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Review Article

Cilostazol, Not Only a Vessel Dilator but Also a Decelerator of Diabetic Nephropathy

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Abstract

Cilostazol, a specific inhibitor of phosphodiesterase 3, can prevent platelet aggregation and dilate blood vessels via an increase in cyclic adenosine monophosphate (cAMP). Recent studies suggested that cAMP regulates several signaling pathways involved in the development and progression of renal disease, including mitogenesis, inflammation, and extracellular matrix synthesis. Cilostazol administration in streptozotocin-induced diabetic rats was reported to improve diabetic nephropathy as well as significantly decrease reactive oxygen species activity in the kidneys. In addition, cilostazol improved the serum cholesterol, triglyceride, and low density lipoprotein-cholesterol levels. Transforming growth factor-b and nuclear factor-kB are up-regulated in diabetic kidneys, but cilostazol treatment reduced the expression of these proteins. In conclusion, the ability of cilostazol to reduce oxidative stress and improve dyslipidemia may prevent the progression of diabetic nephropathy and diminish the risk of cardiovascular disease in diabetic patients.

Key words: Cilostazol, oxidative stress, diabetic nephropathy, TGF-β, NF-κB

Phosphodiesterases (PDEs) are a superfamily of enzymes involved in the degradation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP)[1,2]. cAMP and cGMP are both intracellular secondary messengers. The actions of numerous hormones and neurotransmitter signals involved in cell growth, differentiation, survival, and inflammation are mediated by changes in the intracellular concentrations of these cyclic nucleotides[3,4]. Recent studies have suggested that cAMP and cGMP regulate several signaling pathways involved in the development and progression of renal disease, including mitogenesis, inflammation, and extracellular matrix (ECM) synthesis[5-7]. Cilostazol {6-[4-(1-cyclohexyl-1H-tetrazol-5-yl) butoxy]-3, 4-dihydro-2(1H)- quinolinone} is a specific inhibitor of PDE-3. Its major effects are the prevention of platelet aggregation and dilation of blood vessels via an increase in cAMP levels[8]. Cilostazol has been shown to inhibit vascular smooth muscle cell proliferation *in vitro* and to suppress neointimal formation in the balloon-injured rat carotid artery model due to its antiplatelet and vasodilator properties[9,10]. In addition, cilostazol has been shown to prevent re-stenosis after percutaneous transluminal coronary angioplasty[11]. These results suggest that cilostazol has the potential to elicit beneficial effects against the atherogenic process. Moreover, Lee et al. demonstrated that cilostazol suppresses the formation of atherosclerotic lesions in low-density lipoprotein receptor (LDLR)-null mice[12]. Superoxide and tumor necrosis factor-α (TNF-α) production is significantly lowered by cilostazol in situ as well as in cultured human umbilical vein endothelial cells.

Diabetic nephropathy is characterized by the

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progressive development of renal insufficiency in the setting of hyperglycemia and is the single most common cause of end-stage renal failure in many countries[13]. In general, approximately 1 out of 3 patients with type 1 or type 2 diabetes eventually develop significant diabetic nephropathy[14]. It is believed that the pathophysiological mechanisms of renal disorders are similar in both types of diabetes[15]. The findings of functional as well as pathological changes in kidneys of diabetes patients are characteristic of diabetic nephropathy. Several longitudinal studies have suggested that microalbuminuria, which is defined as urine albumin excretion of 30–300 mg over a 24-hour period, predicts progression to overt proteinuria and subsequent renal insufficiency. Once clinical albuminuria (300 mg/24 hours) develops, the development of renal disease is essentially inevitable[14]. The characteristic pathological changes in diabetic nephropathy involve glomerular lesions, including glomerular basement membrane thickening, mesangial expansion, and hyalinosis of afferent and efferent arterioles[16]. In early diabetic nephropathy, we have demonstrated the "hydropic change," which is characterized by paleness and swelling in the proximal convoluted tubules[17]. Proximal tubular epithelial cells may influence the fibrotic process in the renal interstitium via the generation of profibrotic cytokines and induce the process of epithelial–mesenchymal transition[18]. Tubulointerstitial fibrosis is a common final pathway in diabetic nephropathy. In a previous study, significant diabetic nephropathy was observed as early as 6 weeks after streptozotocin (STZ) treatment[19]. The rats showed an increase in urinary albumin excretion, which led to significant hypoalbuminemia. Cilostazol treatment can ameliorate albuminuria and restore serum albumin levels. Ku et al. also reports an increase in mass and protein content in the kidneys of rats with diabetes induced by 7-day STZ treatment compared with the control group[20]. Yang et al. observed the typical pathological changes of diabetic nephropathy as early as 6 weeks after STZ treatment[21]. These observations indicate that cilostazol may prevent the progression of diabetic nephropathy in cases of early diabetes.

There is increasing evidence that reactive oxygen species (ROS) play a major role in the development of diabetes-related complications[22]. Increased ROS levels can cause vascular endothelium abnormalities, reacting directly with nitric oxide (NO) to produce cytotoxic peroxynitrite and increasing the responsiveness to vasoconstrictors and modifying the ECM proteins[23]. ROS also can damage endothelial cells indirectly by stimulating the expression of various genes involved in inflammatory pathways[24]. High glucose has been found to induce ROS generation and then to upregulate transforming growth factor-β1 (TGF-β1) and ECM expression in glomerular mesangial cells[25]. Studies have also shown that antioxidants can effectively inhibit high glucose-induced TGF-β1 and fibronectin up-regulation[26]. It is therefore suggested that ROS play an important role in high glucose-induced renal injury. In our previous results, cilostazol therapy was shown to significantly improve oxidative stress, including reducing the malondialdehyde (MDA) level and restoring catalase and glutathione levels. The beneficial effect of cilostazol might be due to its activity as a ROS scavenger in diabetic nephropathy. Recently, Agrawal et al. reported that cilostazol can reduce the inflammatory burden and oxidative stress in hypertensive type 2 diabetes mellitus patients[27]. They showed that after 1 month of cilostazol treatment, the plasma MDA and serum C-reactive protein levels in diabetic patients are reduced and that previously reduced glutathione levels in the blood are increased. Omi et al. showed that cilostazol may act directly on endothelial cells to inhibit the expression of adhesion molecules and neutrophil adhesion induced by high glucose levels by increasing NO production[28]. Their results imply that cilostazol may have protective effects against vascular injury mediated by hyperglycemia to prevent diabetes-related vascular complications.

Ha et al. reported that ROS mediate high glucose level-induced activation of nuclear factor-kB (NF-κB) and NF-κB–dependent monocyte chemoattractant protein-1 expression[36]. Overexpression of TGF-β in the kidneys of diabetes patients is believed to contribute to renal growth and accumulation of ECM proteins in diabetes[29]. NF-κB, a nuclear transcription factor, can initiate the transcription of genes associated with the inflammatory response. NF-κB expression is induced by various cell stress-associated stimuli, including growth factors, vasoactive agents, cytokines, and oxidative stress[30]. Advanced glycation end products induced by hyperglycemia stimulate NF-κB activation, thus explaining the sustained activation of NF-κB in diabetes[31]. The

activation of NF-κB and the transcription of certain pro-inflammatory chemokines in tubular epithelial cells are markers of progressive diabetic nephropathy[32]. A previous study showed that both TGF-β and NF-κB levels are increased in the diabetic kidney and are decreased by cilostazol treatment. Interestingly, an analysis of TGF-β and NF-κB expression in glomeruli and renal tubules showed that both TGF-β and NF-κB are up-regulated in the renal proximal convoluted tubules, but only TGF-β is up-regulated in renal glomeruli. The intensive expression area of NF-κB in the proximal convoluted tubules is correlated with the lesion of "hydropic change." This implies that the mechanism of early diabetic nephropathy in renal proximal convoluted tubules may involve ROS, NF-κB, and TGF-β and results in tubulointerstitial fibrosis. In contrast, only TGF-β, but not NF-κB, is upregulated in the renal glomeruli. This finding suggests that the mechanism of glomerulosclerosis is not dependent on NF-κB. Indeed, in the studies of Mezzano et al.[33] and Morcos et al.[34], NK-kB was found to be activated mainly in cortical tubular epithelial cells and less activated in glomerular cells in kidneys of diabetic humans and rats, which is in agreement with our findings. Cilostazol treatment improves the lesions both in renal glomeruli and tubules. Therefore, the results of these studies indicate that oxidative stress, NF-κB expression, and TGF-β expression are reduced by cilostazol, which may be capable of reversing the clinical course of early diabetic nephropathy.

