nearly 90% of the monocytes circulating in humans^[17]. The patients with coronary artery disease present with increased amount of pro-inflammatory CD14⁺CD16⁺ monocytes and serum TNF- α levels^[18], and this monocyte subset is in negative correlation with fibrous cap thickness^[19].

After chemokinesis, monocytes adhere to and spin on

endothelial cells by interacting with E- and P-selectins^[20,21]. Lipoprotein-binding proteoglycans are secreted by monocytes in the intima, leading to enhanced accumulation of modified LDL, which carries on inflammation^[22,23].

Tissue damage and repair are closely linked to monocytes, and a discrepancy to occur in these processes may have critical results for plaque formation and stability. Importantly, monocytes consist of dissimilar subsets along with different cell surface markers and functional features, and this diversity of components may be associated with the angiogenic processes in atherosclerosis^[24].

The formation of atherosclerotic lesions is heavily dependent on the transformation of monocytes into macrophages; for instance, M-CSF-knockout mice show resistance to the development of atherosclerosis^[25].

Every phase of the course of disease includes abundant amounts of monocyte-derived macrophages^[12], and these cells an important role in lipid accumulation and advancement of atherosclerosis^[24]. Also, their crucial role in atherogenesis has been proven by the reduction of lesion formation in monocyte-deficient apolipoprotein E (ApoE) knockout mice and LDL receptor knockout mice^[26,27].

The polarization of macrophages towards a specific phenotype has been reported to be positively affected by lipids, growth factors, and cytokines; the M1 macrophages that are classified by means of classical methods may result in plaque vulnerability, whereas the M2 macrophages which are activated by alternative methods may increase plaque stability^[28]. The phenotypes of M1/M2 macrophages can be exchanged depending on the conditions of their microenvironment^[29].

Many macrophages and dendritic-like cells are known to have membrane-bound lipid droplets in the cytoplasm even at very early phases of atherogenesis. As they comprise lipid deposits, these cells are called "foam cells" and their course of development is initiated when apolipoprotein B-containing lipoproteins (apoB-LPs) are absorbed and processed by phagocytes^[21]. While producing matrix metalloproteinases with regards to plaque rupture, macrophages can be primed by oxLDL to develop a foam cell macrophage which bears the characteristics of M1 and M2 activation^[28]. Inflammatory cytokines and chemokines that promote inflammation and contribute to the regulation of monocyte/T cell infiltration are generated by macrophages/foam cells^[30-33]. With the macrophages in the atherosclerotic plaque, it is possible to generate a wide range of proinflammatory cytokines such as IL-1, IL-6, IL-12, IL-15, IL-18, TNF family members, and MIF, as well as anti-inflammatory cytokines like IL-10 and transforming growth factor beta family members^[34,35]. Additionally, IFN γ may trigger the macrophages to produce ROS and neopterin. It has been reported that neopterin levels increased in acute coronary syndrome and neopterin may be useful for the assessment of inflammation related to atherosclerosis^[36].

Being the most abundant cell type in atherosclerotic plaques, macrophages have a strong effect on plaque

development and progression due to its overwhelming influence on intra-plaque cholesterol homeostasis, inflammation, necrotic core initiation, and extracellular matrix degradation^[37].

Toll-like receptors (TLRs) represent the most comprehensively studied and described type of pattern recognition receptors. TLRs are characterized as type 1 transmembrane proteins involving an ectodomain with leucine-rich patterns that are needed to recognize pathogen associated molecular patterns, a transmembrane region, which determines the locations of the cells, and an intracellular toll interleukin 1 receptor region required for downstream signaling. Up to now, a minimum of 13 TLRs have been described, and each of them present with a degree of specificity for a number of endogenous and exogenous ligands^[38]. Expression of TLRs is performed by a number of various cells, such as leukocytes, DCs, and T and B lymphocytes^[39]. Atheroma development can be directly influenced by TLRs since the lipid uptake is promoted when the stimulation of macrophages is conducted with TLR2, TLR4 and TLR9 ligands^[40,41]. According to recent studies on ApoE^{-/-} mice, even small amounts of TLR4 and TLR2 have positive effects on the deposition of early-stage intimal foam cells in some regions in the aorta which are sensitive to lesion development^[42]. The macropinocytosis of lipids in differentiated macrophages can be stimulated by TLR4^[43]. Increased expression of scavenger receptors induced by TLR3, TLR4 and TLR9 can be used as a mediator for increased lipid absorption^[39,44]. These receptors and their ligands may also interrupt the cholesterol efflux mechanisms, which may have a contributory role in the development of foam cells^[28].

THE DENDRITIC CELLS

Dendritic cells, which are antigen-presenting cells (APCs), exhibit a variety of antigens to T cells in addition to initiating and sustaining immune responses as well as inhibiting the activation of T cells. The capacity of DCs in the activation or inhibition of T cells relies on its cytokine production profile and expression of cell surface co-stimulatory molecules. DCs are transformed by activated innate immune receptors, such as the TLR, into APCs that activate T effector cells, whereas, immunological tolerance is produced by antigen presentation which develops when TLR activation is not present. Therefore, DCs play a critical role as a connector between innate and adaptive immune responses^[45].

DC has a heterogeneous population with four major categories: conventional DCs (cDCs), plasmacytoid DCs (pDCs), monocyte-derived DCs, and Langerhans cells^[46]. Monocytes or DC precursors, which are present in the bone marrow, constitute the two sources of DCs.

Monocytes are completely transformed into monocyte-derived DCs in inflammation and as a reaction to growth factors like GM-CSF or TLR4 ligands. The capacity of

presenting antigens along with the ability to cross-present antigens belongs to the DCs that originate from monocytes^[37]. DCs are capable of generating a wide range of anti-inflammatory and proinflammatory cytokines. As an example, some proinflammatory cytokines, such as TNF, IL-6, and IL-12, which have been proven to contribute to the atherosclerosis can be generated by TLR binding^[47-49]. However, TLR binding may also generate IL-10, which is known as an atheroprotective cytokine^[50].

The DCs in mice are best known for their expression of CD11c and they present with healthy mouse aortas, predominantly in the adventitia^[51]. In mice, the amount of mRNA expression of CD11c is higher in the sites of the aortic arch susceptible to atherosclerosis, compared to the sites that are resistant to atherosclerosis. Contrary to healthy vessels, most of the DCs in atherosclerotic aortas are localized in the intima^[52].

The deposition of CD11c⁺ DCs at the vascular regions prone to atherosclerosis is associated with the increase in the expression of VCAM-1^[53]. Mature DCs are more abundant in advanced lesions. High level of expression of human leukocyte antigen (HLA)-DR and interactions with T cells are mostly observed in the sites of the plaque that are predisposed to rupture^[54]. The deposition process of the dendritic cells in the intima may be interrupted if the fractalkine receptor CX3CR1 in the aorta is impaired, and this may be an indication that these cells may be transformed from Ly-6Clo monocytes which are known to induce high levels of CX3CR1^[55]. OxLDL, in line with the elevation in the production of T cells, functions as an antigen upregulator for the DC expression of HLA-DR and its co-stimulatory molecules^[56]. DCs carry out the expression of scavenger receptors (LOX-1, CD36 and CD205) which facilitate their uptake of oxLDL activating the NFκB pathway, and evolution to DCs with a pro-inflammatory cytokine profile^[57]. Once DCs are activated by oxLDL in the plaque, they move to secondary lymphoid organs and initiate the clonal proliferation of the T cells that are specific to oxLDL^[28].

Following TLR9 activation, it is a common event for pDCs to produce high amounts of IFNα and β, and TLR9 has been reported to contribute to atherosclerosis by promoting macrophage recruitment^[58]. The recruitment of monocytes, memory T cells, and DCs to the region of inflammation is reportedly influenced by the CCL2 secreted by DCs^[59].

DCs, as prominent mediators of immune responses, may also act as the regulators of innate or adaptive immunity against the potential antigens that are engaged in atherosclerosis^[60]. In brief, the roles of dendritic cells in atherosclerosis can be summarized as the induction of chemokines and cytokines, presentation of antigens, and lipid absorption that might trigger inflammation or promote tolerance^[37].

T CELLS

The role of adaptive immunity in atherosclerosis was

verified by the presence of antibodies and oxLDL-specific T cells along with the accumulation of oligoclonal T cells in lesions^[6,61]. T cells are targeted to the vessel wall in line with macrophages, but to a lesser extent. Activation of T cells in the arterial wall is a reaction to antigens, and after this activation, the T cells initiate the production of pro-inflammatory mediators, by which the inflammatory response is intensified and thus the disease development is worsened^[62]. Moreover, most of the pathogenic T cells in atherosclerosis have the characteristics of Th1 since they generate pro-inflammatory cytokines such as IFN- γ and perform the activation of macrophages^[63,64]. The reactions mediated by Th1 have harmful effects on the development of atherosclerosis. Vascular smooth muscle cells are recruited by IFN- γ to inhibit the synthesis of collagen, and this leads to harmful effects for the protective thick fibrous cap of the plaque. Also, the activation of monocytes/macrophages and dendritic cells by IFN- γ results in the continuation of the pathogenic Th1 response^[30].

Previous studies report that the removal of IFN γ or its receptors leads to a reduction in atherosclerosis, whereas the injection of recombinant IFN γ results in a growth in the size of the lesions^[65-67]. The detection of Th2 cells in the atherosclerotic lesions is a rare occurrence. The cytokines produced by Th2 cells include IL-4, IL-5, IL-9, and IL-13. Th2 cells also have contributory effects on the production of antibodies by B cells. As the production of IFN- γ is decreased by these cells, the responses caused by Th2 were thought to be the antagonists of proatherogenic Th1 effects, hence rendering atheroprotection. Nevertheless, how atherosclerotic progress is affected by Th2 pathway has yet to be proven and the role Th2 pathway relies not only on the phase and location of the lesion but also on the method of experimentation to be used^[62]. According to some studies on animals, both Th1 and Th2 responses are involved in the progression of atherosclerosis, and lesion formation is started primarily by Th1 activation through a switch towards a proatherogenic response by Th2 in the chronic stage of plaque formation^[68]. The expansion and cytokine induction of highly activated effector T cells can also be inhibited by another T cell called TCR $\gamma\delta^+$ CD4 $^-$ CD8 $^+$, and this cell may need to be further analyzed since it is likely to have antiatherogenic characteristics^[69,70]. The regulatory T cells (Tregs) have critical roles in the inhibition and suppression of inflammation and also in the regulation of adaptive immune responses. Moreover, these cells can induce tolerance by inhibiting the effector CD4 $^+$ and CD8 $^+$ T cells^[71,72].

IL-10 has been reported to inhibit atherosclerosis, and thus the athero-protective effects of regulatory T cells may be improved when they generate IL-10^[73,74]. Studies also report that IL-10 has a protective function in the development and stability of atherosclerotic lesions^[72,73].

Th17 lymphocytes represent another T helper subset

associated with inflammation, and this subset does not share the same lineage with Th1 and Th2^[75]. IL-17 has been demonstrated to have protective and pathogenic effects in a number of autoimmune diseases^[76,77].

The main cytokines expressed by Th17 cells include IL-17A and IL-17F along with IL-21 and IL-22. The role of Th17 is still debatable despite the detection of Th17 cells in the atherosclerotic lesions in mice and humans, because both atherogenic and atheroprotective effects have been attributed to these cells^[78-80]. IL-17 is also considered to enhance plaque stability since elevated IL-17 induction in human lesions results in a decrease in the number of macrophages, an increase in SMC deposit, and a phenotype with a more fibrotic profile^[81].

Proatherogenic profile of IL-17 has been shown previously by many studies^[82-85]. In these studies, the evidence for the proatherogenic effect of IL-17 is attributed to the fact that both IL-17 and IFN- γ are expressed by the CD4 $^+$ T cells that are separated from atherosclerotic coronary vessels^[86].

CD8 $^+$ T cells are detected in both murine and human plaques^[87,88]. The number of CD8 $^+$ T cells is low in the early stages of lesions; however, these cells seem to be the dominant T cell type in the advanced stages of human lesions^[88]. CD8 $^+$ T cells may have a proatherogenic function since the lesion size was increased and also the recruitment of these cells to the lesion site was promoted when the responses of these cells were stimulated with a CD137 agonist^[89].

B CELLS

The responses produced by the Th2 cell have important roles in the activation of B cells, the differentiation of plasma cells, and the production of antibodies that are unique to antigens. B cells are evident in atherosclerotic lesions, but their population is smaller than that of T cells^[90]. However, the role of B cells in atherosclerosis remains controversial as two recent studies have reported that the atherosclerotic progression in mice is inhibited when B cells are blocked by the use of an antibody against CD20^[91,92]. The evidence that some types of IgM and IgG have atheroprotective effects may suggest that B cells have the ability to protect against atherosclerosis. Moreover, plaques have been detected with both IgM and IgG at all phases of lesion progression^[93]. Anti-oxLDL IgM antibodies have been proven to provide protection against atherosclerosis, probably because they achieve oxLDL binding and thus suppress oxLDL absorption by using macrophages and avoid the development of foam cells^[94,95]. On the other hand, to what extent the oxLDL-specific IgG is effective remains a controversial issue because both beneficial and inverse effects have been reported in epidemiological studies^[96]. OxLDL-specific antibody IgG titers are associated with atherosclerosis^[94,97,98], whereas oxLDL-specific IgM titers are related to atheroprotection^[99,100]. Nonetheless, the B cell subsets and their roles in atherosclerosis need to be further

analyzed^[37].

CONCLUSION

Atherosclerosis is a multiphase process which is characterized with the activation of endothelial cells with the expression of adhesion molecules and monocytes/macrophages, and the transmigration of DCs, T cells and some B-cells into the intima, and also the transfer of modulated types of LDL to matrix components. Monocytes/macrophages are highly abundant and differentiate into foam cells which are rich in modulated LDL.

According to clinical and experimental data, the atherogenic process involves the cells of both the innate and the adaptive immune system, and these cells generate diverse cytokines that may have both pro and anti-inflammatory functions^[101-103]. To immunomodulate the atherosclerosis is the primary aim of some clinical studies. Among these, the experimental studies with anti-LDL antibodies and vaccination studies with LDLs are under way^[1,104]. Oral administration of oxidized LDLs is reported to be effective on the inhibition of atherosclerosis and production of Tregs in peripheral lymphoid tissues^[105]. The functions of immune and inflammatory modulators in the formation and development of atherosclerosis have been better analyzed in recent years and thus provided a deeper insight into these mechanisms. Accordingly, more and more advanced techniques in the diagnosis and prognosis of atherosclerosis, along with new treatment procedures for inflammatory and immune factors, have been developed^[106]. However, there is still much to learn about immune cells and their mechanisms affecting atherosclerosis. We believe that further studies investigating immune cells and their mechanisms will help to shed light on atherosclerosis.

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Retrospective Study

Endoscopic papillary large balloon dilation for bile duct stones in elderly patients

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Abstract

AIM: To investigate whether endoscopic papillary large balloon dilation (EPLBD) can be safely and effectively performed in patients aged ≥ 80 years.

METHODS: Lithotomy by EPLBD was conducted in 106 patients with bile duct stones ≥ 13 mm in size or with three or more bile duct stones ≥ 10 mm. The patients were divided into group A (< 80 years) and group B (≥ 80 years). Procedure success rate, number of endoscopic retrograde cholangiopancreatographies (ERCP), and incidence of complications were examined in both groups.

RESULTS: Group B tended to include significantly more patients with peripapillary diverticulum, hypertension, hyperlipemia, cerebrovascular disease/dementia, respiratory disease/cardiac disease, and patients administered an anticoagulant or antiplatelet agent ($P < 0.05$). The success rate of the initial lithotomy was 88.7 (94/106)%. The final lithotomy rate was 100 (106/106)%. Complications due to treatment procedure occurred in 4.72 (5/106)% of the patients. There was no significant difference in procedure success rate, number of ERCP, or incidence of complications between group A and group B.

CONCLUSION: EPLBD can be safely performed in elderly patients, the same as in younger patients.

Key words: Elderly patients; Endoscopic papillary large balloon dilation; Endoscopic sphincterotomy; Large bile duct stones; Choledocholithiasis

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Core tip: Endoscopic treatment by papillary large balloon

dilation for large stones can be safely performed in elderly patients, the same as in younger patients.

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INTRODUCTION

The number of elderly patients with common bile duct stones has been increasing associated with the global prolongation of life expectancy^[1]. Endoscopic retrograde cholangiopancreatography (ERCP) has been recognized as a treatment with less risk and lower mortality than surgery^[2]. Endoscopic treatment for choledocholithiasis should be attempted as the first choice of treatment because of its high success rate in addition to its low invasiveness and low incidence of complications^[3]. Although a report indicated that ERCP related procedures may be hazardous for patients with common bile duct stones as well as in elderly patients aged ≥ 80 years^[4], it is often reported that this procedure can be useful and safely performed even in elderly patients^[5-20]. The usefulness of endoscopic treatment using endoscopic papillary large balloon dilation (EPLBD) which is a new papillary treatment using a balloon of large diameter for large bile duct stones or multiple bile duct stones has been recently reported. Most of the reports described the procedure as safe and useful^[20-34]. However, there have been some cases of death^[35]. Since elderly patients often have an underlying disease, they may follow a fatal course, thus they require special attention^[4]. There are few reports on the usefulness of this procedure in elderly patients^[20], and it has not been examined sufficiently. This report examined usefulness of EPLBD in patients aged ≥ 80 years.