Dyslipidemia is common in patients with diabetes. Diabetic nephropathy is known to be associated with many protein abnormalities, including higher levels of LDL and triglycerides and lowers level of high-density lipoprotein (HDL)[34]. Many studies show that lipids may induce both glomerular and tubulointerstitial injury through mediators such as cytokines, ROS, and chemokines as well as through hemodynamic changes. A recent study demonstrating that hyperlipidemia and hyperglycemia act synergistically to induce renal injury in LDLR-deficient mice further indicates that lipids can exacerbate diabetic nephropathy[35]. Dyslipidemia may also cause or exacerbate diabetic nephropathy by altering the coagulation–fibrinolytic system, changing membrane permeability, damaging endothelial cells, and increasing atherosclerosis[36]. The relationship between the risk of atherosclerotic coronary heart disease (CHD) and serum lipoprotein levels is well known. Elevated levels of total cholesterol and LDL-cholesterol and a low level of HDL-cholesterol are linked to an increased risk for CHD[37]. In previous studies, significant increases in total cholesterol, triglyceride, and LDL-cholesterol were found in patients with diabetic nephropathy. Nakamura et al. reported a significant improvement in triglyceride levels after 1 month of cilostazol treatment in patients with type 2 diabetes and peripheral vascular diseases[38,39]. They proposed that the beneficial effect of cilostazol extends beyond treating nephropathy, also including cardiovascular risk reduction by reduction of lipid levels.

In conclusion, the beneficial effects of cilostazol have been demonstrated in early diabetic nephropathy. The effect of cilostazol on reducing oxidative stress and improving dyslipidemia may prevent the progression of diabetic nephropathy and the associated increase in cardiovascular disease risk.

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Cilostazol, 不僅是血管擴張劑，且是糖尿病腎病延緩劑

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摘要

Cilostazol，一種磷酸雙酯酶抑制劑，可經由增加組織 cAPM 而預防血小板凝集及擴張血管。近來研究指出 cAMP 會在腎病發展過程中調節一些訊息傳遞路徑而改變有絲分裂、發炎及包外基質合成，因此 cilostazol 被指出在 streptozotocin 誘導的糖尿病鼠腎臟中，可有效改善腎病及活性氧活性；另外也可改善血脂 。Cilostazol 在降低活性氧及改善血脂的特性可能是延緩糖尿病腎病變進程的因素 。

關鍵詞：Cilostazol 、氧化壓力 、糖尿病腎病變 、TGF-β, NF-κB

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Original Article

Apple Polyphenols Decelerate Acetaminophen-induced Oxidative Stress

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Abstract

Background and purpose: Acetaminophen (AAP)-induced oxidative stress can cause cell death and consequent liver damage. Apple polyphenols (APs) are known to exert antioxidative effects. In this study, we investigated the effect of AP on AAP-induced oxidative stress in mouse liver injury.
Methods: BABL/c mice were orally fed with AP (100, 200, 300 mg kg^{-1}) for two weeks, and then injected with 1000 mg kg^{-1} of AAP.
Results: Pretreatment with AP decreased the level of lipid peroxidation and increased catalase activity and glutathione levels.
Discussion: AP demonstrably protects the liver from AAP-induced injury, possibly by a mechanism that reduces oxidative stress.

Key words: Acetaminophen, antioxidation, apple polyphenol

Introduction

Excess intake of acetaminophen (AAP) causes severe hepatotoxicity and consequent liver injury in many animals, including humans [1]. A major portion of AAP is conjugated with glucuronic acid and sulfate; a smaller portion is metabolized by cytochrome P-450 [2]. Cytochrome P-450 oxidizes AAP to form a hepatotoxic, chemically reactive metabolite called *N*-acetyl-*p*-benzoquinone imine (NAPQI), which reacts with glutathione (GSH) to form a non-toxic AAP–GSH complex. However, once the GSH is eliminated, NAPQI binds to a number of mitochondrial proteins, possibly leading to hepatocellular death [3]. AAP inhibits mitochondrial oxidative phosphorylation and subsequently exhausts adenosine triphosphate in mouse hepatocytes [4-6]. Both cytosolic and mitochondrial GSH can be sequestered by AAP [7]. Some natural products and antioxidants can ameliorate AAP-induced liver toxicity by increasing GSH levels and catalase activity [8].

Several previous studies have demonstrated that a relationship exists between AAP-induced oxidative stress and cell death. Cell death is initiated by the phosphorylation of JNK to its active form (pJNK) and Bax is translocated to the mitochondria in AAP-induced liver toxicity [9]. The inhibition of JNK promotes survival and reduces cell death; conversely, postponing JNK inhibition promotes cell death [10]. Two of the three known JNK genes in liver cells, JNK1 and JNK2, are activated by death receptors and the ER stress pathway in apoptosis [11]. Survival and death are associated with transient and prolonged activation of JNK, respectively. Regulated by Bcl-2 family proteins, JNK activates Bim, thereby causing mitochondrial dysfunction [12], or induces caspase 8 activation, Bid cleavage, and mitochondrial cytochrome *c* release [13]. Prolonged JNK1 activation can also cause the degradation of cFLIP (an endogenous inhibitor of

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death receptor signaling) to enhance cell death via TNFR1, Fas, or TRAIL receptor 1/ TRAIL receptor [14].

The phenolic substances in many dietary and medicinal plants possess striking antioxidative and anti-inflammatory properties, which partially contribute to their cancer chemopreventive potential [15]. Polyphenols are secondary plant metabolites that are classified into phenolic acid derivatives, flavonoids, stilbenes, or lignans depending on their structure [16]. Apples (*Rosaceae Malus sp.*), which rank among the most commonly consumed fruits in the world, contain a variety of phenolic acid derivatives and flavonoids, including flavan-3-ols, flavonols, procyanidins, chalcones, and anthrocyanins [17]. The extracts from apples and apple polyphenols (APs) are biologically active against oxidation, allergies, tumors, and obesity, and also promote hair growth [18-21]. In addition, fruits containing relatively high concentrations of flavonols, anthocyanins, and procyanidines are effective against cardiovascular risk factors such as antihypertensive effects, inhibited platelet aggregation, increased endothelial-dependent vasodilation, and hypocholesterolemic effects. The cardioprotective properties of fruits have been previously attributed to polyphenols [22]. Denis et al. (2013) demonstrated the beneficial effects of apple peel polyphenols on oxidative stress and inflammation in inflammatory bowel disease. They proposed that apple peel polyphenols exert their antioxidant and anti-inflammatory effects by preventing lipopolysaccharide-induced inflammation. The proposed mechanism was repression of COX-2 expression and activity, down-regulation of the transcription factor NK-κB, and up-regulation of Nrf2 expression.

This study evaluates the preventive effect of AP in acute liver damage initiated by high AAP dosage.