MATERIALS AND METHODS

The study involved 106 patients (A) with bile duct stones ≥ 13 mm in their short diameter, or (B) multiple (≥ 3) bile duct stones with the smallest more than 10 mm in the shortest diameter, but without confluence stones. These patients were selected from among those with bile duct stones visiting our hospital or our affiliated hospitals from November 2009 to June 2014. Inclusion criteria were patients who could undergo endoscopic sphincterotomy (EST), and who gave their informed consent to the procedure. Exclusion criteria were coagulopathy (international normalized ratio > 1.5), marked thrombocytopenia

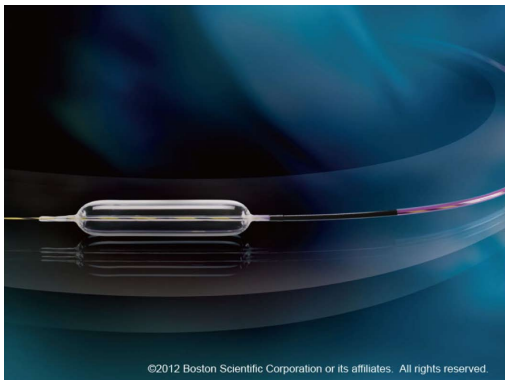
(platelet count $< 50000/\text{mL}$), patients who could not discontinue the administration of an anticoagulant or antiplatelet agent, patients for whom endoscopic biliary drainage was difficult (Billroth-II or Roux-en-Y), patients with the papilla within the diverticulum, patients with stenosis of the intrapancreatic bile duct, stone diameter > 30 mm (shortest diameter), and patients who do not give their informed consent.

We selected 79 patients with new bile duct stones and 27 with recurrent stones. All cases of recurrent stones were those after EST. We performed EST in 65 patients and it had been already performed in 41 patients. Fourteen patients whose stones were not recurrent and EST had been already performed were difficult cases referred to our hospital for a lithotomy. The average diameter of the stones was 14.29 (10-28) mm, the number of stones was 5.73 (1-30) and the diameter of the bile duct was 16.97 (10-28) mm. As for the gall bladder, 77 patients were calculous, one was acalculous and 28 had undergone cholecystectomy. Parapapillary diverticulum was noted in 50 patients. The patients were divided into group A (< 80 years) and group B (≥ 80 years). The clinical background of patients in these 2 groups is shown in Table 1. Patients in group B tended to have significantly more frequently peripapillary diverticulum, hypertension, hyperlipemia, cerebrovascular disease/dementia, respiratory/cardiac disease, or were taking an anticoagulant or antiplatelet agent. There was no significant difference in other factors between group A and group B. One session of treatment lasted up to 60 min after inserting the endoscope. The condition of the patients was observed, and if the patient showed much discomfort, the procedure was completed after inserting the drainage, even while in the process of treatment. Before ERCP, all patients were given a standard premedication consisting of intravenous administration of midazolam (3 to 10 mg), and the dose depended on age and tolerance. Scopolamine butylbromide or glucagon was used for duodenal relaxation. During ERCP, arterial oxygen saturation was continuously monitored using a pulse oximeter. Patients were kept fasting after the procedure for at least 24 h with drip infusion of 2000 mL and remained hospitalized for at least 72 h. For cannulation, catheters PR-104Q, R110Q-1 and PR233Q were used. A 0.025-inch or 0.035-inch guidewire (Jagwire: Microvasive, Boston Scientific Corp., Natick, MA; Revo Wave: PIOLAX, or VisiGlide: Olympus Corp.) was used. The endoscopes used were JF240, JF260V, TJF260V (Olympus Corp.), backward side-viewing endoscope, for patients with no history of gastric resection and patients of Billroth-I. After cholangiography, a guidewire was placed in the bile duct to conduct EST. Clever-Cut3V (Olympus Corp.) was used as the knife for EST. EST was conducted using a single electrosurgical current generator (PSD-20, Olympus Corp.) at a power of 25 watts. For those in which an incision had been already

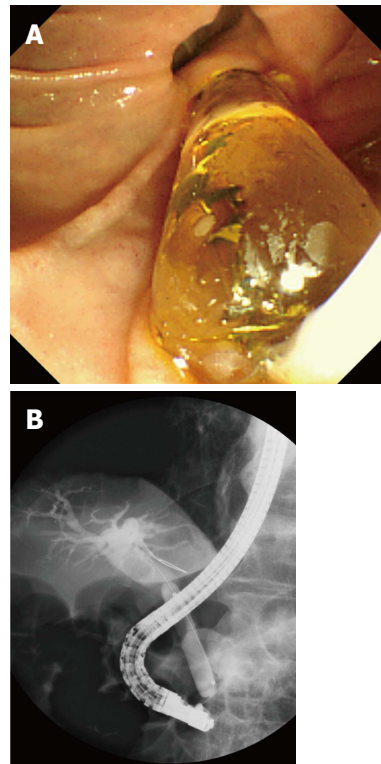
Table 1 Patient background

	< 80 yr old (Group A)	≥ 80 yr old (Group B)	P-value
Number of patients	59	47	
Male	36	20	NS
Female	23	27	NS
Choledocholith			
Number of stones	5.24 ± 5.52 (1-30)	6.44 ± 6.98 (1-25)	NS
Stone diameter (mm)	14.03 ± 3.00 (10-28)	14.52 ± 4.48 (10-25)	NS
Common bile duct diameter (mm)	16.62 ± 3.52 (10-28)	17.44 ± 3.93 (10-25)	NS
Gallbladder			
Calculous	43	34	NS
Acalculous	0	1	NS
Cholecystectomy	15	13	NS
Primary case	43	36	NS
Recurrence	17	10	NS
Endoscopic sphincterotomy	36	29	NS
Post endoscopic sphincterotomy	23	18	NS
Diverticulum	15	35	< 0.05
Hypertension	23	37	< 0.05
Hyperlipidemia	9	21	< 0.05
Diabetes mellitus	10	8	NS
Chronic respiratory disease	0	5	< 0.05
Cardiac disease	8	18	< 0.05
Chronic liver disease	1	0	NS
Chronic kidney disease	2	3	< 0.05
Anticoagulant/antiplatelet	9	23	< 0.05

NS: Not significant.

**Figure 1 Endoscopic papillary large balloon dilation.** CRE 12-20 mm (Wire-guided type 5.5 cm, Boston Scientific Corp., Natick, MA).

made, a guidewire was placed in the bile duct after cholangiography to perform EPLBD. In performing EPLBD, CRE 12-20 mm (Fixed wire type 8 cm or Wire-guided type 5.5 cm: Boston Scientific Corp.) was used depending on the diameter of the bile duct (Figure 1). For balloon dilation, a contrast agent mixed with saline solution at a volume ratio of 1:1 was used to slowly inflate it. Inflation was performed until the notch on the balloon disappeared (Figure 2). However, regardless of the disappearance of the notch, balloon dilation was completed when the papilla was dilated enough for stone removal. The balloon was dilated in a position where it was possible to confirm the tip of the balloon in the papillary side on the endoscopic image, and the position was maintained. After the notch on the balloon disappeared, the balloon was promptly

**Figure 2 The papilla.** A: The papilla was gradually dilated using a large balloon. Dilation was continued until the notch on the balloon disappeared (endoscopic image); B: The papilla was gradually dilated until the notch on the balloon disappeared (fluoroscopic image).

deflated. When we considered it necessary to perform lithotripsy of the stone, we did it without hesitation.

The basket catheter used for lithotripsy was LBGT-7245S (ZEON Medical) or BML-V237QR-30 (Olympus Corp.). Peroral cholangioscopy (POCSL) was performed by mother-baby system using CHF-B260 (Olympus Corp.) as the cholangioscope and Autholith (Northgate) as the electrohydraulic lithotripsy probe. The basket catheter used for collecting stones was FG-22Q or FG-V416Q (Olympus Corp.), LBGT-7245S (ZEON Medical) or BML-V237QR-30 (Olympus Corp.) The balloon catheter used was EXP718200 (ZEON Medical) or FS-QEB-XL-B (COOK). No drainage tube was inserted when lithotomy was successful, while it was inserted when we thought a stone still remained.

Iatrogenic morbidity was assessed according to the criteria of Cotton *et al.*^[36]. The observation period was 30 d after the procedure and any coincidental event noted during the period was considered as an early coincidental event. All the treatment procedures were performed after obtaining the informed consent from the patients in writing. This study was conducted after the study protocol was approved by the ethics committee of Chiba University.

Statistical analysis

Pearson χ^2 test with Yates correction and Fisher's exact test, when appropriate, were used for statistical analysis of categorical variables. Data were analyzed using SPSS software version 11 (SPSS, Chicago, IL). Differences with a *P* value of < 0.05 were considered statistically significant.

RESULTS

The success rate of lithotomy in the initial treatment was 88.7 (94/106)%. The final lithotomy rate was 100 (106/106)%. The time necessary to perform lithotomy was 39.4 (10-128) min and the mean treatment frequency was 1.21 (1-4) times. Lithotripsy was needed in 11.3 (12/106)% of the patients. Among the patients requiring lithotripsy, 6 had a highly tortuous bile duct and 6 had significantly large bile duct stones. For lithotripsy, endoscopic mechanical lithotripsy was performed in 10 patients and POCSL in 2. Complications due to the treatment procedure were observed in 4.7 (5/106)% of the patients, including bleeding in 1.9 (2/106)%, perforation in 0.9 (1/106)%, pneumonia in 0.9 (1/106)%, and acute cholangitis in 0.9 (1/106)%. Patients were classified into group A or group B for the analysis of data (Tables 2 and 3). The lithotomy success rate was 88.1 (52/59)% in group A, and 89.4 (42/47)% in group B and that for final lithotomy was 100%, both in group A (59/59)% and in group B (47/47). The lithotripsy rate was 10.2 (6/59)% in group A, and 12.8 (6/47)% in group B. Operation time was 37.59 ± 26.94 (12-125) min in group A, and 42.02 ± 27.12 (10-128) min in group B. The number of ERCP was 1.24 ± 0.683 (1-4) in group A, and 1.17 ± 0.529 (1-4) in group B. The incidence

of complications was 6.8 (4/59)% in group A and 2.1 (1/47)% in group B, and there was no significant difference between group A and group B, regarding other parameters.

DISCUSSION

This study showed that elderly patients aged ≥ 80 years often have underlying diseases, however, results of treatment for large bile duct stones or multiple bile duct stones using EPLBD lithotomy were equivalent to those aged < 80 years in terms of success rate, lithotripsy rate, procedure time, number of ERCP, and complications caused by the procedure. EPLBD is the endoscopic treatment for bile duct stones reported by Ersoz *et al.*^[21] in 2003. Recently, the reports on the results of treatment for choledocholithiasis using EPLBD have been increasing^[20-35]. Ordinary endoscopic papillary balloon dilation (EPBD) employs a balloon 4-10 mm in diameter for papillary dilation, whereas EPLBD is performed using a balloon 12-20 mm in diameter. Before this procedure was reported, lithotomy of large bile duct stones or multiple bile duct stones was difficult without lithotripsy of the stone. This procedure has the advantage that compared with EPBD or EST a larger papillary aperture can be obtained. It is reported in randomized controlled trials and meta-analyses that the larger papillary aperture enables easy insertion of the device as well as lithotomy of stones the same size as that of the dilated balloon without lithotripsy of the stones in many patients^[34,37,38], which may be advantageous because the duration of the procedure would be shortened^[26]. In this study many patients were cured after one session of treatment. There are many reports describing that in the nature of things, elderly patients have many underlying diseases, whereas the comparison of patients aged 80 years or greater with those aged less than 80 years showed the similar tendency^[11,19]. Shorter treatment time is naturally an advantage even in young patients, and this study confirmed that a shorter treatment time was desirable for elderly patients because many of them have underlying diseases such as respiratory disease. Shorter treatment time is beneficial for elderly patients. There was no difference in the success rate of the procedure itself, however, many patients aged ≥ 80 years have peripapillary diverticulum according to a past report^[19], and this study also showed elderly patients tended to develop it, thus when performing the procedure, it may be necessary to pay attention to perforation. The presence of peripapillary diverticulum may cause deviation of the course of the bile duct leading to difficulty in cannulation^[39]. However, this study revealed that there was no difference in the success rate of the procedure between the two groups. The reason may be due to recent advancement of the endoscope and its related treatment instruments. In this study, EPLBD was performed after EST. There are past reports describing

Table 2 Lithotomy by endoscopic papillary large balloon dilation

ERCP procedures	< 80 yr old (Group A; n = 59)	≥ 80 yr old (Group B; n = 47)	P-value
Lithotomy success rate			
Initial	52 (88.1%)	42 (89.4%)	NS
Final	59 (100%)	47 (100%)	NS
Lithotripsy	6 (10.2%)	6 (12.8%)	NS
Procedure time: min	37.59 ± 26.94 (12-125)	42.02 ± 27.12 (10-128)	NS
Number of ERCP	1.24 ± 0.683 (1-4)	1.17 ± 0.529 (1-4)	NS

ERCP: Endoscopic retrograde cholangiopancreatography; NS: Not significant.

that it is possible to safely perform EPLBD without performing EST^[35]. According to this study many elderly patients not only have peripapillary diverticulum but also are taking an anticoagulant or antiplatelet agent, thus if it were possible to safely perform EPLBD without performing EST, the procedure time would be shortened even further and the risk of perforation or bleeding would also be reduced.

Although a shorter procedure time and success of the procedure are very important for elderly patients, a low rate of complications derived from the procedure is also required. Past reports showed that complications caused by this procedure occurred at a low rate^[20-35]. In the present study, complications occurred at a low rate and there was no difference between the two groups, suggesting it is possible to safely perform EPLBD even in elderly patients. The most problematic complications among ERCP related procedures is pancreatitis. Although it is reported that pancreatitis is less likely to occur in elderly patients because of their reduced pancreatic function^[40], this study revealed there were no such results at all, suggesting that safety of the procedure is not only ensured for elderly patients but also that of the procedure itself is ensured. Reports describing usefulness and safety of EPLBD in elderly patients are currently limited to retrospective studies, thus a prospective study is necessary to confirm our findings.

EPLBD can be safely performed in elderly patients the same as in younger patients.

COMMENTS

Background

The usefulness of endoscopic treatment using endoscopic papillary large balloon dilation (EPLBD), which is a new papillary treatment using a large diameter balloon for large bile duct stones or multiple bile duct stones has been recently reported. Most of the reports have described this procedure is safe and useful. However, there are some cases of death. Since elderly patients are often complicated with underlying diseases, they may follow a fatal course after EPLBD, thus they require special attention. There are only a few reports on the usefulness of this procedure in elderly patients, and sufficient examination has not been conducted. This report examined the usefulness of EPLBD in patients aged ≥ 80 years.

Research frontiers

The results of EPLBD in patients with bile duct stones ≥ 13 mm in their short diameter or patients with three or more bile duct stones ≥ 10 mm in their short

Table 3 Complications after endoscopic papillary large balloon dilation

Related complications	< 80 yr old (Group A; n = 59)	≥ 80 yr old (Group B; n = 47)	P-value
Pancreatitis	0	0	
Perforation	1 (mild)	0	NS
Bleeding	2 (mild)	0	NS
Cholangitis	0	1 (mild)	NS
Cholecystitis	0	0	
Others	1	0	NS
Total	4	1	NS

NS: Not significant.

diameter were examined.

Innovations and breakthroughs

EPLBD for bile duct stones was reported by Ersoz *et al* in 2003. Recently, its indication has widened. The reports describing the usefulness and safety of EPLBD in elderly patients are currently limited to retrospective studies. A prospective study is necessary to confirm our findings.

Applications

In patients with large common bile duct stones, endoscopic sphincterotomy (EST) + EPLBD is a good alternative to conventional EST. Before this procedure was reported, lithotomy of large stones or multiple stones was difficult without lithotripsy of the stones. Endoscopic treatment by papillary large balloon dilation can be safely performed in elderly patients the same as in younger patients.

Terminology

Treatment by EPLBD, which is lithotomy without lithotripsy for large stones by dilating the papilla using a large balloon, after performing EST has been reported. Endoscopic treatment by papillary large balloon dilation can be safely performed in elderly patients the same as in younger patients.

Peer-review

This is a retrospective study evaluating whether EPLBD can be safely and effectively performed in elderly patients. This study may be of interest to the readers.

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Prospective Study

Efficacy of different doses of sugammadex after continuous infusion of rocuronium

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Abstract

AIM: To evaluate the effects of two different doses of sugammadex after maintenance anesthesia with sevoflurane and remifentanyl and deep rocuronium-induced neuromuscular blockade (NMB).

METHODS: Patients between 20 and 65 years of age, with American Society of Anesthesiologists physical status classification I - II, undergoing gynecological surgery were included in a prospective, comparative and randomized study. NMB was induced with an injection of 0.6 mg/kg of rocuronium followed by continuous infusion of 0.3-0.6 mg/kg per hour to maintain a deep block. Anesthesia was maintained with sevoflurane and remifentanyl. Finally, when surgery was finished, a bolus of 2 mg/kg (group A) or 4 mg/kg (group B) of sugammadex was applied when the NMB first response in the train-of-four was reached. The primary clinical endpoint was time to recovery to a train-of-four ratio of 0.9. Other variables recorded were the time until recovery of train-of-four ratio of 0.7, 0.8, hemodynamic variables (arterial blood pressure and heart rate at baseline, starting sugammadex, and minutes 2, 5 and 10) and adverse events were presented after one hour in the post-anesthesia care unit.

RESULTS: Thirty-two patients were included in the study: 16 patients in group A and 16 patients in group B. Only 14 patients each group were recorded because arterial pressure values were lost in two patients from each group in minute 10. The two groups were comparable. Median recovery time from starting of sugammadex administration to a train-of-four ratio of 0.9 in group A and B was 129 and 110 s, respectively.

The estimated difference in recovery time between groups was 24 s (95%CI: 0 to 45 s, Hodges-Lehmann estimator), entirely within the predefined equivalence interval. Times to recovery to train-of-four ratios of 0.8 (group A: 101 s; group B: 82.5 s) and 0.7 (group A: 90 s; group B: 65 s) from start of sugammadex administration were not equivalent between groups. There was not a significant variation in the arterial pressure and heart rate values between the two groups and none of the patients showed any clinical evidence of residual or recurrent NMB.

CONCLUSION: A dose of 2 mg/kg of sugammadex after continuous rocuronium infusion is enough to reverse the NMB when first response in the Train-Of-Four is reached.

Key words: Rocuronium; Sugammadex; Neuromuscular block antagonism; Monitoring neuromuscular function; Neuromuscular block rocuronium

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Core tip: The release of sugammadex in recent times has been a global shift in the strategy of the reversal of neuromuscular blockade (NMB) induced by aminosteroid neuromuscular blocking. The use of this drug has been increasing slowly, and consequently, we receive more and more questions in regards to its efficacy and safety. In this study we compared the dose of 2 mg/kg to 4 mg/kg sugammadex to reverse the NMB when first response in the train-of-four is reached after continuous infusion of rocuronium. Both doses have been shown to be effective for recovery from NMB.

Soto Mesa D, Fayad Fayad M, Pérez Arviza L, Del Valle Ruiz V, Cosío Carreño F, Arguelles Tamargo L, Amorín Díaz M, Fernández-Pello Montes S. Efficacy of different doses of sugammadex after continuous infusion of rocuronium. *World J Clin Cases* 2015; 3(4): 360-367 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v3/i4/360.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v3.i4.360>

INTRODUCTION

Neuromuscular blockade (NMB) is an important technique in modern anesthesia because it improves surgical conditions by suppressing voluntary movements or muscular reflexes. The use of neuromuscular blockers is highly beneficial in determined types of surgery, such as laparoscopy, as it improves the surgical access and the visual field^[1]. However, the extended use of NMB is associated with increased postoperative morbimortality due to the risk of residual neuromuscular paralysis or recurarization and the development of subsequent complications^[2,3]. Such complications can be reduced

by objective monitoring of muscle relaxation and NMB reversal after the surgical procedure.

The release of sugammadex [Bridion®, merck sharp and dohme, Oss, The Netherlands] triggers a change in the way of reversing aminosteroid neuromuscular blocking drugs. Sugammadex is a gamma-cyclodextrin with a lipophilic cavity that traps aminosteroid neuromuscular blocker molecules to form an inactive complex, thus preventing their union with nicotinic receptors and reversing their effects^[4,5]. Clinical data suggests that sugammadex has a favorable efficacy and safety profile^[4,6,7], allowing a safer and faster recovery-even from deep NMB^[8]-than the commonly used combination of acetylcholinesterase inhibitors and anticholinergic agents.

Halogenated anesthetics, such as sevoflurane, increase the effect and duration of rocuronium^[9], and this effect is clinically most significant when using a continuous infusion of rocuronium^[10]. However, such do not appear to alter the efficacy or safety of sugammadex^[11-13]. We hypothesize that a dose of sugammadex could result in a suitable recovery time although it depends on the individual redistribution and elimination of rocuronium as well^[14]. The provider has not defined what the ideal dose of sugammadex for reversal the NMB when first response in the train-of-four (TOF) is reached. So, we have designed a study based upon on this hypothesis: after a surgical procedure, a dose of 2 mg/kg sugammadex is comparable to a dose of 4 mg/kg for reversal the NMB induced by a continuous infusion of rocuronium administered when first response in the TOF (T1) is reached.

MATERIALS AND METHODS

Patients and methods

A prospective, randomized and comparative study was designed to include patients undergoing a gynecological surgery, and took place over one year. The study was approved by the Regional Research Ethics Board of Principality of Asturias (Ref 118/2013; approved in August, 2013) and, after being given a verbal explanation, all patients gave their written informed consent. Applicable regulations and good clinical practice guidelines concerning NMB were followed in all cases^[15].

The study included patients between 20 and 65 years of age, with American Society of Anesthesiologists (ASA) physical status classification I - II, who were scheduled for elective gynecological laparoscopy procedures under general anesthesia with sevoflurane requiring NMB with a minimum duration of 1 h, and carried out by the same surgical team.

The sample size was calculated on the basis of data for previous recovery time from NMB to first response in the TOF after sevoflurane anesthesia followed by 4 mg/kg sugammadex^[14]. A 50% increase in recovery time was considered to be clinically relevant. To obtain statistically significant results with a probability of

type I error ($\alpha = 0.05$), probability of type II error ($\beta = 0.10$), and a statistical power of 90%, a total of 22 patients were required. Therefore, 32 patients were recruited to compensate for any possible losses.

Patients were randomized to receive a dose of 2 mg/kg (group A) or 4 mg/kg (group B) after surgical procedure by the responsible anesthesiologist as previously had been determined. A manual randomization method was performed.

Exclusion criteria were as follows: previous known neuromuscular disease, obesity [defined as a body mass index (BMI) ≥ 30 kg/m²], allergy to any drug used in the general anesthesia, history of malignant hyperthermia, liver or kidney insufficiency, predicted difficult airways or a previous history of difficult intubation, use of drugs that affect the neuromuscular system (for example: magnesium, anticonvulsants, aminoglycosides), pregnancy or lactation, or any other medical condition which could affect level of consciousness.

Anesthesia and neuromuscular monitoring

All patients received intramuscular 2 mg midazolam as premedication. Standard monitoring was performed once the patients were in the operating room (pulseoximetry, capnography, electrocardiography and noninvasive arterial pressure). Patients were preoxygenated with FIO₂ of 1.0 for 3 min before induction of anesthesia with intravenous propofol (1.5-2.5 mg/kg) and fentanyl (1-2 mcg/kg).

Neuromuscular function was monitored through kinemyography (KMG) in form of the Mechanosensor-Neuromuscular Module Transmission (M-NMT®) (GE Healthcare, Helsinki, Finland) integrated in the Datex-Ohmeda anesthesia machine. The right arm was placed at an angle of 90° to the longitudinal axis of the body and the electrodes were placed on cleaned skin 3-6 cm apart over the ulnar nerve at the wrist. M-NMT was placed on the adductor pollicis muscle. Physical means were used to maintain the peripheral temperature above 35 °C.

Once the induction of anesthesia was finished and before the administration of rocuronium, the M-NMT monitor was calibrated using 200 μ s pulses at a rate of 2 Hz, starting at 5 mA with increments of 5 mA. The maximal current was increased by 15%, yielding the supramaximal stimulation. The 0.6 mg/kg of rocuronium bolus was then injected provided that a first 2 Hz TOF stimulation for 1.5 s yielded four equal responses within 15% of the calibration. When there was no measurable response to TOF stimulation, the patients were intubated and mechanical ventilation was initiated. This initial dose was followed by a continuous infusion of 0.3-0.6 mg/kg per hour of rocuronium which was adjusted to maintain a deep block with a TOF response of zero and PTCs less than 10 for the duration of the procedure. TOF stimulations were repeated every 15 s throughout the study. A PTC mode was initially applied 5 min after obtaining

complete NMB and repeated every 6 min. Anesthesia was maintained with sevoflurane 1%-3% end-tidal. In both groups analgesia was provided by remifentanyl with a dose of 0.05-0.5 mcg/kg per minute.

Upon completion of the surgery, the administration of sevoflurane, remifentanyl and rocuronium ended. At the reappearance of the T1, every patient received a dose of sugammadex according to the group in which they had been randomized (2 mg/kg in group A, or 4 mg/kg in group B), and they were awoken once complete NMB reversal (TOF ratio ≥ 0.9) was reached. Neuromuscular monitoring was continued until patients were extubated. Once recovered, they were transferred to the post-anesthesia care unit.

After one hour in the post-anesthesia care unit, a member of the team who was blind to the sugammadex dose that the patient had received, evaluated in each patient the presence of any residual paralysis through neuromuscular monitoring and performed a clinical assessment by signs of muscular weakness and clinical tests (lifting the head for more than 5 s, holding a tongue depressor between the teeth and generalized muscular weakness). The post-anesthesia oxygen saturation, breathing rate and any possible hemodynamic instability as well as the appearance of any adverse effect was also recorded. The same post-surgical analgesia protocol was applied to all patients.

Statistical analysis

Patient baseline quantitative variables in the two groups were compared by two-sided Student *t*-test if they followed a normal distribution. Categorical variables were analyzed by Pearson χ^2 test (or Fisher Exact test if expected count less than 5). Odds ratio (OR) and its CI was calculated if necessary.

The primary efficacy variable was the time (in seconds) between commencing sugammadex administration and reaching recovery of the TOF ratio to 0.9. The time until recovery of TOF ratios to 0.7 and 0.8 were studied too. We used the statistical approaching method described by Rex *et al.*^[14]. The CI approach was used to demonstrate equivalence in recovery of the TOF ratios between the two treatment groups. Non statistical signification was established if the two-sided 95%CI for the estimated difference of median between group A and group B was within the interval ranging from 0% to 50% of the median of group B. The 95%CI was obtained by using the nonparametric methods of Hodges-Lehmann. Similarly, TOF ratio to 0.7 and 0.8 were studied.

The hemodynamic variables were the evolution of arterial blood pressure (AP) and the heart rate (HR) after sugammadex injection. AP and HR were recorded every 5 min throughout the intervention: previously, during the start of sugammadex, and 2, 5 and 10 min after initiating administration of the drug. Any possible secondary effect associated to its administration was also recorded.

Table 1 Demographic characteristics

Sugammadex (dose)	Group A (n = 16)		Group B (n = 16)		P-value
Age (yr)	43.6	(SD 12.01)	47.1	(SD 14.18)	0.46
Weight (kg)	65.5	(SD 11.22)	60.9	(SD 10.62)	0.25
Height (cm)	163.2	(SD 4.76)	160.1	(SD 5.91)	0.12
BMI (kg/m ²)	24.1	(SD 3.56)	23.2	(SD 3.65)	0.47
Intervention (time-minute)	95.2	(SD 26.91)	94.7	(SD 30.02)	0.96
ASA (1-2)	1.4	(SD 0.51)	1.2	(SD 0.48)	0.28
ASA 1 ^a	n = 9	(56.25%)	n = 12	(75.00%)	0.23

Analyzed by student *t*-test. Both groups are similar. ^aASA 1 is expressed as percentage of patients with an ASA index of 1 in its group and a Fisher exact test was executed. BMI: Body mass index; ASA: American Society of Anesthesiologists.

Data for AP and HR were analyzed by repeated measure analysis of variance (ANOVA-RM). The within-subjects terms were the AP and HR values for each patient, and the repeated term was the time point (baseline, starting, and minute 2, 5 and 10). Pillai's Trace^[16] is calculated for AP and HR and their interactions with sugammadex doses. They were corrected with epsilon multipliers if the assumption of circularity had been violated following Mauchly's test^[17]. Lower bound was elected to be the most conservative. Post-hoc analyses were executed. The *P*-values < 0.05 were considered significant. All tests were 2-sided. Data was analyzed using SPSS 17.0 for Windows (SPSS Inc., Chicago, United States).

RESULTS

A total of 32 patients were included in the study, 16 patients in group A and 16 patients in group B. All descriptive variables are summarized in Table 1. However, AP was not taken in the 10th minute in two patients in each group. Because AP in the 10th minute is a related sample within temporal evolution (the others are AP baseline, pre-sugammadex, minute 2th and minute 5th), only 14 patients from each group were computed (another two were excluded). So, all results were analyzed by per-protocol; however, AP values were lost in two patients in each group for the 10th minute.

The gynecological interventions were fourteen vaginal assisted laparoscopic hysterectomies (43.7%), eleven laparoscopic ovarian cystectomies (34.4%) and seven laparoscopic adnexectomies (21.9%). The two groups were comparable in terms of age, BMI and ASA (Table 1). Surgical time was more than 60 min in all cases.

All patients recovered to a TOF ratio of 0.9 within 3 min (maximum value 175 s). Median recovery time from starting of sugammadex administration to a TOF ratio of 0.9 was 129 s in group A and 110 s in group B. The estimated difference in recovery time between the two groups was 24 s (95%CI: 0 to 45 s, Hodges-Lehmann estimator). This CI was entirely within the predefined equivalence interval (for a median of

110 s in group B = 0 to 52.5 s), so equivalence was assumed. Times to recovery to TOF ratios of 0.8 and 0.7 from start of sugammadex administration were not equivalent between groups. Median time to recovery to a TOF ratio of 0.8 was 101 s in group A and 82.5 s in group B, with an estimated difference of 18 (95%CI: -5 to 39 s, Hodges-Lehmann estimator). 95%CI was out of predefined equivalence interval of 0 to 43.7 s. Median time to recovery to a TOF ratio of 0.7 was 90 s in group A and 65 s in group B, with an estimated difference of 10 (95%CI: -10 to 35, Hodges-Lehmann estimator). So, 95%CI was out of predefined equivalence interval of 0 to 32.5 s. Equivalences were not assumed for TOF ratio 0.8 and TOF ratio 0.7 (Table 2).

There was no significant variation in the AP and HR between the two groups. Although both of them maintained AP and HR within normal ranges the entire time, there was a logical increment of AP and HR as time passed until the effect of anesthetic drugs disappeared. So, post-hoc analyses were statistically significant across the 2nd, 5th and 10th minute within each group (Figure 1).

Based on neuromuscular monitoring and clinical signs, none of the patients showed any clinical evidence of residual or recurrent NMB. Although group B had more adverse events than group A, there was no statistical difference between them (group A: 12.5% vs group B: 18.7%, OR = 1.62; 95%CI: 0.23-11.26, *P* = 0.99). There were no severe adverse effects, even with an increased dosage of sugammadex. As a consequence, in the immediate post-operative period in group A, there was one case of nausea and another case of pain, while in group B, there was one case of nausea, one case of pain and one patient suffered tremors in lower limbs (Table 3). Habitual symptomatic treatments were adopted and they were effective without any more clinical relevance.

DISCUSSION

Our study suggests that a dose of 2 mg/kg sugammadex is enough for the recovery of NMB induced by a continuous infusion of rocuronium in patients who kept anaesthetized with sevoflurane. This lower dose did not

Table 2 Train-of-four ratio studies

	Group A (n = 14)		Group B (n = 14)		Assumed calculated interval (increased of 0% to 50% of median in group B)	Estimated difference median by Hodges-Lehmann estimator	95%CI	
	Mean	Median	Mean	Median				
TOF ratio 0.9	118.8	129	96.6	105	0 to 52.5	24	0 to 45	Differences not assumed
TOF ratio 0.8	96.7	101	80.1	82.5	0 to 43.7	18	-5 to 39	Assumed
TOF ratio 0.7	78.4	90	66.3	65	0 to 32.5	10	-10 to 35	Assumed

Based on the value of the median of TOF ratio in the Group B, an interval was calculated to establish the acceptable variation of the median values in the Group A (an increase from 0% to 50% respect Group B). The Hodges-Lehmann estimator was calculated for the differences between TOF ratio 0.7, 0.8 and 0.9 medians with their 95%CI. All values are expressed in seconds. If the Hodges-Lehmann 95%CI was contained in the 95%CI based on medians of the Group B, no statistical and clinical differences would be assumed. TOF: Train-of-four.

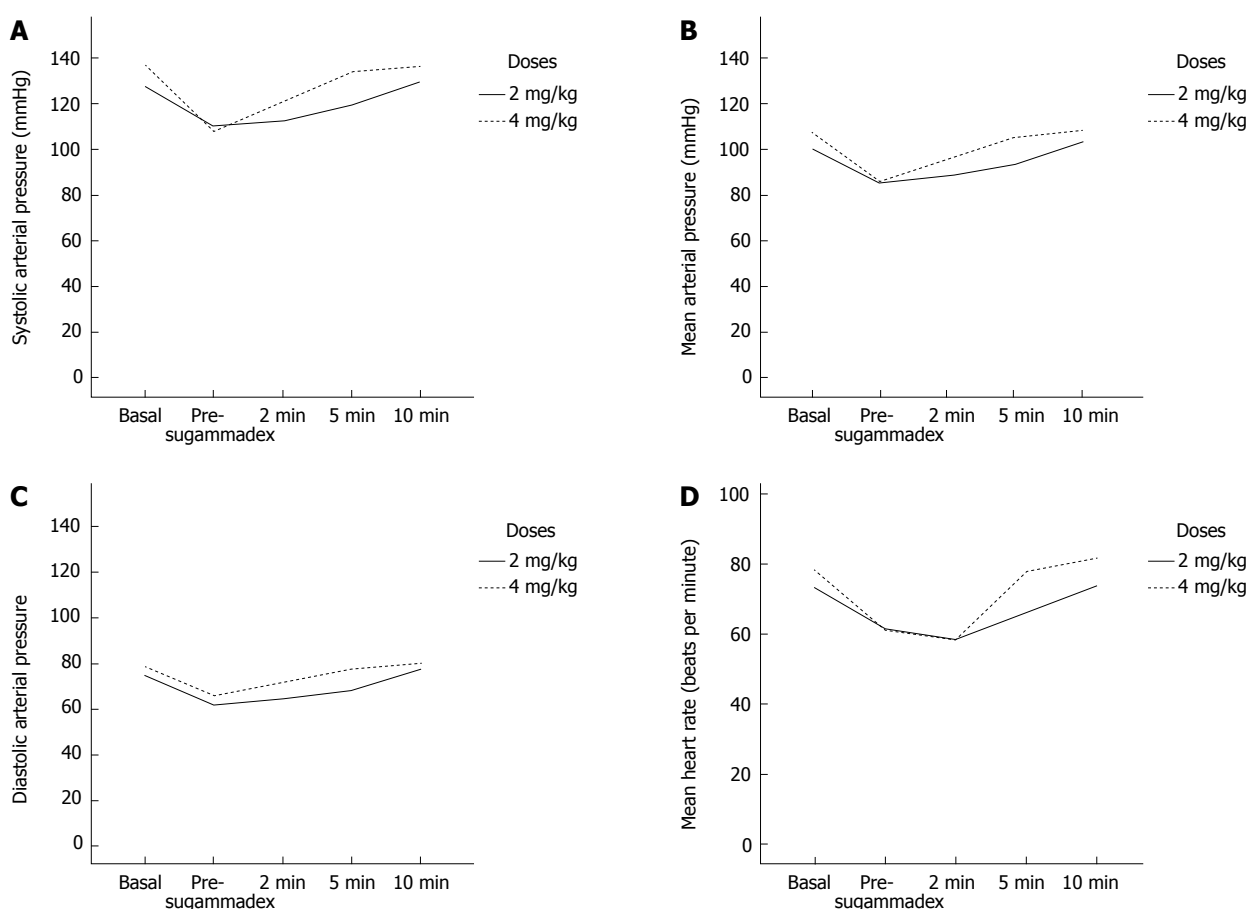


Figure 1 Arterial pressures and heart rate after sugammadex administration. A: Systolic arterial pressure; B: Mean arterial pressure; C: Diastolic arterial pressure; D: Mean heart rate. The increased amount of arterial pressures and heart rate after sugammadex administration was statistically significant as the time passed (post hoc analysis in ANOVA-RM). But the values were in the normal range the entire time. So, it only shows the activity of both administered doses and there was no statistical significance between them.

have any clinically relevant recovery time augmentation or increased risk of residual recurarization. We have not been able to observe other adverse events in our patients.