Materials and Methods

Animals and Experimental Design

AP was purchased from Asahi Co. (Japan). All animal experimental protocols adopted in this study were approved by the Institutional Animal Care and Use Committee of the Chung Shan Medical University (IACUC, CSMU), Taichung, Taiwan. Male BABL/c mice (27±2.5g) (National Laboratory Animal Breeding and Research Center Taipei, Taiwan) were housed in laboratory conditions (18–23°C, 55–60% humidity, 12 h light/dark cycle) for at least 1 week before each study. The mice were provided with standardized food (Purina Lab Chow, obtained from Purina® Mills, Inc., US) and water *ad libitum* and divided into six groups (ten mice per group). Group 1: untreated control group, fed with standardized diet; Group 2: DMSO control group, IP injection with DMSO: H_2O = 3:7, fed with standardized diet; Group 3: AAP 1000 mg kg^{-1} group, IP injection with AAP 1000 mg kg^{-1} dissolved in DMSO/H_2O, fed with standardized diet; Group 4: AP 100 mg kg^{-1} group, fed with AP 100 mg kg^{-1} and IP injection with AAP 1000 mg kg^{-1}; Group 5: AP 200 mg kg^{-1} group, fed with AP 200 mg kg^{-1} and IP injection with AAP 1000 mg kg^{-1}; Group 6: AP 300 mg kg^{-1} group, fed with AP 300 mg kg^{-1} and IP injection with AAP 1000 mg kg^{-1}. BABL/c mice were orally fed with AP once a day for two weeks, followed by 1000 mg kg^{-1} of AAP injected IP. Mice were decapitated 6 h after AAP injection. A 2 mL blood sample was collected and the plasma separated to determine liver function. Liver tissues were also collected for further analysis.

Determination of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), albumin, blood urea nitrogen (BUN), and creatinine

Plasma AST, ALT, ALP, albumin, BUN, and creatinine were measured by enzymatic colorimetric methods using an automatic analyzer (Olympus AU 2700, Olympus Co., Tokyo, Japan).

Thiobarituric acid-reacting substances (TBARS)

To determine the lipid peroxidation, 0.5 g of liver specimen was homogenized with 5 mL of 50 mM phosphate buffer (pH 7.4) and centrifuged (1000 g) for 30 min, yielding a supernatant homogenate. Protein content of the supernatant was determined with a Bio-Rad protein assay kit using bovine serum albumin as the standard. The calibration curve ranged from 0 to 400 mg mL^{-1} (r^2 = 0. 9938). 0.3 mL of the homogenate was added to 0.3 mL of TBA (1% thiobarbituric acid in 0.3% NaOH) and incubated for 40 min at 95 °C in the dark. After the reaction, samples were analyzed in a Hitachi F2000 spectrophotofluorimeter with excitation at 532 nm and emission at 600 nm. The calibration curve was prepared from 0–50 nmol malondialdehyde (MDA) standards (r^2 = 0. 9902). The TBAR concentrations were expressed as MDA equivalents in units of M/mg protein.

Catalase Assay

Catalase activity in the liver homogenates was assayed as previously described [23]. The protein concentration was determined using a Bio-Rad protein assay kit adjusted to 50 mg mL^{-1}. 20 µL of homogenate was added to 980 µL of H_2O_2 solution (containing 30 µL ddH_2O, 50 µL 1 M Tris-HCl, and 5 mM EDTA (pH 8.0) plus 900 µL 10 mM H_2O_2). After 10 s at room temperature, the optical density of H_2O_2 was recorded at 240 nm for 1 min. The catalase activity was determined from the linear portion of the optical density versus time plot (average r^2 = 0. 9846). A unit of catalase activity was defined as units of H_2O_2 consumed mg^{-1} protein.

Determination of GSH content

The hepatic GSH content was determined as described in Hissin and Hilf [26] A stock solution of the fluorescent probe o-phthalaldehyde (OPT) was freshly prepared in methanol (1 mg mL^{-1}). 10 µL of the homogenate was mixed with 100 µL of OPT and incubated for 15 min in the dark. We then monitored the fluorescence intensity under excitation at 350 nm and emission at 420 nm. The GHS concentration was quantified from a GSH calibration curve (0–20 ng mL^{-1}; r^2 = 0. 9901). The result was expressed as ng GSH mg^{-1} protein.

Statistical Analysis

All results are expressed as mean ± SD. Statistical differences were analyzed by one way ANOVA and Student's *t*-test. Differences were considered significant at the $P < 0.05$ level.

Results

Effect of AP on Liver and Kidney Function in AAP Treated BABL/c Mice

Levels of ALT and AST were significantly elevated in AAP-treated mice. AP treatment significantly reduced the ALT and AST levels in a dose-dependent manner. APP induced significant increases in serum BUN and creatinine; various concentrations of AP treatment reduced the levels of both compounds. Serum albumin was significantly reduced in the AAP-injected animals ($P < 0.05$) but was significantly improved in the AP treated groups ($P < 0.005$) (Table 1).

Effect of AP on the MDA Content, Catalase Activities, and GSH in AAP Treated BABL/c Mice

In the murine group subjected to AAP-induced liver injury, MDA contents were significantly increased while catalase and GSH activities were suppressed. Under the same condition, pretreatment with AP (100, 200, 300 mg kg^{-1}) reduced the lipid peroxidation and enhanced the catalase activity. GSH levels were also increased in the same groups (Table 2).

Table 1. Characteristics of biochemical parameters in the animal blood

Parameters[a,b]	Normal	DMSO	1000 mg kg^{-1} AAP	AAP + 100 mg kg^{-1} AP	AAP + 200 mg kg^{-1} AP	AAP + 300 mg kg^{-1} AP
Body weight, g	32.40 ± 4.32	34.90 ± 3.31	36.90 ± 2.26[c]	35.60 ± 2.90	34.60 ± 2.91[d]	33.05 ± 3.08[e]
Liver weight, g	2.05 ± 0.25	2.52 ± 0.29	3.54 ± 0.37[c]	2.97 ± 0.13[f]	2.15 ± 0.33[f]	2.07 ± 0.23[f]
AST, U dL^{-1}	95.60 ± 31.99	99.80 ± 26.36	976.50 ± 313.88[c]	736.10 ± 230.24[d]	698.10 ± 269.91[d]	396.10 ± 185.55[f]
ALT, U dL^{-1}	56.20 ± 25.13	73.80 ± 12.43	1639.00 ± 295.06[c]	854.30 ± 258.15[f]	453.80 ± 53.40[f]	299.60 ± 36.32[f]
ALP, U dL^{-1}	121.30 ± 15.13	126.20 ± 13.23	185.10 ± 37.55[c]	148.60 ± 16.87[d]	160.40 ± 18.01	150.30 ± 31.78[d]
Albumin, g dL^{-1}	3.63 ± 0.50	3.97 ± 0.33	2.60 ± 0.24[c]	2.96 ± 0.29	3.15 ± 0.37[e]	3.33 ± 0.50[e]
BUN, mg dL^{-1}	22.30 ± 2.01	24.90 ± 1.73	53.70 ± 2.17[c]	39.50 ± 10.17[f]	35.00 ± 12.26[f]	31.5 ± 10.13[f]
Creatinine, mg dL^{-1}	0.40 ± 0.05	0.49 ± 0.07	0.85 ± 0.14[c]	0.77 ± 0.21[f]	0.60 ± 0.24	0.51 ± 0.33[d]

[a], Data was represented as mean ± SD, n=10.
[b], AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; BUN, blood urea nitrogen.
Statistical significance analyzed by one-way ANOVA and Student's *t*-distribution.
[c], $P < 0.05$, compared to the normal group; [d], $P < 0.05$, [e], $P < 0.005$, and [f], $P < 0.0005$, compared to the AAP treated group.

Table 2. Oxidative parameters in the liver specimen of mouse

Parameters [a, b]	Normal	DMSO	1000 mg kg^{-1} AAP	AAP + 100 mg kg^{-1} AP	AAP + 200 mg kg^{-1} AP	AAP + 300 mg kg^{-1} HSE
MDA, μM mg^{-1} protein	0.93 ± 0.38	1.12 ± 0.19	2.24 ± 0.87[c]	1.04 ± 0.42[d]	0.87 ± 0.17[e]	0.91 ± 0.17[e]
CAT, units mg^{-1} protein	1.62 ± 0.30	1.54 ± 0.26	0.78 ± 0.09[c]	1.23 ± 0.29[e]	1.25 ± 0.25[e]	1.58 ± 0.42[e]
GSH, ng mg^{-1} protein	1.57 ± 0.20	1.47 ± 0.29	0.63 ± 0.08[c]	0.96 ± 0.27[e]	1.23 ± 0.27[e]	1.24 ± 0.41[e]

[a], Data was represented as mean ± SD, n=10.
[b], MDA, Malondialdehyde content; CAT, catalase activity; GSH, glutathione.
Statistical significance analyzed by one-way ANOVA and Student's t-distribution.
[c], $P < 0.001$, compared to the normal group; [d], $P < 0.005$, and [e], $P < 0.0005$, compared to the AAP treated group.