The main limitation in our study was the lack of rocuronium and sugammadex plasma concentration determinations at different moments of the study. Although previous studies have shown a similar rocuronium pharmacokinetic profile when compared

continuous infusion vs intravenous bolus dose^[18], significant variations in plasma concentrations of rocuronium were also observed in those continuously infused with this drug (highly variable, up to 30% for some patients)^[14]. For this reason, neuromuscular transmission monitoring suggested a better option in patients who received continuous infusions of rocuronium as a more realistic approach to the global effect of the drug. This is not routinely used in current

Table 3 Adverse events

Adverse events	Group A	Group B
Arterial hypertension	0%	0%
Arterial hypotension	0%	0%
Bradycardia	0%	0%
Cough	0%	0%
Headache	0%	0%
Nausea	6.20%	6.20%
Pain	6.20%	6.20%
Residual neuromuscular blocking	0%	0%
Vomiting	0%	0%
Others	0%	6.20%

daily monitoring in clinical practice^[19,20] and a study published in the United Kingdom in 2007 reported that 62% of anesthetists surveyed had never used monitors to evaluate the effect of NMB^[20].

Another point of interest was the use of a dose of 4 mg/kg of sugammadex. It has been demonstrated as preferable in the reversion of deep NMB^[8]. The provider recommends a dose of 4 mg/kg if recovery has reached at least 1-2 PTCs, and a dose of 2 mg/kg sugammadex when spontaneous recovery has occurred up to least the reappearance of second response in the TOF^[21]. Other authors consider in clinical practice that the appropriate dose of sugammadex for reversing a moderate block (TOF-count 1-3) is 2 mg/kg of sugammadex^[22].

A TOF ratio ≥ 0.9 was used as the main desirable objective variable because a postoperative residual curarization TOF ratio < 0.9 is associated with increased morbidity and extended stay in the post-anesthesia care room^[23]. It has been published that with 4 mg/kg of sugammadex, the time to recover a TOF ratio of 0.9 from 1-2 PTCs (induced by a bolus of rocuronium under anesthesia with sevoflurane) was 1.7 min compared to 3.2 min with a dose of 2 mg/kg of sugammadex^[12]. However, studies comparing the efficacy of sugammadex in surgical patients when NMB was induced through the infusion of rocuronium are very scarce. Rex *et al.*^[14] demonstrated that just one dose (4 mg/kg) of sugammadex administered at a NMB to T1, after continuous infusion of rocuronium, was sufficient and safe with both sevoflurane and propofol. This use of continuous infusion of rocuronium has been shown to lengthen the NMB recovery time compared with one single bolus^[24], thereby providing a more stable drug concentrations with a constant degree of paralysis. In our series, we find that difference between the means of the TOF 0.9 of both groups is lower than previously described: approximately an increase of only 23% vs the estimated published of 88%^[12]. This difference can be attributed to different time of reversal of NMB and different procedures.

A limitation of our study is the age of the patients and the kind of surgical intervention (young and gynecological patients). In contrast, these patients were elected because they were attended by the same

surgical team; hence similar laparoscopic conditions were expected in all cases. We decided to limit the age to 65 years because, even though reversal from profound block with sugammadex can be performed safely and effectively, there have been reports regarding older patients who recover more slowly than younger ones^[25,26]. This slower recovery could be due to age-related decreased cardiac output and muscular blood flow^[26].

Another possible bias in our study could be that surgical procedures lasted 60 min. They may be classified as insufficient. Nonetheless, it has been seen that a dose of 2 or 4 mg/kg of sugammadex is sufficient for reversion of NMB, even when deep NMB (1-2 PTCs) is maintained for 2 h or more, with reversal being performed when the second TOF response occurs^[8,27].

We also observed the safety of using sugammadex. Adverse events related to the administration of sugammadex have been reported in the literature with an incidence of 14%, the most common being nausea, vomiting, bradycardia, hypertension and hypotension, oliguria, vertigo, headache, cough, dry mouth and intraoperative movements^[28]. However, these adverse effects were not related with the use of sugammadex^[11,12] or the dose administered. In our series, we found a similar occurrence in the two groups and there was no statistical difference between them. We consider that they were expectable, without direct relationship with the studied drug and not clinically relevant.

It could be supposed that the use of sugammadex would lead to a reduction of adverse events in the immediate postoperative period. They require additional resources and a longer recovery time. So, sugammadex could improve efficiency and reduce the costs related to surgical activities^[29,30]. Nevertheless, the reduction of the sugammadex dose to save costs could be a mistake which may lead to other complications, such as the recurrence of NMB after an apparently successful recovery^[31]. In this study we do not analyze the economic implications of the lower dose. We think that the group size is too small to establish conclusions, because they were selected and calculated to observe the effect on TOF 0.9 of sugammadex in two different doses. A dose of 2 mg/kg is evidently the half of cost of 4 mg/kg but it is only in respect to a simple drug expenditure and we cannot apply it to the complete surgical procedure and its multiple non-contemplated influent variables.

Only future investigation will make enable us to consider readjusting the currently recommended doses in specific circumstances, without an increase in the risks^[32]. So, more studies are necessary in different surgical sceneries to understand all possibilities of sugammadex.

In conclusion, in our study, a dose of 2 mg/kg sugammadex was found to be efficient and safe for reversing the NMB when first response in the TOF is

reached, after a continuous infusion of rocuronium without increasing the risk of residual recurarization. Future studies are required to determine any possible readjustments of doses and the consequent risks that lower doses of sugammadex may cause in the reversal of NMB. In the future, with the absence of plasma level of drugs, neuromuscular monitoring will be essential in the daily anesthetic practice, especially when rocuronium is given as a continuous infusion for the immediacy of its results.

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COMMENTS

Background

The introduction of sugammadex to antagonize non-depolarising neuromuscular blockade (NMB) has led to significant changes in anaesthesia practice. Residual effects of neuromuscular block can have significant clinical consequences and can cause critical respiratory events. The superiority of sugammadex (vs neostigmine) for reversing neuromuscular block has now been well established.

Research frontiers

Sugammadex should be dosed according to the prescriber information issued by the manufacturer. The provider recommends a dose of 4 mg/kg if recovery has reached at least 1-2 PTCs, and a dose of 2 mg/kg sugammadex when spontaneous recovery has occurred up to at least the reappearance of second response in the train-of-four (TOF), but they don't define the ideal dose of sugammadex for reversal the NMB when first response in the TOF is reached.

Innovations and breakthroughs

This study suggests that a dose of 2 mg/kg sugammadex (vs 4 mg/kg) is enough for the recovery of NMB induced by a continuous infusion of rocuronium in patients who kept anaesthetized with sevoflurane when first response in the TOF is reached. This lower dose did not have any clinically relevant recovery time augmentation or increased risk of residual recurarization. The authors have not been able to observe more adverse events in the patients.

Applications

A dose of 2 mg/kg sugammadex was found to be efficient and safe for reversing the NMB when first response in the TOF is reached without increasing the risk of residual recurarization. Future studies are required to determine any possible readjustments of doses and the consequent risks that lower doses of sugammadex may cause in the reversal of NMB. In the future, quantitative neuromuscular monitoring is mandatory and increased postoperative vigilance is required in order to identify the problems of incomplete reversal.

Terminology

After injection of a nondepolarizing neuromuscular blocking drug in a dose sufficient for smooth tracheal intubation, TOF recording demonstrates three phases of NMB: intense, moderate or surgical blockade, and recovery. Intense NMB is also called the period of no response because no response to TOF or single-twitch stimulation occurs. Although this phase it is not possible to determinate exactly how long intense NMB will last, correlation does exist between PTC stimulation and the time to reappearance of the first response to TOF stimulation. Moderate blockade begins when the first response to TOF stimulation appears. This phase is characterized by a gradual return of the four responses to TOF stimulation. The return of the fourth response in the TOF heralds the recovery phase. Satisfactory recovery from NMB has not occurred until the TOF ratio is > 0.9.

Peer-review

This is a study comparing the efficacy and safety of two different doses of sugammadex. The paper is well written and designed.

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Hair thread tourniquet syndrome in a toe of an 18 mo old girl

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tourniquet is not cut through, the affected body part may become ischemic and even necrotic.

Key words: Hair; Thread; Tourniquet; Syndrome; Toe

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Core tip: Hair thread tourniquet syndrome is rare and usually affects little children. We present a case of an 18 mo old girl with a strangulated toe. After incision of the hair tourniquet the symptoms soon subsided. The diagnosis is easily made if the clinical features are recognized. However, if the tourniquet is not cut through, the affected body part may become ischemic and even necrotic.

Kuiper JWP, de Korte N. Hair thread tourniquet syndrome in a toe of an 18 mo old girl. *World J Clin Cases* 2015; 3(4): 368-370
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Abstract

Hair thread tourniquet syndrome is rare and usually affects little children. If the tourniquet is not incised, the affected body part becomes ischemic or even necrotic. An 18 mo old girl was seen in the emergency ward with a painful, red and swollen third toe of the left foot. The toe appeared to be strangulated with a hair, and the diagnosis hair thread tourniquet syndrome was made. After incision of the hair tourniquet the symptoms soon subsided. The diagnosis is easily made if the clinical features are recognized. However, if the

INTRODUCTION

Hair thread tourniquet syndrome (HTTS), or hair tourniquet syndrome, is a syndrome in which children experience strangulation of small extremities (fingers, toes or external genitalia) with a hair or thin wire^[1,2]. If the strangulation is not recognized, the affected body part becomes ischemic, and can even necrotize in a few hours to weeks^[2,3]. In this report, a patient with HTTS of the third toe is presented, for which she was surgically treated.

CASE REPORT

An 18 mo old girl was presented in the emergency ward, after her mother had noticed a constriction

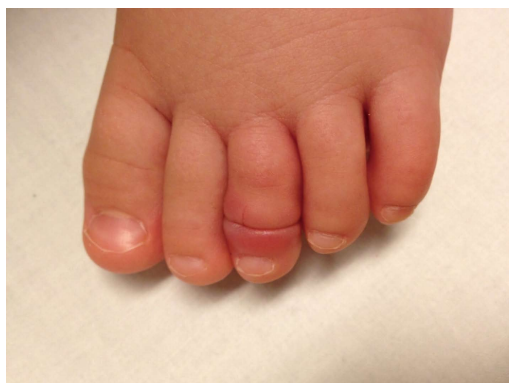


Figure 1 Strangulation of the third toe: Typical clinical picture of hair thread tourniquet syndrome.

around her third toe of the left foot, that morning. She thought this may have had been caused the previous day, when the child's father had removed some hairs from under the toes, after a visit to the swimming pool. The girl was otherwise healthy and did not take any medication. The mother had had a normal partus (C-section), and the girl had afterwards been in the hospital only once, with fever caused by a viral infection.

On physical examination we saw a healthy looking 18 mo old girl, with a strangulation around the third toe of the left foot. No hair or thread could be seen around the toe. Redness and swelling was seen around the strangulation. A normal capillary refill (< 2 s) was seen. Upon palpation, the toe was painful (Figure 1).

An attempt was made to remove (remains of) the strangulating hairs with a stitch cutter, without success. With the idea that possibly all the hairs had already been removed by the father, the patient was sent home, and the mother was advised to return the next day if the strangulation remained.

Indeed, they returned the next day. Physical examination was similar to the previous day, with unchanged strangulation, and still good capillary refill.

It was decided to incise the hair tourniquet in the operating room under general anesthesia. After incision to the bone-medial, between the proximal and distal interphalangeal joint-some hairs were removed.

One day after surgery, the swelling had largely subsided, and the constriction had almost disappeared. After two weeks the girl was seen again, and all symptoms were gone.

DISCUSSION

HTTS is a strangulation of a small limb, usually a finger or toe, or sometimes external genitalia. When the diagnosis is made correctly, treatment is simple and effective. Differential diagnoses may include cellulitis, erysipelas, or other irritation of the skin (for example after being bitten by an insect), or trauma^[3].

Approximately a hundred cases of HTTS are previously

described, mostly occurring for fingers (24%-47%), toes (25%-43%) or penises (44%)^[3]. The typical age of affected children is around 5 years, and fingers are more frequently affected in younger children (up to 1.5 years)^[3]. When a toe is affected, this is usually the third or fourth toe^[2]. The material causing the strangulation is mostly either nylon or hair (both around 50% of the cases)^[2]. However, HTTS in toes is more often caused by hairs^[3].

The etiology of HTTS is, as previously mentioned, a hair or thread around a small body part and causing strangulation and sometimes even ischemia or necrosis. The patient can sometimes shed light on the origin of this hair or thread, but in other cases this remains unclear. How a hair can cause such a strangulation is not entirely clear, but one study mentions that that wet hair is longer than dry hair and thus, when drying, a hair tourniquet contracts and thus causes strangulation^[3]. With this strangulation, swelling occurs, gradually causing a decrease in arterial blood supply and therefore tissue ischemia and necrosis^[2,3].

HTTS diagnosis is easy to make when the clinical picture is recognized. It is however very important that HTTS is not missed, because prolonged HTTS can cause necrosis^[3]. Therefore, it is important to always assess capillary refill in such patients^[3].

Treatment for HTTS is simple: removal of the strangulating hair or thread. This may be difficult with extensive local swelling, and often surgical incision is required. This incision should be to the bone, to be certain that all the constricting material is dissected^[3]. As turned out in this case, after such treatment the symptoms quickly disappear.

COMMENTS

Case characteristics

An 18 mo old girl with a painful swollen third toe was seen at the emergency ward.

Clinical diagnosis

A strangulated third toe was seen, presumably by a hair.

Differential diagnosis

Hair thread tourniquet syndrome is a clinical diagnosis with a very typical representation.

Treatment

Treatment for hair thread tourniquet syndrome consists of incision of the tourniquet.

Related reports

Hair thread tourniquet syndrome usually occurs in little children en generally affects toes, fingers or external genitalia.

Term explanation

Hair thread tourniquet syndrome is abbreviated as hair thread tourniquet syndrome.

Experiences and lessons

Hair thread tourniquet syndrome is a clinical diagnosis and is easily treated when recognized.

Peer-review

This is a nice case and well documented paper about the hair thread tourniquet.

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Dysbetalipoproteinemia: Two cases report and a diagnostic algorithm

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It is associated with an increased risk for premature cardiovascular disease. Thus, making a diagnosis of dysbetalipoproteinemia aids in assessing cardiovascular risk correctly and allows for genetic counseling. However, the diagnostic work-up can be challenging. Diagnosis of dysbetalipoproteinemia should be considered in patients mixed dyslipidemia when the apolipoprotein B concentration is relatively low in relation to the total cholesterol concentration or when there is significant disparity between the calculated low density lipoprotein (LDL) and directly measured LDL cholesterol concentrations. Other indices are also informative in the diagnostic process. We present herein two phenotypically different cases (a 44-year-old man with severe hypertriglyceridemia and a 49-year-old woman with mixed dyslipidemia) of genotypically proven familial dysbetalipoproteinemia and a diagnostic algorithm of the disease.

Key words: Dysbetalipoproteinemia; Chylomicronemia; Hyperlipoproteinemia type III; Hypertriglyceridemia

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Core tip: Dysbetalipoproteinemia is associated with an increased risk for premature cardiovascular disease and its diagnosis may be challenging since its phenotype may significantly vary when specific environmental, hormonal and genetic factors that affect triglyceride (TG) metabolism co-exist. An algorithm with a number of dysbetalipoproteinemia indices may be helpful for the diagnosis of the disease and roughly equally elevated levels of both total cholesterol (TC) and TG and a low apolipoprotein B to TC ratio seem to comprise the two most helpful indices.

Abstract

Dysbetalipoproteinemia is a rare familial dyslipidemia characterized by approximately equally elevated serum cholesterol and triglyceride levels due to accumulated remnant lipoproteins in apolipoprotein E2/E2 homozygotes.

Kei A, Miltiadous G, Bairaktari E, Hadjivassiliou M, Cariolou M, Elisaf M. Dysbetalipoproteinemia: Two cases report and a diagnostic algorithm. *World J Clin Cases* 2015; 3(4): 371-376 Available from: URL: <http://www.wjgnet.com/2307-8960/full/>

INTRODUCTION

Apolipoprotein E (apoE) in plasma is mainly carried by chylomicrons, very-low-density lipoproteins (VLDL) and high-density lipoproteins (HDL). When associated with these lipoproteins, apoE serves as the ligand for the low density lipoprotein (LDL) receptor and the LDL-receptor related protein on the surface of hepatic cells^[1]. In humans, three common apoE isoforms have been described, designated E2, E3, and E4^[2,3]. ApoE2 and apoE4 differ from the more frequent apoE3 isoform by a single amino-acid substitution due to a single point mutation, conferring a more acidic or more basic charge to the protein. When compared with the apoE3 isoform, apoE2 has a markedly reduced affinity (< 1%) for the LDL receptor. Only a modest accumulation of cholesterol-enriched lipoprotein remnants of both hepatic and intestinal origin, or β -VLDL is observed in most apoE2/E2 homozygotes, which is not sufficient to cause an elevation of plasma cholesterol and triglyceride (TG) levels above normal. However, in individuals with predisposing genetic, hormonal, or environmental factors, this phenotype is associated with dysbetalipoproteinemia, also known as hyperlipoproteinemia type 3^[2,4].

We present herein two phenotypically different cases of genotypically proven familial dysbetalipoproteinemia.

Methods

Blood samples for laboratory tests were obtained after a 12 h overnight fast. All serum laboratory measurements including fasting plasma glucose, creatinine, thyroid hormones, total cholesterol (TC), HDL cholesterol (HDL-C), and TG were determined enzymatically in the laboratory of the University Hospital of Ioannina using an Olympus AU 600 analyzer (Olympus Diagnostica GmbH, Hamburg, Germany). LDL cholesterol (LDL-C) was calculated using the Friedewald equation (provided that TGs were < 350 mg/dL (3.95 mmol/L)). Apolipoproteins, serum and urinary proteins were measured with a Behring Nephelometer BN100 with reagents (antibodies and calibrators) from Dade Behring Holding GmbH (Liederbach, Germany). Antinuclear antibodies (MB Laboratories, Sidney, BC, Canada) were assessed by immunofluorescence. A commercial enzyme-linked immunosorbent assay was used to evaluate the levels of anti-extractable nuclear antigen (AESKU Diagnostics, Wendelsheim, Germany), while levels of serum globulins, C3 and C4 fractions of complement and rheumatoid factor were evaluated using nephelometry (Siemens Healthcare Diagnostics, Erlangen, Germany).

VLDL was isolated from plasma by two sequential ultracentrifugations according to the method of Gaw *et al.*^[5]. In brief, chylomicrons-deficient plasma firstly was prepared by plasma ultracentrifugation in a Beckman

SW41 Ti rotor at 20000 rpm for 70 min at 23 °C. The chylomicrons fraction was carefully removed from the top of the tube and the chylomicrons-deficient fraction was next submitted to ultracentrifugation at density of $d = 1.019$ g/mL at 45000 rpm for 8 h at 14 °C. The VLDL fraction floating to the top of the tube was carefully collected.

DNA was extracted from the whole blood specimen according to standard procedures. ApoE genotyping was performed as described by Hixson and Vernier^[6]. Polymerase chain reaction (PCR) was used to amplify a 244-bp sequence of the *apoE* gene, including the two polymorphic sites. The PCR product was then digested with the restriction enzyme Hha I and the different genotypes were detected after electrophoresis on 6% NuSieve agarose gel.

CASE REPORT

Case 1

Two years earlier a 44-year-old Caucasian man had received the diagnosis of mixed dyslipidemia based on the following lipid profile; TC: 420 mg/dL, TG: 580 mg/dL, HDL-C: 36 mg/dL. He had no family history of dyslipidemia or established cardiovascular disease, while physical examination was unremarkable. Secondary causes of dyslipidemia were excluded by evaluation of thyroid and renal function, urinary protein excretion, serum protein electrophoresis, erythrocyte sedimentation rate and autoantibodies. A low-fat diet was recommended and patient was given gemfibrozil, 600 mg, twice a day. His lipid profile improved after 2 mo, but he stopped taking the drug and was lost to follow-up. At age 46, the patient had consulted a dermatologist because of the lesions shown at Figure 1 and was referred for serum lipid assessment. He consumed small amount of alcoholic beverages and had stopped smoking 5 years earlier. For the past 6 mo, he experienced symptoms that suggested intermittent claudication. A Doppler ultrasonic study revealed mild stenosis of left femoral artery.

Seen at Figure 1 are the characteristic for dysbetalipoproteinemia tuberous xanthomas over the patient's elbows (they were also present on his knees) and the pathognomonic striated palmar xanthomas, while skin lesions typically associated with chylomicronemia, namely eruptive xanthomas, on his buttocks were also present (Figure 1). Laboratory assessment revealed: fasting plasma glucose: 300 mg/dL, TC: 1055 mg/dL, TG: 2900 mg/dL, HDL-C: 18 mg/dL, VLDL-C: 316 mg/dL, VLDL-TG: 831 mg/dL. The diagnosis of dysbetalipoproteinemia was verified by apoE2/E2 homozygosity genotype.

We suggested the patient to stop fat and alcohol consumption. He received metformin 850 mg twice a day and ciprofibrate 100 mg/d. Four weeks later the patient's skin lesions had regressed significantly and serum laboratory parameters improved (fasting

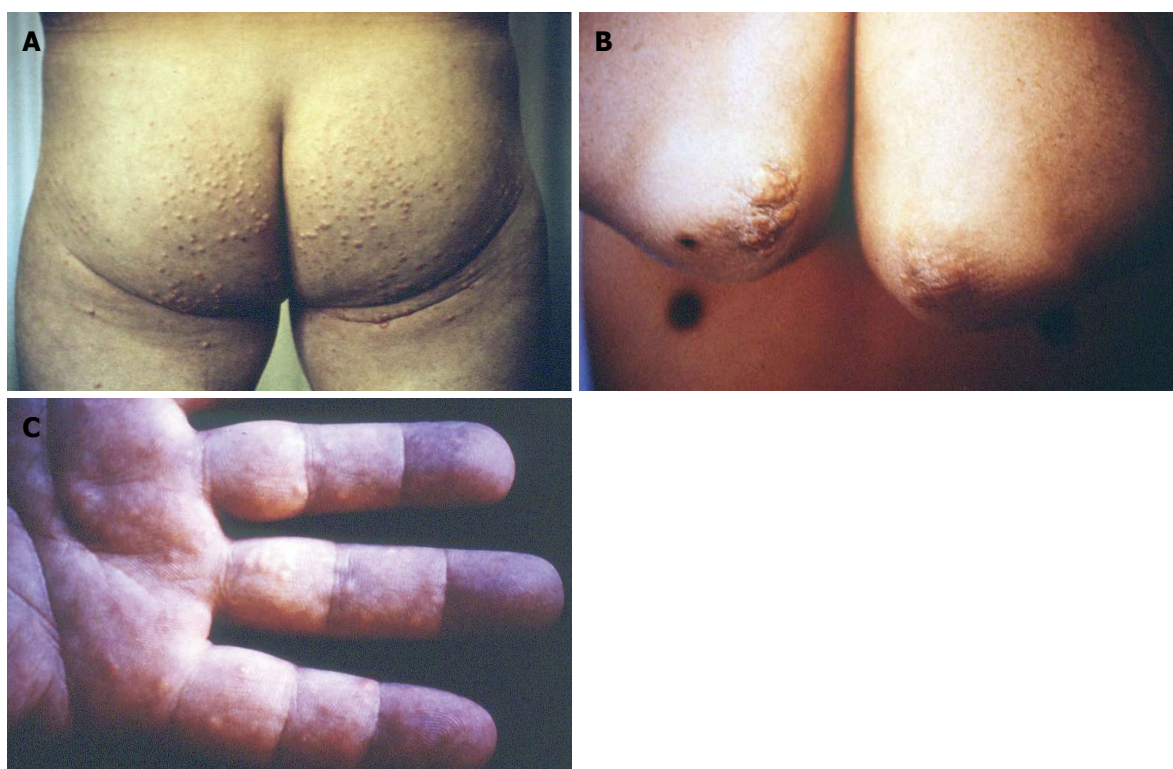


Figure 1 Tuberous xanthomas over the patient's elbows, striated palmar xanthomas and eruptive xanthomas on his buttocks. A: Eruptive xanthomas; B: Tuberous xanthomas; C: Striated palmar xanthomas.

plasma glucose: 150 mg/dL, TC: 412 mg/dL, TG: 754 mg/dL, HDL-C: 27 mg/dL). The dosage of ciprofibrate was increased to 100 mg, twice a day and glimepiride 2 mg/d was added.

Case 2

A 49-year-old Caucasian woman was referred to the Outpatient Lipid and Obesity Clinic of the University Hospital of Ioannina, Greece by her family doctor due to increased TC and TG levels. The patient denied any symptoms indicative of cardiovascular disease but her mother had been diagnosed with peripheral artery disease at the age of 40. In addition the patient had been diagnosed with breast cancer 2 years ago and her body mass index (BMI) was 28 kg/m². She was on tamoxifen 20 mg/d and there had been no changes in her medication for the last 11 mo. Clinical examination revealed no pathologic findings, while her electrocardiogram was normal. Treatment naïve lipid profile analysis revealed elevated TC (325 mg/dL), TG (321 mg/dL), LDL-C (214 mg/dL), apoE (147 mg/dL) and lipoprotein a [Lp(a), 47.5 mg/dL] levels, while HDL-C (47 mg/dL), apoA1 (178 mg/dL) and apoB (77 mg/dL) levels were within normal range. Other secondary causes of hyperlipoproteinemia were excluded as in case 1 patient. Dysbetalipoproteinemia was suspected by the equally elevated levels of both TC and TG (TC/TG is approximately 1), before treatment initiation and the low apoB to TC ratio (< 0.33) (Figure 2). We first assessed a number of

dysbetalipoproteinemia indices, while the apoE2/E2 homozygosity genotype verified the speculated diagnosis (Table 1, Figure 2).

Patient was advised to switch to a diet low in saturated fats and carbohydrates. She received rosuvastatin 40 mg/d, ezetimibe 10 mg/d and fenofibrate 145 mg/d. Four weeks later patient's lipid profile significantly improved (TC: 238 mg/dL, TG: 160 mg/dL, HDL-C: 50 mg/dL, LDL: 156 mg/dL).

DISCUSSION

Only untreated dysbetalipoproteinemia patients > 30-year-old, like case 1 patient, suffer from diagnostic skin lesions, including tuberous or tuberoeruptive xanthomas on the extensor surfaces of extremities (elbow, knees and buttocks)^[7,8]. Striated palmar xanthomas are considered pathognomonic of dysbetalipoproteinemia, but they are not present in all patients (case 2 patient)^[8].

Dysbetalipoproteinemia is characterized by increased serum TG and cholesterol rich lipoprotein remnants [mostly intermediate density lipoprotein (IDL) and chylomicron remnants], also known as β -VLDL particles^[7,8]. As dysbetalipoproteinemia is associated with increased premature cardiovascular disease demanding aggressive therapeutic management, it is important for the physician to suspect the disease when a mixed dyslipidemia is further characterized by approximately equally elevated levels of both TC and TG (TC is approximately 250-450

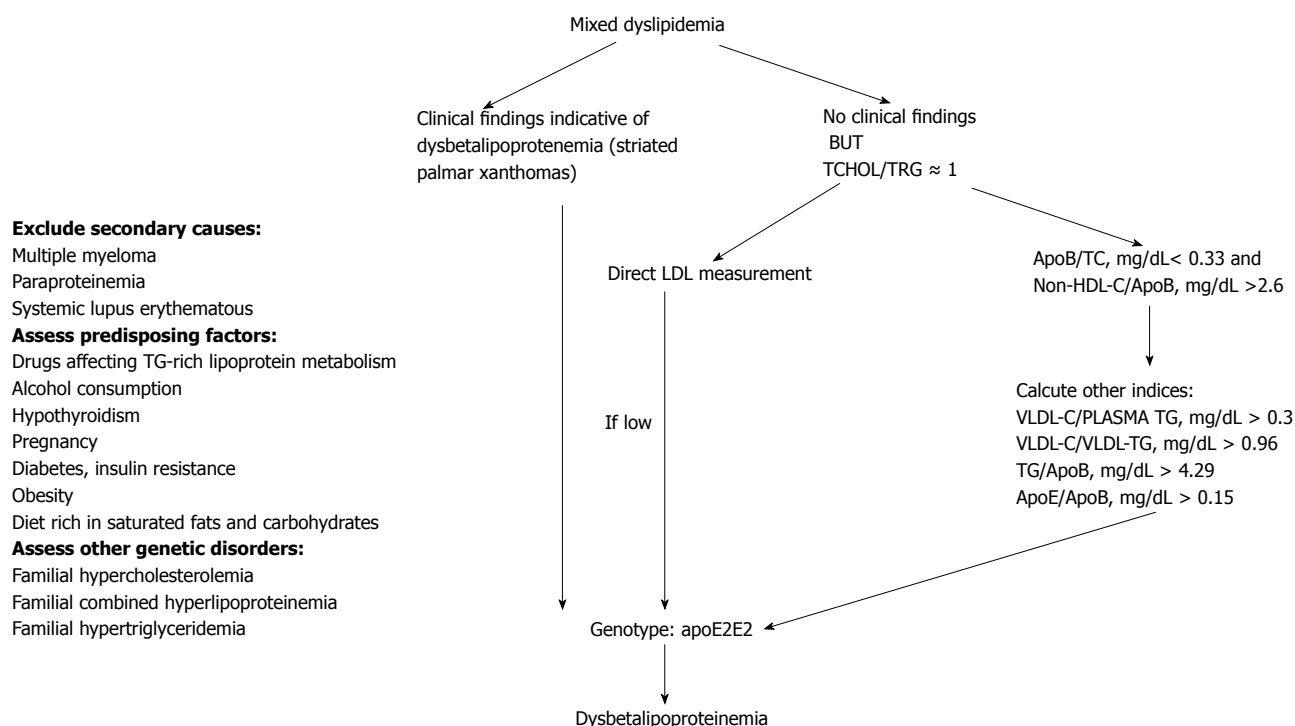


Figure 2 Diagnostic algorithm of dysbetalipoproteinemia. TC: Total cholesterol; TG: Triglycerides; ApoB: Apolipoprotein B; VLDL-C: Very low density lipoprotein cholesterol; VLDL-TG: Very low density lipoprotein triglycerides; ApoE: Apolipoprotein E; Non-HDL-C: Non high density lipoprotein cholesterol.

Table 1 Dysbetalipoproteinemia indices

Index	Patient's 2 values	Indicative for dysbetalipoproteinemia values
TC/TG (mg/dL)	1.01	Approximately 1
ApoB/TC (mg/dL)	0.23	< 0.33
ApoB/non-HDL-C (mg/dL)	0.27	< 0.38
VLDL-C/PLASMA TG (mg/dL)	0.35	> 0.3
VLDL-C/VLDL-TG (mg/dL)	1.06	> 0.96
TG/ApoB (mg/dL)	4.40	> 4.29
ApoE/ApoB (mg/dL)	0.20	> 0.15

TC: Total cholesterol; TG: Triglycerides; ApoB: Apolipoprotein B; VLDL-C: Very low density lipoprotein cholesterol; VLDL-TG: Very low density lipoprotein triglycerides; ApoE: Apolipoprotein E; Non-HDL-C: Non high density lipoprotein cholesterol.

mg/dL, TG is approximately 250-900 mg/dL) and a low apoB to TC ratio (< 0.33) (as it was the case with our second patient)^[7,8]. The apoB to TC ratio represents the cholesterol in the circulating lipoproteins, but it does not include the cholesterol that circulates in HDL and other non-apoB-containing lipoproteins^[9]. However, the apoB to non-HDL-C ratio was proven to be a less specific dysbetalipoproteinemia index compared with apoB to TC ratio^[9]. When available, directly measured LDL-C is lower compared to that of calculated due to impaired conversion of VLDL to LDL^[7,8,10]. In addition, an elevated VLDL cholesterol to total TG ratio (> 0.3) is indicative of dysbetalipoproteinemia and was also found in case 2 patient (Table 1)^[7,8,10]. However, this ratio should not be used in normolipidemic subjects as they may have elevated ratios. Falsely low ratios, on the other hand, can

be found in some dysbetalipoproteinemia patients who additionally have marked chylomicronemia and typical eruptive xanthomas (in the buttocks) as it was with case 1 patient. In this case, patient should be reassessed after several days on a low fat diet. In such cases another point distinguishing dysbetalipoproteinemia from type 5 hyperlipidemia is that the VLDL from a patient with dysbetalipoproteinemia is colored brown, whereas normal VLDL and that from type 2b and type 5 hyperlipidemia is white. Other dysbetalipoproteinemia indices have been also reported including elevated VLDL-C to VLDL-TG (> 0.96) as it represents high levels of cholesterol-enriched VLDL. In addition, elevated apoE to apoB has also been associated with dysbetalipoproteinemia and this index was elevated in our patient (Table 1)^[9]. Last, the presence of a broad β band in electrophoresis is diagnostic but it is found in < 50% of cases^[11].

Dysbetalipoproteinemia is observed in apoE2 homozygous persons when also a genetic or environmental risk factor for dyslipidemia is also present^[7,8]. The disease generally presents after adulthood in men and menopause in women^[7,8].