Discussion

AAP is useful as an analgesic and antipyretic drug, but high AAP doses are injurious to the liver [25]. Bajt *et al.* reported that oxidative stress precedes cell injury in mice hepatocytes exposed to AAP [26]. Researchers have previously demonstrated the beneficial actions of apple peel polyphenols on oxidative stress and inflammation in inflammatory bowel diseases. Reportedly, apple peel polyphenols prevent lipopolsaccharide-induced inflammation by decreasing the expression and activity of COX-2. In this study, we found that AP pretreatment in BABL/c mice can protect the liver from AAP-induced damage. The major findings were that AP pretreatment reduces the level of lipid peroxidation, increases catalase activity, and increases GSH levels. The observed TBARS increase in the AAP-treated group agrees with previously reported results. Oxidative stress is always accompanied by lipid peroxidation, which is a critical step in AAP-induced hepatotoxicity [27-29].

A number of medicinal plants are known to diminish AAP-induced lipid peroxidation. Catalase, a key enzyme in oxidative defense mechanisms, is significantly reduced following ingestion of a toxic AAP dose [30]. Other researchers reported that pretreatment with a novel nutritional mixture of various phytochemicals prevents AAP-induced cell apoptosis and deprogramsprograms cell death by enhancing Bcl-XL expression and reducing oxidative stress in the liver. Similarly, our study demonstrated a significant decline in catalase activity following AAP treatment. It appears that reactive oxygen species and hydrogen peroxide accumulate to levels that aggravate hepatocellular damage initiated by NAPQI. Our results show that AP consumption might elevate the antioxidative condition in human individuals, protecting their livers from AAP-induced injury.

Although the current findings suggest that AP improves the antioxidative status of liver cells, and may therefore protect against AAP-induced hepatotoxicity, the constituent that is chiefly responsible for this protective effect and the mechanisms involved, require elucidating in a future study.

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蘋果多酚在動物模式中延緩 acetaminophen 誘導的氧化壓力

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摘要

背景及目的：Acetaminophen (AAP) 誘導氧化壓力會使細胞死亡而引起肝臟損傷，先前研究顯示蘋果多酚 (apple polyphenol, AP)，具有抗氧化力，因此本研究將探討在動物模式中，AAP 誘導氧化壓力時，AP 的作用為何。

方法：BABL/c 小鼠以管餵方式給予 AP (100, 200, 300 mg kg^{-1}) 2 周，之後以腹腔注射給予 1000 mg kg^{-1} 的 AAP。

結果：預處理 AP 會降低肝臟脂質過氧化、增加 catalase 活性及 glutathione 含量。

討論：AP 被證明可以保護肝臟免於 AAP 誘導的損傷，而此機轉可能包括了降低氧化壓力。

關鍵詞：乙醯胺基酚、抗氧化作用、蘋果多酚

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Original Article

Quality of Service: A Survey of Patient Satisfaction from a Self-paid Physical Examination Program

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Abstract

Background*:* Understanding the needs and satisfaction of participants can improve the quality of service of a physical examination program.
Methods: This study recruited participants from a self-paid physical checkup program at Taichung Veterans General Hospital. Data on the quality of service, needs, and satisfaction of participants were collected from the participants through both interviews and questionnaires.
Results: For the 2001 and 2011 surveys, participants recruited for the study were satisfied with the program [759 (89.9%) and 785 (90.1%), respectively]. Most examinations were regarded as necessary, particularly those for gastroenteroscopy, colonoscopy, and abdominal echonography for cancer screening. However, dental and physical examinations and HIV screening were regarded as the least important. Participants wished for bone density testing, breast imaging, and echonography to be included in the program. In addition, participants wanted to receive their health reports earlier. Reasons for participation in the program were aging, feelings of poor health, and requests by family members. Participants agreed that physicians and consultants were competent (94% and 89%), and that their privacy was good (92%); more than half did not consider to be re-examined by other health institute. Participants also agreed that history taking (92%), health consultation (98%), and scheduling of return visits (93%) were necessary. There was a high association (97%) between the participants' satisfaction and their willingness to return for the next physical examination.
Conclusions: Satisfaction with the quality of service of a physical examination program would bring the return and recommendation to the program.

Key words: Self-paid physical examination program, health maintenance, quality of service

Introduction

Prevention is better than treatment. However, disease prevention plans from current health insurance systems cannot satisfy the needs of the population[1-3]. Health surveys have found that two-thirds of patients and physicians believe that it is important for adults to receive preventive health examinations[4,5], and that these examinations are considered to strengthen physician–patient relationships[6,7].

Recently, the National Health Insurance of Taiwan has been promoting free-of-charge health screening programs for adults. The coverage rate of these programs is approximately 6.0% and 19.5% for typical rural and city areas, respectively[8]. These preventive physical examinations have been further supplemented with four free additional cancer screening programs for different populations: Pap

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smear every three years (for women over 30 years old), mammography (for 40–69-year-old females with a family history), oral screening (for betel quid chewers), and fecal occult blood screening biannually (for those aged 50–69 years) in recent years. Other studies have shown that most preventive physical examinations have been paid for by commercial insurance plans, and that these examinations have not been recommended by the Canadian Task Force on the Periodic Health Examination or the Medical Practice Committee, American College of Physicians[9,10]. van Walraven et al.[11] and the Council on Scientific Affairs, American Medical Association[12], have recommended a more individualized package of preventive health examinations for patients. Therefore, a self-paid physical examination program might complement the shortcomings of current health insurance systems.

According to the evidence-based preventive care and guidelines, health care providers should limit the types of medical examinations to avoid discretionary or unnecessary laboratory testing[13,14]. Health consumers in the past had less opinions expressed but the situation is changed by the demands of self-paid health program. The market for self-paid physical examinations is very competitive in Taiwan because patients have more options to choose from for their needs. The results from a study on patient satisfaction may push health providers to improve their services in all areas, including the self-paid physical examination program.

The simplest way to learn about patient satisfaction is through questionnaires[15-17]. Qualitative and quantitative questionnaires can be trustworthy and valid[18]. While participants complete the questionnaire, the investigators could also communicate with them. Because the healthcare system and health insurance systems of Taiwan are a free market and very competitive, a patient can select any medical institute based on their personal view of their medical environment, the quality of service, and the medical expense. Because there have only been a few reports on patient satisfaction and the quality of service of a physical examination program in the English literature, our objective for this study was to investigate patient satisfaction and the quality of service of this program. The survey covered both the hardware and software of the self-paid program and the reliability/credibility of the physical examination. Through the analysis of this survey, the consumers' satisfaction about the quality of the facility and examination items and the consumers' needs and expectations could further be improved.

Methods

Study participants

During the periods from January to June 2001 and from January to June 2011, a total of 2,230 and 2,200 people participated, respectively, in the self-paid physical checkup program at the Health Management Center of Taichung Veterans General Hospital (TCVGH). We randomly chose 1,000 from participants over the two periods. The study was approved by the Institutional Review Board of TCVGH (Certificate No. CE11135). A questionnaire was answered by each participant after signing a consent form for this study. Demographic information, such as sex, age, education, occupation, number of times utilizing a self-paid physical checkup examination, annual family income, residence, and marital status, were collected. The physical examination consisted of height and weight, blood pressure, pulse rate, and respiratory rate evaluations, as well as evaluations for vision, ear, nose and throat, teeth, lung, chest, and abdomen; gastroenteroscopy, colonoscopy, blood tests, and routine urine analysis were also included.

Study design

For the qualitative study (from January to February 2001), we developed a questionnaire. Sample adequacy for importance and appropriateness was achieved by saturation and replication after 12 revisions with a total of 50 participants. The final version with verified comprehension and completeness was used to construct the quantitative questionnaire. Two pretests were performed on 22 and 16 participants and revised by the investigators and three advisors. The questionnaire was finalized after the third pretest that was taken by 32 participants with the help of a language teacher from a local high school to achieve face validity.