In most cases secondary factors are required for the expression of dysbetalipoproteinemia. These include additional genetic susceptibility variants, or other hormonal or environmental factors, such as obesity, type 2 diabetes, female gender, drugs affecting the metabolism of TG-rich lipoproteins, alcohol consumption or hypothyroidism (Table 2)^[8,12]. Of note, case 1 patient was a diabetic man who consumed alcohol, while case 2 patient was an overweight woman who also received tamoxifen, which has been associated with disturbed

Table 2 Factors associated with dysbetalipoproteinemia overt expression

Environmental-hormonal	Genetic	Secondary dysbetalipoproteinemia
Drugs (corticosteroids, tamoxifen, retinoids, antipsychotics)	Familial hypercholesterolemia	Multiple myeloma
Alcohol consumption	Familial combined hypercholesterolemia	Paraproteinemia
Hypothyroidism	Reduced hepatic lipase activity	Systemic lupus erythematosus
Pregnancy	Decreased lipoprotein lipase activity	
Diabetes, insulin resistance		
Obesity		
Diet rich in saturated fats and carbohydrates		

TG metabolism. In fact tamoxifen, like estrogens, stimulates the synthesis and secretion from the liver of VLDL, which is the main circulating carrier of TGs, while it decreases VLDL and IDL catabolism as a result of decreasing lipoprotein and hepatic lipase activities. However, the drug can induce only modest elevations in serum TG levels in patients who have a normal lipoprotein metabolism, while it can cause marked hypertriglyceridemia in patients who have a defective TG-rich lipoproteins metabolism^[13-15]. Moreover, some patients may possess additional genetic variants or mutations disturbing the metabolic role of apoE^[7,8]. On the other hand, less than 5% of dysbetalipoproteinemia patients have dominant mutations in apoE, which *per se* induce mixed dyslipidemia^[7,16]. These mutations impair both the chylomicron remnants and IDL particles uptake by liver and the conversion of VLDL and IDL to LDL particles^[7]. Of note, patients with dysbetalipoproteinemia show a marked interindividual variation in the serum concentrations of cholesterol and TG, clinically presented as mixed dyslipidemia (case 2 patient) or chylomicronemia (case 1 patient). Furthermore a combination of the apoE2/2 phenotype and additional genetic factors associated with diseases like familial hypercholesterolemia, familial combined hyperlipoproteinemia, or familial hypertriglyceridemia, can determine the expression of dysbetalipoproteinemia^[17]. According to the Dutch Lipid Clinic Network criteria proposed by the European Atherosclerosis Society, the diagnosis of familial hypercholesterolemia was not probable in both our patients^[18].

Noteworthy, it is important to exclude secondary causes of dysbetalipoproteinemia, including multiple myeloma, paraproteinemia and systemic lupus erythematosus can mimic the disease, including the presence of typical xanthomas and the ultracentrifuge findings^[19,20]. Thus, a detailed clinical and laboratory assessment is always required.

Dysbetalipoproteinemia patients have increased risk of both coronary artery disease and peripheral vascular disease, even though the LDL-C concentration is low^[7,8]. Beta-VLDL is an atherogenic particle that rapidly transforms monocyte-macrophage cells to foam cells; the histologic hallmark of atherosclerosis and xanthomas^[21]. Additionally, remnant lipoproteins induce endothelial plasminogen activator inhibitor I expression and activity in cultured aortic endothelial cells contributing to a prothrombotic state^[22]. Males

with homozygosity for the ApoE2 isoform present with coronary disease at their 4th or 5th decade of their life and there is a predisposition for peripheral vascular disease in these patients^[23]. Last, lipoprotein glomerulopathy and pancreatitis in severe hypertriglyceridemic patients with dysbetalipoproteinemia have also been described^[24].

Treatment of dysbetalipoproteinemia is the same as for hypertriglyceridemia. Weight loss, diet fat restriction and treatment of secondary factors, such as diabetes and hypothyroidism are important for all dysbetalipoproteinemia patients^[7]. In addition, administration of fibrates, statins, omega-3 fatty acids and niacin or their combinations is very effective. However, it has to be underlined that fibrates, with or without statin, seem to comprise the cornerstone of dysbetalipoproteinemia treatment^[25].

In conclusion, physician should keep in mind that dysbetalipoproteinemia may present as chylomicronemia when other genetic or environmental causes affecting TG metabolism co-exist. Moreover, dysbetalipoproteinemia has to be suspected in all mixed dyslipidemia cases with equally elevated TC and TG levels (TC/TG = 1) (Figure 2).

COMMENTS

Case characteristics

The two patients presented with dissimilar lipid profile; one presented with extremely high triglycerides (TG) levels and the other presented with equally elevated levels of total cholesterol (TC) and TG.

Clinical diagnosis

The physical signs of the two cases were also dissimilar; one patient presented with tuberous and eruptive xanthomas, while the other patient had no skin lesions.

Differential diagnosis

Type 5 dyslipidemia, chylomicronemia, secondary causes of mixed dyslipidemia and dysbetalipoproteinemia.

Laboratory diagnosis

The first patient had the following lipid profile: TC: 1055 mg/dL, TG: 2900 mg/dL, high density lipoprotein cholesterol: 18 mg/dL, while the second patient had the following lipid profile; TC: 325 mg/dL, TG: 321 mg/dL, low density lipoprotein cholesterol (LDL-C): 214 mg/dL.

Genetic diagnosis

The diagnosis of dysbetalipoproteinemia was verified by Apolipoprotein E2 (apoE2)/E2 homozygosity genotype in both patients.

Treatment

Fibrate with or without statin improved lipid profile in both patients.

Related reports

Dysbetalipoproteinemia is seen in approximately 1 in 10000 people.

Term explanation

Dysbetalipoproteinemia is a rare familial disease characterized by marked elevations of serum cholesterol and triglyceride levels caused by an accumulation of remnant lipoproteins in apolipoprotein E2/E2 homozygotes.

Experiences and lessons

This case report presents the clinical characteristics and lipid profile of dysbetalipoproteinemia and also suggests a diagnostic algorithm. The authors recommend that diagnosis of dysbetalipoproteinemia should be considered in patients mixed dyslipidemia when the apolipoprotein B concentration is relatively low in relation to the total cholesterol concentration or when there is significant disparity between the calculated low LDL-C and directly measured LDL-C concentrations.

Peer-review

This is a nice article that deserves be published.

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Saccular trilobed aneurysm of azygos anterior cerebral artery

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cerebral artery (ACA) at the distal segments A2-A5 are very rarely reported. Distal anterior cerebral artery (DACA) aneurysms represent approximately 2%-7% of all cerebral aneurysms. We present the case of an Albanian 62-year-old male, admitted at our service after sudden onset of severe headache and vomiting. Computerized tomography (CT) of the head showed hemorrhage in the front of corpus callosum. CT angiography followed by digitally subtracted angiography (DSA) documented a large necked aneurysm with three lobes at the origin of calloso-marginal artery and a single DACA, also known as AACA. A frontal parasagittal craniotomy was performed. Obliteration of the aneurysm was done only by separate clipping of each three lobes at the respective neck. Postoperative DSA demonstrated complete exclusion of the aneurysm and a regular flow of AACA. The patient recovered uneventfully. Despite it is a rare occurrence, an aneurysm of distal segments of anterior cerebral artery A2-A5, concomitant to AACA should be studied with DSA. In the era of embolization, conserving good microsurgical skills is fundamental for dealing with multilobar cerebral aneurysms, associated with rare anatomical variations.

Key words: Azygos; Cerebral; Aneurysm; Clipping

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Core tip: This is a detailed description of radiological and surgical findings in a very rare case of trilobed aneurysm of distal anterior cerebral artery. The characteristics of this aneurysm are exposed and its difficult exclusion by separate three clips is argued with a thorough discussion of the literature.

Seferi A, Alimehmeti R, Rroji A, Petrela M. Saccular trilobed aneurysm of azygos anterior cerebral artery. *World J Clin Cases* 2015; 3(4): 377-380 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v3/i4/377.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v3.i4.377>

Abstract

Multiple saccular or giant aneurysms of azygos anterior

INTRODUCTION

The incidence of true azygos distal anterior cerebral artery (DACA) ranges from 0% to 5%^[1,2]. The rarest is the form of unpaired DACA. An azygos artery is better studied through carotid angiography with contralateral compression. In the presented case, there was a trilobed aneurysm of A3 segment in a single or azygos variant of DACA.

CASE REPORT

A 62-year-old man showed up at a local hospital complaining of severe headache with sudden onset. Neurological examination revealed nuchal rigidity but no neurological deficits. Unenhanced computed tomography (CT) of the head revealed a hyperdense lesion in front of the knee of corpus callosum interpreted as hemorrhage with edema of the left frontal lobe (Figure 1).

With the event taking place in 2008, a thorough history was requested. Back to 1990 the patient had been admitted at the same rural hospital after an episode of acute headache and loss of consciousness. A CT of the head at that time had shown same hemorrhage as in recent episode, but the patient had been discharged without any in-depth examinations or treatments (Figure 2).

At present episode the patient was promptly transferred at our neurosurgical facility. The CT angiography revealed A3 aneurysm of DACA. Digitally subtracted angiography (DSA) confirmed a trilobed and a complex broad-necked A3 aneurysm at the origin of the callosomarginal (CM) artery (Figure 3), in presence of azygos anterior cerebral artery (AACA).

Cerebral DSA with contra-lateral carotid artery compression confirmed the presence of AACA. Endovascular option of treatment was not considered and microsurgical clipping of the aneurysm with or without a bypass was planned.

Left frontal parasagittal craniotomy anterior to coronal suture was done in order to control at first the distal tract of CMA. Once identified, the CMA led us to the pericallosal artery proximal to the aneurysm. Then the aneurysm with its three lobes was dissected exposing at first the proximal segment of pericallosal artery, although the interhemispheric approach offers small space. After clearing the adhesions, the broad aneurysm neck and its three lobes were exposed, each of which extended in a different direction (Figure 4).

The neck wall of the aneurysm was sclerotic. Single clip closure of the neck was initially tried, but its hard wall shifted the clip away towards the single pericallosal artery reducing its lumen. Therefore separate clipping was deemed the only possible way to exclude the aneurysm (Figure 5). Uneventful postoperative course followed. Carotid angiography documented preserved flow in the parent artery and complete exclusion of the aneurysm (Figure 6).

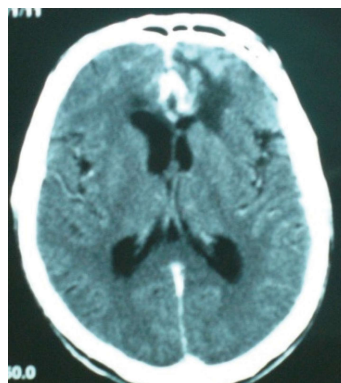


Figure 1 Computerized tomography scan of the year 2008. Second episode of the intracerebral hemorrhage.

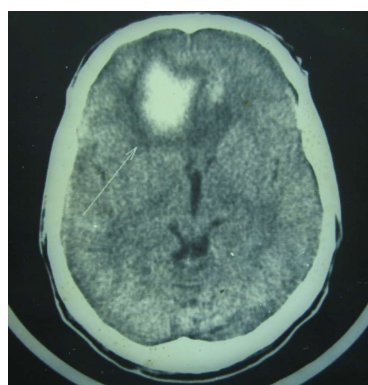


Figure 2 Computerized tomography scan of the year 1990. First episode of intracerebral frontal hemorrhage (white arrow).

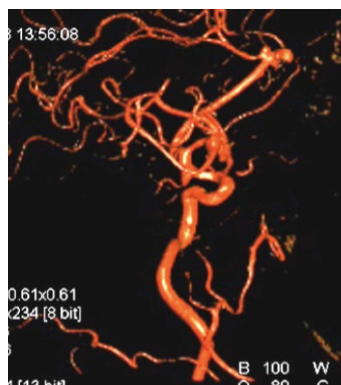


Figure 3 Preoperative digitally subtracted angiography.

DISCUSSION

In 1963 Baptista^[2] presented a scale of three groups for the anatomical variations DACA. Years before Wilders coined the term azygos pericallosal artery for the fusion of two A2 arteries. During angiographic and autopsy studies the incidence of this variation is reported from 0.3% to 2%^[2-4]. The aneurysms of DACA are seen in 2%-6.7% of the intracranial aneurysms and they are usually saccular, small and single-lobed^[2,5-7]. Giant aneurysms of azygos

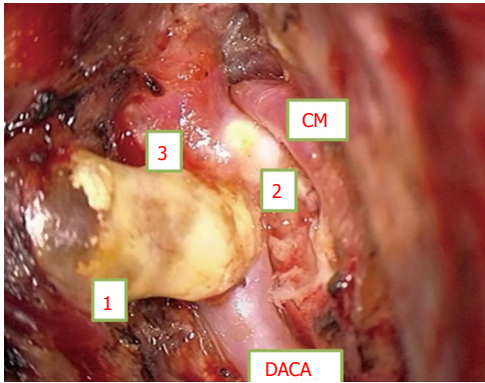


Figure 4 Intraoperative pre-clipping photo. Numbers 1, 2 and 3 refer to respective lobes of the trilobed aneurysm. CM: Callosal-marginal; DACA: Distal anterior cerebral artery/pericallosal artery.

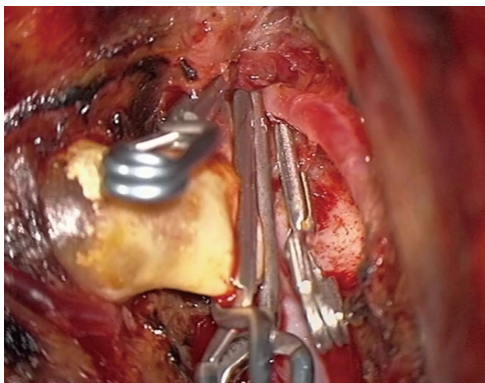


Figure 5 Intraoperative post-clipping photo. Three separate clips exclude the three lobes of the aneurysm.

pericallosal artery and those multi-lobular are extremely rare, and usually situated at the callosal-marginal bifurcation^[1,8-12]. Auguste *et al.*^[13] reported a series of 876 aneurysms surgically treated, with five ACA aneurysms in the presence of an azygos pericallosal artery that represent 0.5% and 1.7% of ACA and ACoA aneurysms of his series. It seems needless to stress the importance of angiography in such cases, not only for a preoperative evidence of the morphology of the aneurysm, but also for the documentation of any variation of AACA, which will influence the surgical technique.

In our reported case preoperative DSA showed a trilobed aneurysm originating from a single neck with different spatial orientation. Single clip closure of the neck was initially tried, but its hard wall shifted the clip away towards the single pericallosal artery reducing its lumen. Therefore we opted for a separate clipping.

The hypothesis of creation of three lobes stands on the blood flow dynamics of the parent artery. The more curved the parent artery, more blood enters the aneurysm.

In case of AACA the blood flow is increased compared with the blood flow of any of the ACAs in a normal anatomical setting. The angled direction of entry and

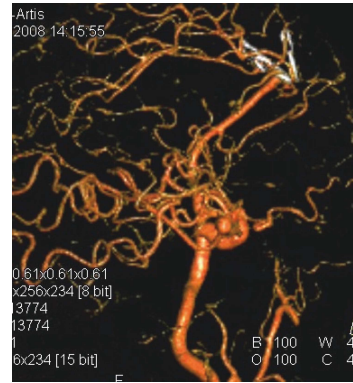


Figure 6 Postoperative digitally subtracted angiography showing preserved blood flow in the pericallosal artery and the exclusion of the aneurysm.

increase of blood flow in the aneurysm space influence the stress over the aneurysm wall. Perioperative morphological study of the single pericallosal artery evidenced the location of the aneurysm at the knee of corpus callosum. At this point the pericallosal artery bends posteriorly. It creates the prerequisite of the scenario mentioned above, that favors aneurysm formation.

In order to explain the origin of such a rare morphology aneurysm, several experimental paradigms are suggested^[14]. A larger neck width increases the blood flow rate within the aneurysm. Draining vessels from the aneurysm contribute in the increase of blood flow inside the aneurysm. Both factors increase the pressure on the aneurysm wall and influence multiple lobe formation^[14-16].

We suppose that the three lobes in our case were influenced by a change of aneurysm neck and dome, perhaps due to the rupture eighteen years before. We also believe there might be a relationship between the previous supposed rupture of the aneurysm and its rare morphology.

The aneurysm conformation with three lobes, in the background of a very rare anatomical variation of ACA tract, makes our case a clinical rarity. The three lobes of the aneurysm we dealt with are the result of blood flow impact and parent vessel modification after the first hemorrhage, as documented with the CT performed more than a decade prior to the second episode, requiring neurosurgical intervention. We think that vascular neurosurgeons should be prepared to handle such complicated cases.

COMMENTS

Case characteristics

Three lobed azygos anterior cerebral artery (AACA) is an exception. Digitally subtracted angiography (DSA) is the gold standard method of study.

Clinical diagnosis

Repeated episode of subarachnoid hemorrhage was observed in this case.

Differential diagnosis

The differential diagnosis with other type of acute onset of headache was done by computerized tomography scanner.

Laboratory diagnosis

DSA showed AACA aneurysm unsuitable for embolization.

Imaging diagnosis

Surgical clipping was challenged by three lobed shape of the aneurysm, which was excluded only through separate clipping.

Treatment

Excellent surgical skills are necessary for dealing with such rare difficult case.

Peer-review

Interesting case report.

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Importance of cardiological evaluation for first seizures

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following cardiac arrest associated with LQTS. Case 2, CD presented initially with tonic-clonic seizure and because of experience with AB, CD was assessed for LQTS which was subsequently confirmed. The legal medicine experience re Dobler v Halverson, which involved a young boy with LQTS, who suffered cardiac arrest without prior diagnosis of LQTS, has reinforced the requirement to seriously consider LQTS as an aetiological factor in first seizure presentations.

Key words: Long QT syndrome; Prolonged QT; Torsades de pointes; Seizure; Epilepsy

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Core tip: Long QT syndrome (LQTS), with subsequent cerebral ischemia due to cardiac dysrhythmia, may cause seizures. It is imperative to consider LQTS in patients presenting with first seizure so as to avoid possible brain damage from prolonged cerebral hypoxemia. Failure to recognise LQTS may result in successful suit for negligence if not properly investigated and managed.