In this investigation, six parts of the question were surveyed in which part I, a qualitative study and parts II to XI, quantitative study. Through interviews and questionnaires, we hoped to be able to learn about the consumers' needs and expectations for improvement.

Specifically, the questionnaire examined the following queries: (1) the strength and weakness of this physical examination program, (2) the background of participants, (3) satisfaction with the program, (4) which items met the participants' needs and expectations, (5) the validity and reliability of the program, and (6) their willingness to and need for return visits.

The contents of this questionnaire included 52 questions about examination procedures, items, and quality, as well as facilities, equipment, and the quality of services. Participants could answer each question with rating scores: very satisfied (5), satisfied (4), acceptable (3), less than satisfied (2), and not satisfied (1). There were another 18 open questions about reasons for participation in the program, opinions about examination items, and the cost of the examination. The participant was asked to rate the expert validity (physicians and consultants) and reliability of the reports and programs using the following choices: strongly agree, agree, no comment, disagree, and strongly disagree.

Data analyses

Completed questionnaires with more than five contradictory or unfilled answers were labeled "invalid" and were excluded from the analysis. Each related question (item) with three categories of satisfaction was analyzed by chi-square method. A two-tailed *p*-value less than 0.05 was considered statistically significant.

Results

Descriptive Information

The response rate for the 2001 survey was 93.8% (938/1,000). Fifty-six invalid questionnaires were excluded from the analysis, which indicated an effective rate of 94.0%. Table 1 shows the demographic data of participants with 510 males and 372 females ($p < 0.05$). The response rate for the 2011 survey was 59% (1,103/1,867). Fifty-six invalid questionnaires were excluded from this analysis with an effective rate of 94.0%. Invalid questionnaires were defined as having more than five unanswered or contradictory items. Most participants were willing to answer the questionnaire and ignored the less interesting items. The general profile of participants in 2011 was similar to that of participants in the 2001 survey. The major reasons for participation in the program were aging, feelings of poor health, and requests by family members.

Participants' satisfaction

The participants' satisfaction is shown in Table 2. Each category was further analyzed for the participants' satisfaction using cross-analyses. For this program, men were more satisfied than women with the safety (88% vs. 84%), receptionist's service (88% vs. 83%), examination qualities (90% vs. 86%), and physician's service (89% vs. 85%). Participants with higher annual family incomes (one million new Taiwan dollars) were more satisfied with the services

Table 1. Demographic data for participants (2001)

Category	Male (%)	Female (%)	Total (%)
Gender	510 (57.8)	372 (42.2)	882 (100)
Age			
<25	3 (0.3)	5 (0.6)	8 (0.9)
25-34	25 (2.9)	28 (3.2)	53 (6.1)
35-44	111 (12.7)	93 (10.7)	204 (23.4)
45-54	155 (17.8)	97 (11.1)	252 (28.9)
55-64	116 (13.3)	98 (11.2)	214 (24.5)
65-74	78 (8.9)	35 (4.0)	113 (12.9)
>75	19 (2.2)	10 (1.1)	29 (3.3)
Range of age	20-86	15-90	15-90
Mean age	52.4 ± 12.4	50.4 ± 12.7	51.6 ± 12.6
Marital status			
Married	469 (54.0)	307 (35.3)	776 (89.3)
Unmarried	18 (2.0)	31 (3.6)	49 (5.6)
Others	15 (1.7)	29 (3.3)	44 (5.1)
Educational level			
<High school*	94 (10.8)	112 (12.8)	206 (23.6)
High school	210 (24.1)	167 (19.2)	377 (43.2)
College	177 (20.3)	82 (9.4)	259 (29.7)
Graduate school	25 (2.9)	5 (0.6)	30 (3.5)
Residence			
Urban	387 (44.1)	283 (32.2)	670 (76.3)
Rural	121 (13.8)	87 (9.9)	208 (23.7)
Number of examination			
First time	322 (36.5)	277 (31.4)	599 (68.0)
Second time	91 (10.3)	53 (6.0)	144 (16.3)
> Second time	96 (10.9)	42 (4.8)	138 (15.7)

* Educational levels including junior high school, primary school and under.

Table 2. Quality of service: analysis of participants' satisfaction

Category	2001		2011	
	Satisfied (%)	Dissatisfied (%)	Satisfied (%)	Dissatisfied (%)
Receptionist	742 (85.1)*	12 (1.4)	783 (90.1)	8 (0.9)
Time schedule	741 (85.1)	4 (0.5)	777 (86.5)	4 (0.5)
Nurse	803 (91.9)	4 (0.5)	787 (90.8)	4 (0.5)
Physician	671 (77.0)*	10 (1.2)	758 (86.1)	9 (0.9)
Phlebotomy	782 (89.5)	6 (0.7)	777 (86.5)	4 (0.5)
Technicians	771 (88.6)	4 (0.5)	783 (90.1)	4 (0.5)
Examination (Exam) procedure	623 (71.6)	30 (3.5)	787 (90.8)	4 (0.5)
Meal quality	660 (75.9)	12 (1.4)	777 (86.5)	4 (0.5)
Complain	650 (84.2)	7 (0.6)	758 (86.1)	7 (0.6)
Exam. quality	711 (81.5)*	7 (0.9)	758 (86.1)	7 (0.6)
Exam. fee	419 (48.2)*	24 (2.8)	753 (82.3)	4 (0.5)
Counseling service				
Resident	727 (83.2)	3 (0.3)	753 (82.3)	3 (0.3)
Chief	767 (88.0)*	3 (0.3)	769 (88.5)	3 (0.3)
Ophthalmologist	726 (83.5)	5 (0.6)	758 (86.1)	5 (0.6)
Otolaryngologist	741 (85.8)	4 (0.5)	769 (88.5)	4 (0.5)
Dentist	685 (79.2)	8 (0.9)	753 (82.3)	7 (0.6)
Gynecologist[a]	325 (85.3)	5 (1.3)	427 (90.8)	4 (0.5)
Overall Satisfaction	759 (87.9)	4 (0.5)	785 (90.1)	4 (0.5)

[a]For female participants only.
For a clear view, the five categories of satisfaction: very satisfied (5), satisfied (4), acceptable (3), less than satisfied (2) and not satisfied (1) were combined into satisfied (5+4), acceptable (3+2), and dissatisfied (1).
*, $p < 0.05$; the satisfactions in the males and females were compared with the items in that category with 2001 data.

Table 3. Assessment of participants' needs

Category	Items needed, n = 871		Items to be cancelled, n = 316	
	n (%)	Rank	n (%)	Rank
Physician's counseling	831 (95.4)	1	40 (12.7)	4
Colonoscopy	778 (89.3)	2	2 (0.6)	15
Gastroenteroscopy	758 (87.0)	3	3 (1.0)	13
Abdominal echonography	704 (80.8)	4	5 (1.6)	10
Hepatitis viral screening	621 (71.3)	5	4 (1.3)	12
Chest X-ray	498 (57.2)	6	8 (2.5)	9
Tumor markers	487 (55.9)	7	3 (1.0)	13
Pulmonary function	486 (55.8)	8	11 (3.5)	8
Electrocardiography	483 (55.5)	9	5 (1.6)	10
Ear, nose and throat exam.	444 (51.0)	10	21 (6.7)	6
Thyroxine (T4) assay	375 (43.1)	11	20 (6.3)	7
Eye examination	310 (36.5)	12	62 (19.6)	2
Physical examination	250 (28.7)	13	31 (9.8)	5
HIV screening	248 (28.5)	14	59 (18.7)	3
Dental examination	227 (26.1)	15	262 (82.9)	1

of physicians than those with lower family incomes (less than half million new Taiwan dollars; $c^2 = 50.95$, df = 30, $p = 0.010$) and equipment ($c^2 = 47.62$, df = 30, $p = 0.022$). The overall satisfaction rate was 87.95% and 90.1%, for the 2001 and 2011 surveys, respectively. Many items had improved significantly in the 2011 survey including the examination procedures, meal and exam qualities, and fees (Table 2).