Choong H, Hanna I, Beran R. Importance of cardiological evaluation for first seizures. *World J Clin Cases* 2015; 3(4): 381-384 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v3/i4/381.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v3.i4.381>

INTRODUCTION

Long QT syndrome (LQTS) represents channelopathies of cardiac potassium/sodium ion channels. Channelopathies may present with seizures and/or risk sudden death because ventricular dysrhythmia known as torsades de pointes (TdP).

CASE REPORT

Case 1 (Year: 2008)

AB was a 26-year-old Asian female, 6 wk post-partum

Abstract

This paper reports two cases of long QT syndrome (LQTS) which presented with seizures as their initial feature. Case 1, AB was seen in emergency department with post-partum seizure, discharged and re-presented

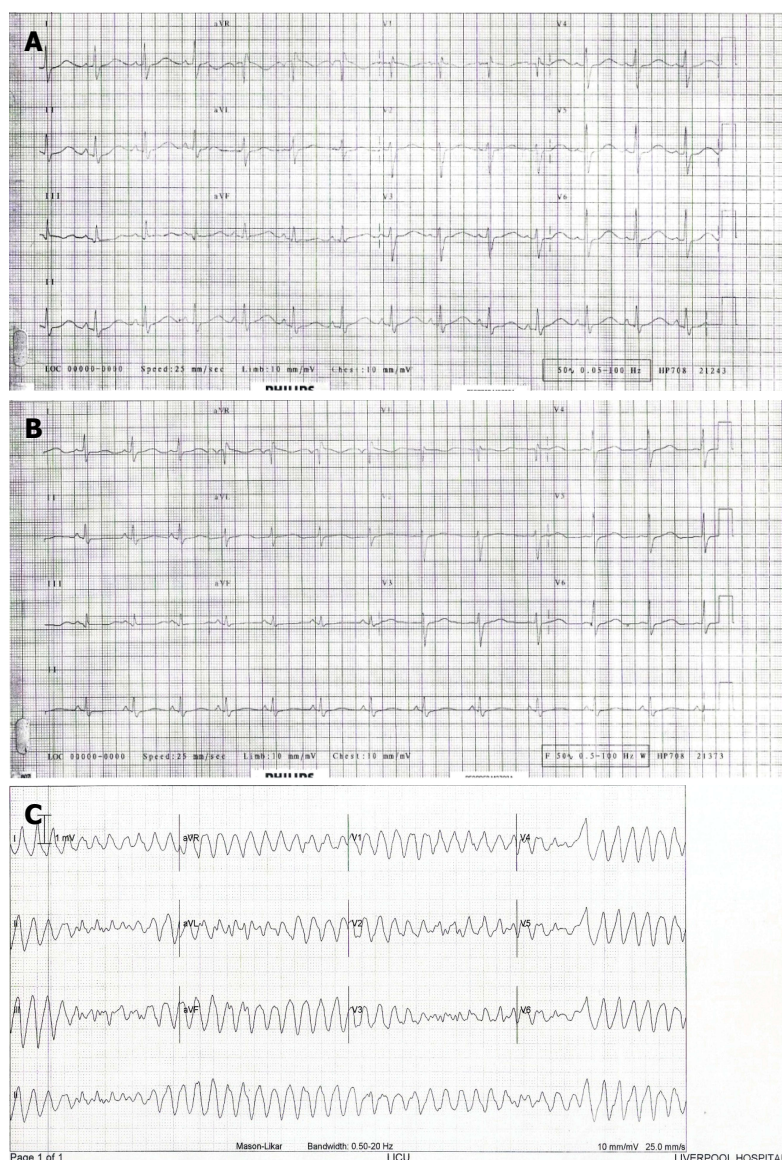


Figure 1 Electrocardiogram of AB. A: Electrocardiogram (ECG) of AB on first presentation showed sinus rhythm, incomplete right bundle branch block (RBBB) and prolonged QTc interval (QTc 526 ms); B: ECG of AB on second presentation showed sinus rhythm, incomplete RBBB and prolonged QTc interval (QTc 505 ms); C: ECG of AB during a syncopal episode on her second admission showed torsades de pointes.

with emergency lower cesarean section at 38 wk into her first pregnancy because of pre-eclampsia and fetal distress. Past medical and family histories were unremarkable and she was not on regular medication.

She had acute “dizziness” when rising from the sitting to standing position, and then collapsed to the floor and was witnessed to be cyanosed. Her husband performed cardiopulmonary resuscitation until the ambulance arrived. Her Glasgow Coma Scale improved with stable vital signs at that time. The paramedics witnessed an episode of generalised tonic-clonic seizure associated with tongue biting that lasted for a few minutes whilst en-route to Liverpool Hospital. In the Emergency Department, she was sedated and intubated because of post-ictal aggression. She was afebrile, blood pressure 127/78 mmHg and pulse rate 70 beats/min. Blood tests were unremarkable with normal computed tomography (CT) pulmonary angiogram, CT brain and CT cerebral venogram. Her electrocardiogram (ECG) showed corrected QT interval (QTc) of 526 ms (Figure 1A), which was above the normal limit for her

gender (QTc < 460 ms). She was extubated 24 h later and was back to her normal state. Full neurological examination was unremarkable. No antiepileptic medication was prescribed as this was her first seizure. Electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the brain were organised but she refused to stay in hospital for those investigations and was to be followed by the neurologist.

She was re-admitted the next day after being found unconscious. She was in ventricular fibrillation requiring cardioversion by the paramedics. Her ECG was similar to the previous recording, demonstrating abnormal QTc of 505 ms (Figure 1B) and hence prompting a diagnosis of LQTS. She had further symptomatic polymorphic ventricular tachycardia suggestive of TdP that required cardioversion (Figure 1C). She was subsequently started on beta-blocker therapy and had implantable cardioverter-defibrillator (ICD) for secondary prevention.

Case 2 (Year: 2012)

CD was a 50-year-old Caucasian male with no regular

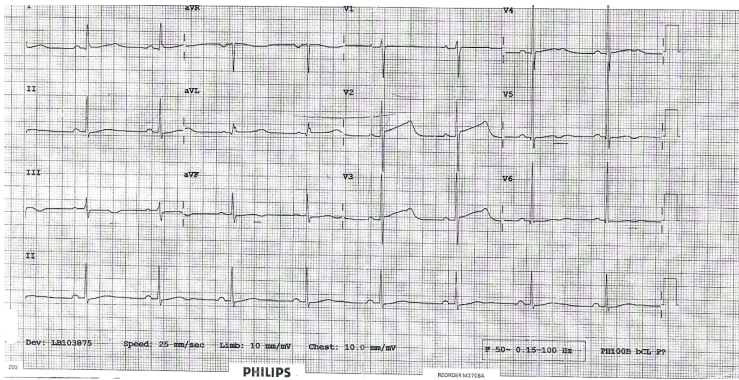


Figure 2 Electrocardiogram of CD showed sinus rhythm and prolonged QTc (QTc 566 ms).

medication. His father died at 57 years old in his sleep.

He presented to Liverpool Hospital with 2 min of witnessed generalised tonic-clonic seizure. This was associated with post-ictal drowsiness but no tongue biting or incontinence. Previously he had three episodes of unconsciousness. The first two were 30 years ago resulting in his being prescribed carbamazepine which he took for a few years but had not taken same for approximately 20 years. He was unable to provide adequate further history nor could he offer more detailed information regarding specific investigations related to those events. Full neurological and cardiological examinations, blood tests, EEG, MRI brain and echocardiography were all unremarkable. ECG showed QTc of 566 ms which was above the normal limit for his gender (QTc < 450 ms) (Figure 2) prompting a diagnosis of LQTS. Beta-blocker therapy was commenced. ICD was indicated due to his family history and possible ventricular dysrhythmias that could have accounted for his previous events of loss of consciousness thought possibly to be misdiagnosed as epileptic seizures.

DISCUSSION

Both patients in Cases 1 and 2 presented with generalised convulsive "seizures". AB was initially discharged with conservative management and LQTS was diagnosed on representation. CD was diagnosed because of the experience with AB. This demonstrates that LQTS crosses age, gender and racial boundaries (AB being a young Asian female and CD a middle-aged Caucasian male) demanding a high index of suspicion and consideration of LQTS in all first seizures.

LQTS is a collection of genetically distinct arrhythmogenic disorders resulting in abnormal cardiac potassium and sodium ion channels causing delayed cardiac depolarization^[1]. LQTS affects approximately 1 in 2000 people^[2,3] and symptomatic cases may present with syncope, seizures or sudden death due to ventricular dysrhythmia known as TdP. These cases are often "erroneously" diagnosed as a primary seizure disorder, having unexplained syncope, or having ill defined "spells"^[4,5] which could potentially lead to expensive legal-medicine consequences, such as the Dobler v Halverson case of 2006. This Australian, NSW Court of Appeal, case involved LQTS in a young

boy diagnosed by a neurologist as a "faint" without further investigation. Halverson was then managed by his general practitioner (GP), Dr Dobler. Halverson experienced cardiac arrest with severe brain damage and the GP was found negligent for not performing an ECG nor organizing for cardiological assessment.

There is increasing support that seizures, in LQTS, are not solely due to acute cerebral hypoxic-ischemic event secondary to ventricular arrhythmias. It has been proposed that the aetiologies of LQTS and epilepsy may partly overlap *via* a possible link between the cardiac and neural ion channelopathies. It has been demonstrated that patients with LQTS type 2 are more commonly associated with epilepsy, hence supporting the possibility that mutation of *KCNH2* gene responsible for LQTS type 2 may also predispose to seizure activity^[5]. Similarly, various case reports and observational studies have suggested that mutation in the *SCN5A* gene, responsible for LQTS type 3, is also associated with epilepsy^[6,7]. It follows that initial diagnosis of seizure disorder or epilepsy, with subsequent neurological investigations and antiepileptic treatment, may be inadequate if it does not also include cardiological evaluation. ECG, Holter monitoring and formal cardiological evaluation should become an integral part of a seizure/epilepsy assessment, to identify a subset of patients who also have concomitant LQTS. Failure to do so may predispose the patient to very serious or even fatal consequences and the treating clinician to subsequent personal and legal medicine ramifications.

COMMENTS

Case characteristics

Two cases presenting to hospital after witnessed generalised seizures.

Clinical diagnosis

Both cases had normal physical examination but had prolonged QTc on their electrocardiograms (ECGs), and evidence of torsades de pointes on the ECG for Case 1, prompting the diagnosis of long QT syndrome (LQTS).

Differential diagnosis

Convulsive syncope, secondary to cardiogenic causes; primary or secondary generalised seizure disorder.

Laboratory diagnosis

Both cases had normal routine blood tests, echocardiogram and electroencephalogram.

Imaging diagnosis

Both cases had normal computed tomography and magnetic resonance

imaging brain.

Treatment

Beta-blocker medication and implantable cardioverter-defibrillator insertion were instigated after the diagnosis of LQTS in both cases.

Related reports

There is a possible link between the cardiac and neural ion channelopathies, hence patients with LQTS may have concurrent primary epilepsy disorder causing seizures rather than solely from the consequences of the ventricular arrhythmias.

Term explanation

TdP refers to Torsades de Pointes which is an uncommon and distinctive form of polymorphic ventricular tachycardia characterized by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line; Channelopathies are diseases caused by disturbed function of ion channel subunits or the proteins that regulate them; and *KCNH2* and *SCN5A* are genetic abnormalities found to occur in both inherited epilepsies and LQTS.

Experiences and lessons

Initial diagnosis of seizure disorder or epilepsy, with subsequent neurological investigations and antiepileptic treatment, may be inadequate if it does not also include cardiological evaluation.

Peer-review

The viewpoint of this paper is useful in clinical practice.

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Poncet's disease: An unusual presentation of tuberculosis in a diabetic lady

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Author contributions: Chakraborty PP and Ray S contributed to conception and design; Ray S and Selvan C contributed to drafting of the article; Selvan C contributed to literature search; Chakraborty PP contributed to analysis and interpretation of data; Bhattacharjee R and Mandal SK contributed to critical revision of the article for important intellectual content; Chakraborty PP, Ray S, Selvan C, Bhattacharjee R and Mandal SK final approval of the article.

Ethics approval: The Institutional Ethical Committee of IPGME and R, Kolkata agreed to give its formal approval to carry out this case study in this institution.

Informed consent: Patient gave informed consent for the information about her to appear in the journal publications.

Conflict-of-interest: No conflict of interest to declare.

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to their diabetes clinic with a three week history of multiple painful and swollen joints. She had been diagnosed with type 2 diabetes 5 years back. On examination, both knee joints and left ankle were swollen. A soft tissue swelling appeared over the medial end of the left clavicle few days later. Rheumatoid arthritis, collagen vascular diseases and other common causes of polyarthritis were ruled out by appropriate investigations. Non steroidal anti-inflammatory drugs failed to give satisfactory pain relief and the arthritis persisted. Conventional cultures of synovial fluid samples including cultures for tuberculosis were negative. Computed tomography showed a space occupying lesion involving the left sternoclavicular joint. Fine needle aspiration from the lesion was performed and acid-fast bacilli were demonstrated in the smear using Ziehl-Neelsen stain. The explanation of her arthritis was therefore tuberculous arthritis in left sternoclavicular joint and reactive arthritis in the rest of the joints. A diagnosis of Poncet's disease was considered in her case. We treated her with standard anti-tuberculosis drugs and the arthritis resolved within a few days. She remained symptom-free at her 2 years' follow-up.

Key words: Poncet's disease; Diabetes; Tuberculous arthritis; Reactive arthritis; Acid-fast bacilli

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Core tip: Poncet's disease (PD) is a form of reactive arthritis that develops in patients with active tuberculosis (TB). It is a rare, non-destructive parainfective symmetric polyarthritis. In cases of unexplained atypical arthritis associated with non-articular TB, PD should be considered. PD remains a clinical challenge and is essentially a diagnosis of exclusion and requires a high degree of clinical suspicion. Correct identification of this rare complication of TB is required to avoid delayed initiation of appropriate treatment. The dramatic response of arthritis in PD on starting anti-tubercular treatment substantiates the diagnosis. Further studies are required for better

Abstract

Authors describe a 53-year-old woman who presented

understanding of the pathogenesis underlying PD.

Chakraborty PP, Ray S, Selvan C, Bhattacharjee R, Mandal SK. Poncet's disease: An unusual presentation of tuberculosis in a diabetic lady. *World J Clin Cases* 2015; 3(4): 385-388 Available from: URL: <http://www.wjgnet.com/2307-8960/full/v3/i4/385.htm> DOI: <http://dx.doi.org/10.12998/wjcc.v3.i4.385>

INTRODUCTION

The association between of diabetes mellitus (DM) and tuberculosis (TB) is becoming more prominent in developing countries where TB remains endemic and the burden of DM is increasing. Atypical presentations are increasingly being recognized in diabetic patients. The diagnosis of joint TB poses a challenge to the clinicians. Although, septic monoarthritis is a well-known complication of tuberculous infection; active TB may be complicated by a sterile reactive arthritis (ReA), known as Poncet's disease (PD), which is not so common and therefore frequently missed. We report here a diabetic patient who initially presented with oligoarthritis, and later on ended with a diagnosis of PD. A review of the literature on diagnostic and therapeutic aspects involved in PD is also included. This case highlights the need for increased awareness among physicians regarding this rare complication of a common disease to avoid delay in diagnosis and starting the appropriate treatment.

CASE REPORT

A 53-year-old lady presented with a three week history of multiple painful and swollen joints. She had been diagnosed with type 2 diabetes in March 2009. Her diabetes was well controlled and she was on insulin and metformin. Her presentation to the clinic had been prompted by her inability to walk in the previous five days. She had been diagnosed with undifferentiated polyarthritis by a family physician. The joint pains started gradually over three weeks involving left ankle and knee joints. Family history for rheumatic or autoimmune diseases was negative. There was no history of mouth ulcers, eye symptoms, skin rash or genito-urinary symptoms. She denied weight loss, coughing, night sweats but mentioned about low grade fever for few weeks.

On examination, she was in pain and was unable to walk. Her blood pressure was 130/80, pulse rate 90 per minute, respiratory rate 24 per minute and a temperature of 36.80 °C. The patient's ankle and knee joints were swollen and tender on palpation with limitation of movement. A soft, boggy swelling appeared at the medial end of the left clavicle during her hospital stay clinically resembling a cold abscess. She had no erythema nodosum on examination. No adventitious sound was detected on chest auscultation. There

was no lymphadenopathy or hepatosplenomegaly. There was no muscle atrophy. She had no signs of peripheral neuropathy. Fundoscopic examination was unremarkable.

Her initial investigation results showed hemoglobin of 11.9 g/dL, a white cell count of $7.6 \times 10^9/L$, platelets of $130 \times 10^9/L$ and an erythrocyte sedimentation rate (ESR) of 88 mm/h. Urine dipstick showed no white cells, protein was trace. Laboratory tests results for antinuclear antigen, rheumatoid factor and anti-cyclic citrullinated peptide antibodies were negative. The patient was nonreactive for HIV 1 and 2 by ELISA. The radiographs of the both knees and left ankle were normal. The intradermal skin test for tuberculosis reading was 17 mm, which was considered strongly positive. Synovial fluid was aspirated from the left ankle and both knees and analysis revealed leucocytes between 4.0 and $8.2 \times 10^9/L$, no crystals and the smears were negative for Gram stain. On bacterial culture of the synovial fluid, no growth was found and synovial fluid cultures for TB were also negative. The plausible explanation of her arthritis would therefore be a form of a reactive arthritis. Since no diagnosis could be made, we went for exploring the neck swelling. Computed tomography scan of the neck was performed which showed a space occupying lesion (SOL) around the medial end of clavicle (Figure 1A). Fine needle aspiration from the lesion showed epithelioid cell collection and multinucleated giant cells on the background of necrotic tissue. AFB stain was positive (Figure 1B).