The participants' views on the items that were needed and those that needed to be eliminated are summarized in Table 3. Most of them agreed that the three most important cancer screening items were the upper gastroenteroscopy (87.0%), colonoscopy (89.3%), and the abdominal echonography (80.8%) from the 2001 survey. In contrast, items wished to be eliminated were the dental examination (82.9%), eye examination (19.6%), and HIV screening (18.7%). Although we did not collect as much detailed data in the 2011 study as in the 2001 survey, the trend for lower satisfaction with the dental, physical, and eye examinations was similar. In the 2001 survey, 92% of participants wished to include the bone density test in the program and 97.5% of female participants wished to include breast echonography or mammography. In the 2011 survey, a free breast mammography was already provided by the Bureau of Health Promotion of the Department of Health, Republic of China. About 10% of participants also expressed the desire to include brain computed tomography or magnetic resonance imaging scans.

It was important to determine whether participants believed that this program was reliable. The result showed that they agreed that the physicians and counselors were competent (94% and 89%), and that their privacy was good (92%); more than half did not consider to be re-examined by other health institute (Table 4). The relationship between the validity and reliability of the physician and participants' job was deemed as high in the military professional vs. those waiting for jobs ($c^2 = 49.523$, df = 27, $p = 0.005$). There were no differences in age, education, or fees. There was a strong association (90.7%) between the participants' satisfaction and their willingness to return for the next physical examination ($c^2 = 26.72$, df = 15, $p = 0.031$, Table 5). For example, when the fees and the level of satisfaction with the program were compared with the rate of return, there was a significant correlation ($c^2 = 15.23$, df = 5, $p = 0.009$). This also agreed with the expert validity of the physicians (93.8%) and counseling (88.5%) and the reliability (privacy, 92.4%) of the program ($c^2 = 226.48$, df = 9, $p = 0.0001$). In addition, we found that there was a high association between the satisfaction with this program and their willingness of participants to recommend the program to their relatives and friends. The number of satisfied participants who were willing to recommend or consider a recommendation to their relatives and friends was approximately 89.9% and 10.1%, respectively. In contrast, only 0.3% of dissatisfied participants would not recommend the program ($c^2 = 218.17$, df = 12, $p = 0.0001$).

Discussion

Patient satisfaction surveys can help healthcare providers improve the quality of healthcare, health education, and the development of healthcare policies[16-22]. This survey helped us to understand the consumers' needs and improve the health service

Table 4. Validity and Reliability of physical examination from participants' view

Category	Agree(%)	Disagree (%)
Physician	817 (93.8)	0
Consultants	746 (88.5)	2 (0.2)
Report	845 (97.0)	3 (0.3)
Re-examine	359 (41.4)	306 (35.2)
Privacy	802 (92.4)	1 (0.1)

Table 5. Analysis of participants' satisfaction and willing to return for the next physical examination

Category	Strongly satisfied	Satisfied	No comment	Dissatisfied	Total
Definite	117 (90.7)	359 (57.0)	19 (18.8)	0 (0)	495
Considered	12 (9.3)	251 (39.8)	66 (65.3)	0 (0)	329
No comment	0 (0)	7 (1.1)	4 (4.0)	3 (100)	11
Uncertain	0 (0)	13 (2.1)	12 (11.9)	0 (0)	28

within our self-paid physical checkup program. The quality of service can be judged by our satisfaction of the participants' needs[23]. The present results showed that most examination items were regarded as necessary, particularly those for gastroenteroscopy, colonoscopy, and abdominal echography. However, dental and physical examinations and HIV screening were regarded as the least important. Participants agreed that physicians and consultants were competent, and that their privacy was good; participants also believed that history taking, health consultation, and scheduling of return visits were necessary. Participants with higher annual family incomes were more satisfied with the services from the physicians than participants with lower family incomes. Men were more satisfied with the space and equipment than women. This reflected the trends of an affluent society and in gender differences that demanded a higher quality of medical service.

Because both the healthcare system and health insurance systems of Taiwan have changed rapidly over the past ten years, health care has improved tremendously. The competition between various medical institutes could have a significant impact on the quality of service. The improvement in the lower satisfaction rating for meal quality and some of the examination procedures between the first survey (2001) and the second survey (2011) reflected this trend. However, the quality of service is mainly based on medical personnel. Conceivably, the services of nurses may have been the most satisfactory in the surveys from both periods. The counseling service with the physicians was also regarded as highly reliable. Interestingly, participants wanted to speak with the physician directly but had less interest in routine physical examinations. This showed that participants wanted the physicians to be listeners and expected them to simply order particular screening tests[24-26]. Because medical technology has advanced tremendously, people often rely on high technology rather than common sense. Participants did not appreciate the fact that a physical examination could help physicians make a correct diagnosis and that laboratory tests and high-tech imaging support the clinical diagnosis but not vice versa[27]. This survey revealed both the needs of participants and key issues for health education. It is important that health education reaches the general population so that medical resources can be used more efficiently.

The findings also highlighted the significant role that the self-paid physical examination program played in our health care system. Among the examination items, gastroenteroscopy, colonoscopy, and abdominal echonography were on the top of the list of requested tests. Conversely, participants regarded the dental, eye, and physical examinations and the HIV screening test as less important. Older people are at risk of chronic diseases of the mouth, including dental infections (e.g., caries and periodontitis), tooth loss, benign mucosal lesions, and oral cancer[28]. The reason for lower satisfaction with the dental examinations was due to the lack of available dental care immediately after the checkup program. HIV screening was regarded as unnecessary by most participants who cared about their health. In the first survey, participants relayed their wish to include the bone density test and breast mammography in the program. This had been partially fulfilled with the implementation of free mammography for women aged 50–69 years (2010) and 45–69 years (2011) by the Bureau of Health Promotion, Department of Health, Taiwan.

Participants from other studies have also wished that advanced evidence-based clinical guidelines be used to limit the use of high technological examinations to the symptomatic patients with known/detectable disease[1,20]. A recent study even suggested that some routine tests were unnecessary for participants receiving preventive health examinations[26]. For those who had no symptoms or only mild illness, the results of these examinations had no significant meaning[24-29]. The physical examination might vary according to the differences in races, ages, and regionally prevalent diseases. Nevertheless, this program had met their needs and was not too expensive. Physicians could understand the participants' health status better and provide individual suggestions and post-checkup health education.

A good health examination program should meet the needs and be satisfactory for the participant. Therefore, the quality of service must be provided in a good facility and by trained personnel as part of the physical examination program. More importantly, from the view of participants, the competency of physicians and consultants is the key issue for a good physical examination program. Because participants strongly believed that certain procedures such as history taking, health consultation, and scheduling of

return visits were necessary, these procedures could be target areas for the improvement of the quality of service. Therefore, the participants' satisfaction would enhance their willingness to return for their next physical examination. The quality of service refers to the satisfaction of participants and also the validity of the physicians and consultants and the reliability of the program.

There were limitations of this study. First, two unrelated cross-sectional questionnaire surveys might not fully reflect the needs and demands of participants. Second, the results came from a specific portion of the population that was willing to answer most of the questionnaire and ignore the less interesting items. Third, the cost of a self-paid physical examination would exclude participants with lower socioeconomic status. Finally, the checkup program might not meet the demands of individuals, because of differences in age, culture, and job hazards.

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服務品質研究：自費體檢的病人滿意度之調查

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摘要

背景：健康檢查的目的是在早期發現、早期治療。因此有必要瞭解體檢過程是否符合顧客需求及滿意程度來提昇體檢服務品質。

方法：本研究以台中榮總自費住院體檢的受檢人為研究對象，採用深度訪談及問卷調查法進行資料蒐集。調查體檢過程是否符合顧客需求及滿意度。

結果：研究發現 2001 及 2011 年受檢人來院進行體檢的（92%）滿意的為 759 人（89.9%）及 785 人（90.1%）。對於健康檢查項目，多數的項目皆認為是必要的且符合需求。其中重視的為胃鏡、大腸鏡、腹部超音波三項，而牙科、醫生檢查身體、愛滋病檢查等項目較不重要。認為標準項目外，應再增加骨質密度、乳房超音波檢查等項目。受檢原因主要是因為上了年紀、感覺健康不佳或家人要求為主。服務品質的研究項目中，除了硬體設施外、人員服務品質方面，都有相當滿意的評價。認為看診醫師及會診醫師的職能不錯（94% and 89%），隱私也良好（92%），過半認為不需要再到其他機構檢查。認為項目中的病史詢問（92%）、健檢咨詢（98%）及安排覆診（93%）相當有必要。研究發現體檢高滿意度，其願意回檢的比例高達 97%。

結論：體檢服務品質，可以由是否符合顧客需求及滿意醫師及會診醫師的職能來驗証。整體而言由於服務品質受到肯定，受檢人對體檢服務滿意度高，回檢的意願相對提高，也願介紹親友。

關鍵詞：自費健檢、體檢服務滿意度、健康維持

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Case Report

Intranasal Z-plasty to Correct Internal Nasal Valve Stenosis: A Case Report

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Abstract

The nasal valve plays a crucial role in determining airflow characteristics of the nasal airway. In addition to respiration, the airflow turbulence created in this region regulates temperature, humidification, and filtration of inspired air. Stenosis of the nasal valve is not only esthetic but also a functional problem for the patient. Even mild stenosis can result in significant and problematic changes in airflow. There are several surgical approaches available to treat and improve constriction in the nasal valve region, from minimally invasive suture techniques to considerably more invasive open rhinoplasty approaches. Surgical correction is often not attempted because conventional surgical techniques require significant surgical dissection or cartilage grafting and have a high risk of relapse and external nasal deformity. Several patients with nasal valve stenosis do not desire a complex procedure, do not need cartilage augmentation, or do not want nose reshaping. For these patients, intranasal Z-plasty, a minimally invasive approach, has been well described to achieve true stenosis within the nasal valve, repair of cleft lip nasal deformities, and repair of narrowing and collapse of the internal nasal valve angle. We present the case of a 25-year-old female who had left-side internal nasal valve stenosis after facial trauma at childhood that was corrected by intranasal Z-plasty 1 year previously. Follow-up has shown that the stenosing process has not recurred and that an esthetically symmetrical aspect of the alar wings and nostrils was achieved.

Key words: nasal valve, intranasal Z-plasty

Introduction

The nasal valve is generally the narrowest part of the nose and is divided into external and internal portions. The external nasal valve is formed by the columella, nasal floor, and nasal rim (or caudal border of the lower lateral cartilage). The internal nasal valve (INV) is formed by the junction of the upper lateral cartilage and nasal septum and averages in the range 10–15°. This area is the narrowest part of the nasal airway. During inspiration, air is forced through this narrow area, which increases its speed and pressure. Immediately after passing the valve, the air expands in the bony cavum, creating turbulence that promotes contact between the air and mucosa. In this way, the inspired air is cleansed of particles, humidified, and heated or cooled (depending on its temperature)[1].

Characteristic signs of internal valve stenosis typically include an hourglass or pinched appearance of the middle segment of the nose, medial collapse of the alar cartilage on deep inspiration or deep alar grooves, unilateral or bilateral sidewall concavities, and inverted V deformities. Characteristic signs of external valve collapse include exaggerated concavity at the nasal alar groove and severe inward alar collapse on inspiration. A modified Cottle maneuver has been proposed to more specifically diagnose nasal valve stenosis. In this modified maneuver, an ear curette separately supports the lower and upper lateral cartilages to examine whether nasal patency

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has increased[2]. Nasal valve (NV) stenosis can show all degrees of narrowing, from slight stenosis to complete atresia, and can occur unilaterally or bilaterally. Narrowing of the internal nasal valve (INV) can be due to congenital deficiencies, post-traumatic deformities, or previous nasal surgery. Scar tissue is responsible for forming nasal vestibule stenosis in burn patients and after total nasal reconstruction, tumor removal, and correction of cleft lip noses[3].

First described by Sheen[4], spreader grafts are the gold standard technique for INV repair. Various surgical techniques have recently been developed to correct nasal valve dysfunction, including butterfly grafts, alar batten grafts, flaring sutures, and lateral suture suspensions[5]. However, surgical correction is not often attempted because conventional surgical techniques require significant surgical dissection or cartilage grafting and have a high risk of relapse and external nasal deformity. Several patients with static NV stenosis do not desire a complex procedure, do not need cartilage augmentation, or do not want nose reshaping. For these patients, intranasal Z-plasty, is justified without the use of cartilage grafting, extensive dissection, or cosmetic change. The Z-plasty procedure has been well described in both otolaryngology and plastic surgery literature for scar revision. This technique, which was first described by Horner in 1837, transversely transfers lateral skin excess to lengthen the area along the line of a tight scar, with a resulting increase in length-relieving contracture[6]. In many ways, the scroll region can be conceptualized as a scar contracture traversing the nasal valve region in patients with nasal valve obstruction. The Z-plasty procedure has been well described for true stenosis within the nasal valve and repair of cleft lip nasal deformities with narrowing and collapse of the internal nasal valve angle.

Intranasal Z-plasty involves a central intercartilaginous incision and side incisions oriented such that the anterior flap will be medially based and the posterior flap will be laterally based (Fig. 1). The triangular flaps are subsequently elevated. The caudal border of the upper lateral cartilage is removed to accommodate flap mobilization. The flaps are subsequently interdigitated and sutured into position with 4-0 chromic sutures. Bacitracin ointment is applied to the bolsters and all suture lines, and the bolsters are left in place for 7–10 days. The patient is administered oral antistaphylococcal antibiotics to prevent wound infections and toxic shock syndrome and oral analgesics for wound pain[7].

In this study, we present the case of a 25-year-old female who had left-side internal nasal valve stenosis after facial trauma in childhood that was corrected by intranasal Z-plasty 1 year ago.

Case Report

A 25-year-old female underwent surgical repair of a left nose avulsion injury because of facial trauma at another hospital when she was a teenager. Severe hemorrhage at that time required anterior nasal packing. The nostril and mucosa were injured, and infection and scarring led to moderate deformity of the left nostril. Subsequently, she complained of moderate-to-severe nasal obstruction of the left side of her nose that was not effectively relieved by medication. Physical examination showed that the left side of the nostril was smaller than the right, and a modified Cottle maneuver was used to demonstrate

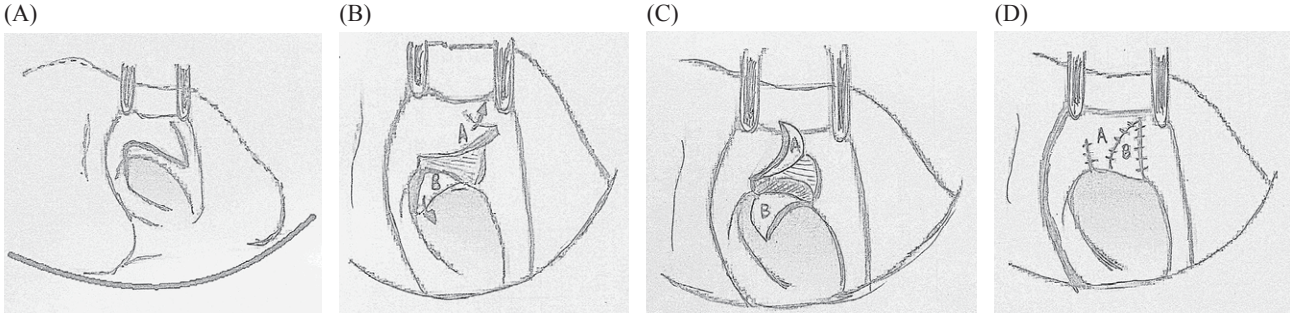

Fig. 1 Intranasal Z-plasty procedure. (A) The incisions are created such that the central incision is an intercartilaginous incision, and the side incisions are oriented such that the anterior flap will be medially based and the posterior flap will be laterally based. (B) The triangular flaps A and B are then elevated. Note the underlying caudal border of the upper lateral cartilage. (C) The caudal border of the upper lateral cartilage is then removed to make room for mobilization of flaps A and B. (D) The flaps are then interdigitated and sutured into position.

that stenotic scarring primarily involved the internal nasal valve area. Physical examination also showed that there was no loss of cartilage or presence of a bony structure deformity of the nose at the internal nasal valve area. The central scar (Fig. 2) was approximately 3.3-mm wide, 2.1-mm long, and 1.0-mm thick at the junction of the upper lateral cartilage and nasal septum. In the intranasal Z-plasty procedure, 3.5-mm long flaps were designed at an approximate 30° angle running transversely to lengthen the area along the line of a tight scar (see Fig. 1). After splitting the stenotic scar and removing all fibrotic tissue from the stenotic area, 6 interrupted 4-0 chromic sutures were used to close the mucosal flaps. The postoperative course was uneventful and without complication. The procedure resulted in nostrils of equal width and good shape with corrected INV position, which can be observed in the photograph taken 1 year after the surgery (Fig. 3).