Treatment with non steroidal anti-inflammatory drugs only gives partial relief. Since there was strong evidences suggesting active joint tuberculosis, she was put on four-drug antituberculosis treatment, including rifampicin, isoniazid, pyrazinamide, and ethambutol. Her joint symptoms showed a remarkable improvement within two weeks of initiation of therapy.

Following treatment with standard anti-tubercular treatment, the arthritis had completely resolved in three weeks period. The consistent association of arthritis with presence of active tuberculosis, the lack of evidence of any other known rheumatic disease and the resolution of symptoms on anti-tuberculosis therapy were all consistent with the diagnosis of PD in our patient. She had remained asymptomatic at 2 years' follow-up.

DISCUSSION

PD or tubercular rheumatism is a form of reactive polyarthritis related with active TB in which no mycobacterial involvement can be found in the affected bones or joints, and there is absence of other detectable causes of polyarthritis^[1-3]. TB reactive arthritis was first described by Poncet^[4] in 1897 and named after him as PD. PD is considered a ReA, but the clinical presentation of PD is different from the classical pattern of ReA^[5]. Unlike ReA,

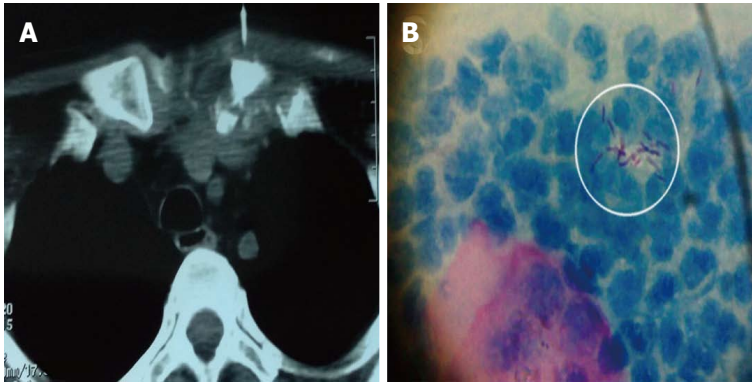


Figure 1 Computed tomography scan of neck showed bone destruction and soft tissue swelling with involvement of articular surfaces of sternoclavicular joint (A); Numerous acid-fast bacilli in the background of necrosis (B) (Ziehl-Neelsen stain, x 1000).

the onset of symptoms in PD prior to the start of arthritis is much longer than only a few weeks, whereas arthritis resolution upon starting of anti-tubercular therapy is generally within a few weeks. Chronic arthritis is not encountered in PD. Although the clinical presentation is somewhat different, the pathogenetic mechanism is considered to be similar. It is thought to occur due to a hypersensitive immune cell mediated response to the tuberculo-protein, resulting in an inflammatory reaction in the joint spaces^[2,6]. Due to the rarity of PD despite the frequency of TB, a genetic predisposition has been suggested in the pathogenesis, with links to the HLA DR3 and HLA DR4 haplotypes^[7].

Clinically the disease is different to the well recognized TB monoarthritis; a septic mycobacterium infection of a joint leading to its destruction. From the cases previously described, Poncet's arthritis is non-destructive and resolves completely following TB treatment. The arthritis mainly affects the larger joints, with the knee being the most common, followed by the ankle and wrist joints. The axial skeleton tends not to be involved. It is described as a symmetrical polyarthritis but many studies^[8] have suggested it to be pauciarticular arthritis, mainly of the larger joints as was the case with our patient. Other common symptoms include lymphadenopathy (mainly cervical and axillary), grumbling fevers (which may be present many weeks prior to developing the arthritis) and skin changes; classically erythema nodosum^[9]. In the review of 50 cases report on PD by Kroot *et al*^[1] erythema nodosum was present only in 6% of the patients.

The diagnosis is usually one of exclusion and should be considered in all patients with a symmetrical arthritis in TB prevalent regions. Extra-pulmonary TB, particularly lymph node TB, is traditionally thought to be the main culprit^[10,11]. The complete resolution of rheumatic symptoms on anti-tuberculosis therapy further confirms the diagnosis. Resolution of the arthritis of PD with anti-tubercular drugs ranged from a week to few months.

To conclude, active tuberculosis needs to be considered in the differential diagnosis of patients presenting with fever and polyarthritis of unclear cause, particularly in regions where the prevalence of tuberculosis is high. The diagnosis of this clinical entity remains a clinical challenge and demands a high index of suspicion. Since not all clinicians are aware of PD, this entity is probably

underdiagnosed.

COMMENTS

Case characteristics

A 53-year-old diabetic woman presented with multiple painful and swollen joints.

Clinical diagnosis

The patient's ankle and knee joints were swollen and tender on palpation with limitation of movement. A soft, boggy swelling appeared at the medial end of the left clavicle during her hospital stay clinically resembling a cold abscess.

Differential diagnosis

Septic arthritis, reactive arthritis, rheumatoid arthritis.

Laboratory diagnosis

Her investigation results showed hemoglobin of 11.9 g/dL, a white cell count of $7.6 \times 10^9/L$, platelets of $130 \times 10^9/L$ and an erythrocyte sedimentation rate of 88 mm/h. Results for antinuclear antigen, rheumatoid factor and anti-cyclic citrullinated peptide antibodies were negative. The intradermal skin test for tuberculosis reading was 17 mm, which is considered a positive test.

Imaging diagnosis

The radiographs of the both knees and left ankle were normal. Computed tomography scan of the neck showed a space occupying lesion (SOL) around the medial end of clavicle.

Pathological diagnosis

Fine needle aspiration from supraclavicular SOL of the left supraclavicular node showed epithelioid cell collection and multinucleated giant cells on the background of necrotic tissue. AFB stain was positive.

Treatment

The patient was put on four drug anti-tuberculosis (TB) therapy since the evidence was strongly suggestive of active joint tuberculosis.

Related reports

Reviewing the literature, more than 50 case reports were found. In most reports "Poncet's disease" was described as an aseptic polyarthritis, presumably reactive arthritis developing in the presence of active TB elsewhere.

Term explanation

Poncet's disease is a reactive polyarthritis associated with active TB in which no mycobacterial involvement can be found in the affected bones or joints.

Experiences and lessons

The diagnosis of Poncet's disease remains clinical and is established on excluding other potential causes of arthritis in a patient with active tuberculosis. In cases with unexplained atypical arthritis and non-articular TB, Poncet's disease should be considered.

Peer-review

It is a case report describing Poncet's disease which goes unnoticed and underdiagnosed. The manuscript is scientifically sound and based on the discovery of facts. Data presented are duly supported by appropriate figures.

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Unusual histological variant of malignant peripheral nerve sheath tumor with rhabdomyoblastic differentiation

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Author contributions: Shete S, Bolde S, Pandit G and Matkari P diagnosed the case and prepared the first draft of manuscript; Ingle SB prepared the final draft of manuscript and revised the intellectual content and gave final approval of manuscript.

Ethics approval: According to our ethical committee, as it's a single case report on tissue histopathology (not on live patient) no need of approval as there is no question of unethical practice.

Informed consent: As we are presenting only histopathological diagnosis, not doing any experiments on the live object, we have done only diagnosis in pathology lab so no question of disclosing the patients details name /his consent that is also not indicated.

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with rhabdomyoblastic differentiation is called as malignant triton tumor (MTT). It is highly aggressive soft tissue tumor with higher local recurrence rate. MTT has poor prognosis than MPNST. MTT seems to be more aggressive in patients with neurofibromatosis (NF-1). We herein, reporting an interesting case of 55 years male with multiple neurofibromas all over the body since 30 years and multiple café-au-lait spots, diagnosed as NF-1. Since 6 years, he had an enlarged mass in left thigh. Wide excision of mass was done. On histopathological examination revealed the diagnosis of MTT and diagnosis of which was confirmed on immunohistochemistry.

Key words: Malignant triton tumor; Neurofibromatosis-1; Desmin; S-100 protein

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Core tip: Meticulous histopathological examination along with immunohistochemistry is the mainstay to arrive at such rare histological diagnosis. The surgical pathologist should keep in mind such rare entity while dealing with such kind of patients.

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INTRODUCTION

Malignant peripheral nerve sheath tumor (MPNST) is an unusual type of soft tissue sarcomas. It accounts for about 5%-10% of all soft tissue sarcomas^[1]. Amongst them malignant triton tumor (MTT) constitutes about 5% of all MPNSTs^[2]. MTT is a subtype of MPNST that

Abstract

Malignant peripheral nerve sheath tumor (MPNST)

has real diagnostic challenge for surgical pathologists with regard to its cell of origin and its relatively aggressive course. It is comprised of malignant Schwann cells coexisting with characteristic malignant rhabdomyoblasts^[3]. It occurs in two forms, one is sporadic form and the other is neurofibromatosis type 1 (NF-1) associated form. Majority of the reported cases are of later variety. Immunohistochemically the rhabdomyoblastic elements are typically positive for skeletal muscle markers such as desmin, myoglobin or muscle actin. MTT has a poorer prognosis than MPNST^[3]. This poor outcome is mainly attributed to the high frequency of grade III histology in this sarcoma^[4].

CASE REPORT

A 55-year-old male patient presented with multiple swellings all over the body ranging from 1-3 cm since 30 years (Figure 1). These nodules were histopathologically reported as neurofibromas. A subcutaneous nodule in left thigh was enlarged to attain a present size of 8 cm × 4 cm × 3 cm. He had café-au-lait spots on the trunk ranging from 0.5-1.8 mm. On family history, patient's mother, sister and brother had similar complaints. So he was diagnosed as a case of NF-1. Ultrasonography was suggestive of neoplastic lesion mostly soft tissue sarcoma.

Fine needle aspiration cytology was done and reported as malignant soft tissue tumor with possibilities of malignant fibrous histiocytoma and rhabdomyosarcoma (Figure 2A). Complete resection of the mass was done and the specimen was sent for histopathological evaluation.

On, gross examination showed a mass of 8 cm × 4 cm × 3 cm in size, covered with skin. Cut surface was soft, pale grey in colour with areas of necrosis.

Histopathological examination showed dense areas of malignant spindle shaped cells with oval nuclei with prominent mitoses, marked nuclear pleomorphism along with foci of necrosis. Many nuclei were bizarre and hyperchromatic. Alternating with hypercellular Antoni A areas, there were hypocellular myxoid areas called as- Antoni B areas. Thick walled congested blood vessels were found. Interspersed within it are seen many Scattered round cells with abundant eosinophilic cytoplasm with atypical nuclei, which were recognized as rhabdomyoblasts (Figure 2B).

The surgical cut margins margins were free of tumor invasion. On Immunohistochemical evaluation, spindle cells showed focal S-100 positivity (Figure 3A) and cells with deeply eosinophilic cytoplasm (rhabdomyoblasts) showed positivity for Desmin (Figure 3B).

After histopathological confirmation patient was under treatment with radiotherapy and doing well without any recurrence on follow up since last 6 mo till date.

DISCUSSION

Peripheral nerve malignant lesions are displaying



Figure 1 Photograph showing multiple neurofibromas, present all over the body.

differentiation towards Schwann cells, perineural cells, fibroblasts are labelled as MPNST. This term now replacing the earlier terminologies malignant schwannoma, neurofibrosarcoma and neurogenic sarcoma^[1]. The diagnostic criteria for NF-1, is presence of two or more of the following signs^[1]: (1) Six or more cafe-au-lait macules; (2) Two or more neurofibromas of any type or one plexiform neurofibroma; (3) Freckling in the axillary or inguinal region; (4) Optic Glioma; (5) Two or more Lisch nodules; (6) Osseous Lesion; and (7) First degree relative (parent, sibling, offspring) with NF-1.

MPNST constitutes 5%-10% of all soft tissue sarcomas, about one fourth to one half occur in the setting of neurofibromatosis^[1]. Patients with NF-1 have propensity to transform in to sarcoma after a prolonged latent period (10-20 years)^[5]. Our patient was diagnosed as having NF-1 and after long latency period of 30 years, he developed MPSNT with rhabdomyoblastic differentiation. MPNST can also arise spontaneously without association of NF-1^[4].

MTT is a rare tumor arising from peripheral nerves. It is an autosomal dominant disorder. It has a strong association with neurofibromatosis (type 1). The common sites of occurrence are head, neck, extremities and trunk^[4]. The symptoms are mainly attributed to mass effect giving rise to neurological signs and symptoms^[4].

In 1973 Woodnelf *et al*^[6] proposed the classification of MTT by establishing three criteria for diagnosis: (1) Tumor with peripheral nerve involvement in a patient with NF-1; (2) Majority of the cells in the tumor are Schwann cells; and (3) Presence of Rhabdomyoblasts^[6].

Our patient had NF-1 and histology showed all the above mentioned criteria. The pathognomic feature of this tumor is the presence of rhabdomyoblasts. The number of rhabdomyoblasts varies from area to area in the same tumor. They are having abundant eosinophilic cytoplasm. Desmin is demonstrated in the rhabdomyoblasts.

The histogenesis of this unusual tumor is discussed by Masson. He postulated that both cell lines have similar origin, *i.e.*, from less well differentiated neural crest cells^[1,7]. The strong relation between neural

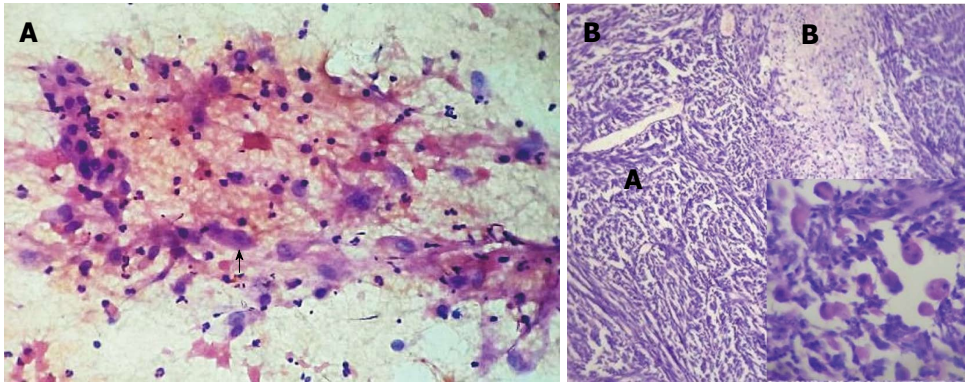


Figure 2 Photomicrograph. A: Photomicrograph of cytological smear showing spindle cells with pleomorphic hyperchromatic nuclei and a plump cell (arrow) with abundant eosinophilic cytoplasm; B: Photomicrograph showing hypercellular areas (Antoni A) of spindle cells having hyperchromatic nuclei and hypocellular areas (Antoni B) (100 ×). Inset shows rhabdomyoblastic differentiation (400 ×).

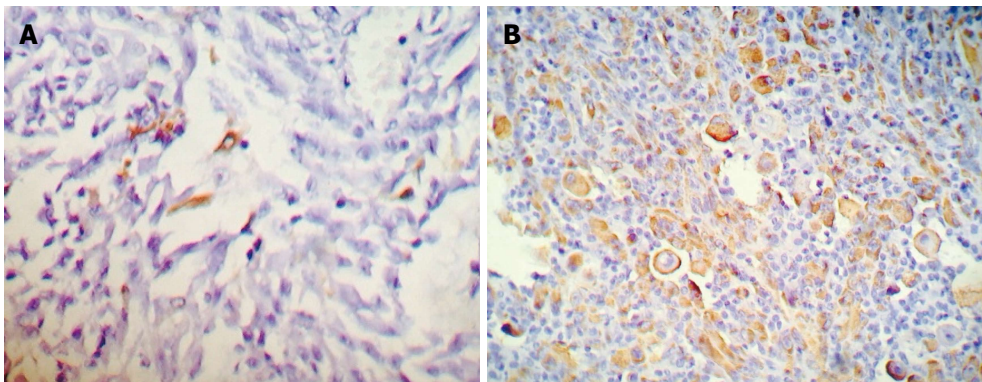


Figure 3 Immunohistochemistry. A: Immunohistochemistry showing focal S100 positivity in spindle cells; B: Immunohistochemistry showing Desmin positivity in rhabdomyoblasts.

tissues and rhabdomyoblastic differentiation has been reported as the development of skeletal muscle differentiation within other neural tumors such as Ocular Medulloblastoma^[8], Ganglioneuroblastoma^[9,10]. The five years survival rate for MTT is only 11% in contrast to 39% for MPNST^[11]. MTT is significantly worse than the usual MPNST. The aggressiveness of MTT is attributed to high grade (grade III) nuclear features with high proliferative capacity^[4]. Radical excision followed by high dose radiotherapy is the conventional treatment for this unusual tumor^[3].

MTT is an uncommon sarcoma which is having high propensity of local recurrence and distant metastases. Histopathologically, the diagnosis of MPNST with mesenchymal differentiation is difficult. So meticulous histopathological examination and immunohistochemical demonstration of neural markers and skeletal muscle markers help to hit the correct diagnosis. Early diagnosis, complete resection of the tumor followed by radiotherapy can help to increase survival of the patient.

COMMENTS

Case characteristics

A 55-year-old male patient presented with multiple swellings all over the body ranging from 1-3 cm since 30 years.

Clinical diagnosis

Multiple neurofibromas.

Differential diagnosis

Neurofibromas, fibrosarcoma, malignant peripheral nerve sheath tumor (MPNST).

Laboratory diagnosis

Fine needle aspiration cytology, histopathology with Immunohistochemistry showing Desmin positivity in rhabdomyoblasts.

Imaging diagnosis

Ultrasonography was suggestive of neoplastic lesion soft tissue sarcoma.

Pathological diagnosis

An unusual histological variant of MPNST with rhabdomyoblastic differentiation.

Experiences and lessons

Careful histological examination along with clinical work up is important to arrive at such unusual diagnosis.

Peer-review

Good overview of the diagnostic challenges in the correct interpretation of this rare tumor.

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