Discussion

The internal nasal valve angle formed by the upper lateral cartilage connection to the nasal septum is of fixed dimensions. The flexibility of these structures allows the nasal valve to act as a Starling resistor, which can limit airflow by collapsing when it is rapid, with partial collapse of the upper lateral cartilages occurring at a flow rate of approximately 30 L/min[1]. Patients with internal valve stenosis primarily report nasal obstruction. Other symptoms are crusting and bleeding, but these are more often associated with septal deviation. Diagnosis can be difficult if the physician does not visualize the valvular area. Examining the valve without disturbing it with a nasal speculum is important because the speculum generally opens the valve. Sometimes, trimming the vibrissae is necessary to obtain a clearer view of the valve. Another method is to use a 0° endoscope. A positive Cottle maneuver, which is not always reliable, is generally indicative of nasal valve collapse. In the classic description, the patient's cheek is lateralized; this movement is translated to the nose, where the soft tissue of the nasal valve is lateralized[2].

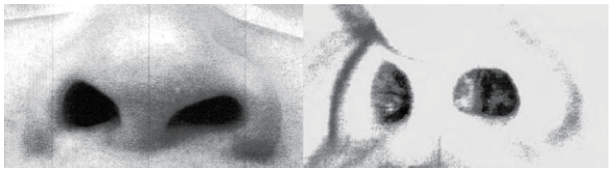

Fig. 2 Preoperative photography.

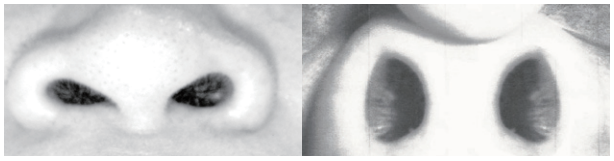

Fig. 3 Postoperative photography.

Unilateral or bilateral stenosis of the NV has to be corrected not only for esthetic reasons but also for functional ones. If stenosis is encountered in children, early surgery is important. The selected surgical procedure depends on the location of stenosis, thickness of the obstructing wall, and condition of the ala. In general, scarring and retraction in the NV are due to a lack of nasal lining, sometimes combined with a loss of cartilage. Incisions for rhinoplasty that reach the lateral angle of the vestibular floor at the alar border may also cause cicatricial stenosis of the NV[3]. In rhinoplasty, NV dysfunction can result from aggressive narrowing of the nasal tip, over-resection of the lateral crus, displacement of weak alar cartilages, excessive narrowing of the dorsum, over-resection of the upper lateral cartilages, or displacement of short nasal bones. Most procedures that specifically target the valve angle use rhinoplasty approaches, most commonly the open rhinoplasty approach[3-5].

Several techniques are used to correct a stenotic or collapsed nasal valve. A common goal is to open the valve to restore the appropriate anatomy. Various surgical techniques have been developed to correct nasal valve dysfunction, including spreader grafts, butterfly grafts, alar batten grafts, flaring sutures, and lateral cartilage suture suspensions. Spreader grafts can be sutured along the length of the upper lateral cartilage to increase the cross-sectional area of the internal nasal valve and augment the structure to prevent collapse[3,4,6].The endonasal technique is less invasive and can be used in conjunction with other procedures[8]. Butterfly grafts are made from left ear conchal cartilage and are placed on the nasal dorsum in a subsuperficial musculoaponeurotic system plane and sutured to the upper lateral cartilages to stent open the INV; it may also be placed through a closed approach[9]. Alar batten grafts are generally placed in pockets just superior to the lower lateral cartilages. The grafts are placed in a subcutaneous pocket and can also be placed inferior

to the lower lateral cartilage when the cartilages are cephalically positioned[10]. Flaring sutures are bilaterally placed sutures tied over the dorsum. The dorsal septum acts as a fulcrum to flare the upper lateral cartilage, widening and supporting the internal valve, and subsequently dilates the caudal margin of the upper lateral cartilages and directly improves the INV angle[11]. Lateral cartilage suture suspensions were approached with infraorbital incisions using multiple suspension sutures to elevate the upper lateral cartilage superolaterally and alleviate the nasal valve stenosis[12]. However, all the above mentioned approaches their drawbacks, which include requiring prolonged healing times from the open rhinoplasty approach, separate donor sites for grafts, or the use of foreign bodies that entail the risk of infection or rejection and offer questionable longevity. Intranasal Z-plasty avoids several of these problems[7].

The use of Z-plasty to relieve contracture has been widely accepted in the field of facial plastic and reconstructive surgery. Intranasal Z-plasty offers several advantages. First, the procedure is minimally invasive. It does not require open rhinoplasty with extended healing times as with spreader graft placement and does not require tissue grafting. The procedure is entirely performed intranasally, and there is significantly less tissue dissection than in closed-tip rhinoplasty. While the suture suspension technique also requires less dissection, it relies on a foreign body for valve suspension and may theoretically be less permanent because suture fixation to soft tissues may considerably relax with time. Intranasal Z-plasty appears to offer a minimally invasive technique that improves nasal airflow due to INV stenosis, with less reliance on extensive tissue dissection, grafting, and foreign bodies than that required with other techniques. The procedure appears to significantly reduce subjective nasal airflow complaints of patients, has a negligible complication rate, and minimal effect on the external appearance of the nose, if any. Perhaps the only drawback is the learning curve because the procedure can be conceptually and technically challenging and requires experience to master.

In conclusion, the surgical correction performed in this report specifically targets the uppermost anatomical aspect of the NV. Consequently, most of the widening occurs near the junction of the upper lateral cartilage with the septum. This minimally invasive surgical method appears to provide the most dramatic relief of obstructions compared with other methods. Intranasal Z-plasty appears to be a safe, effective, and relatively noninvasive technique for repair of internal nasal valve stenosis.

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鼻內 Z- 字型成型術矯治內鼻閥狹窄：案例報告

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摘要

鼻閥是決定鼻道內氣流屬性的關鍵結構，鼻閥範圍產生的氣渦流不僅調節呼吸，也控制溫度、濕度與過濾吸入的空氣。鼻閥的狹窄對病人而言，不只是外觀上的、也是功能上問題。即使是輕微的鼻閥狹窄也能引起顯著、且造成困擾的鼻道內氣渦流改變。目前有許多手術的方式，從微創性的縫合術到侵襲性的開放式鼻整形術，可以利用來治療與改變鼻閥區的狹窄程度。人們常不願意嘗試手術矯治，乃是因為常規的鼻整形手術法，常常需要明顯的切割傷口、或是應用軟骨移植，而且有高度復發性與鼻外觀變型的風險。許多有鼻閥狹窄的病人並不想要複雜的手術法、用軟骨移植增強，更不願意被鼻型重建。本篇文章為了這群病患提供一種微創性的手術方式，鼻內 Z- 字型成型術；這個術式已經有完整的文獻記載來應用於真性鼻閥狹窄，也用來修補唇額裂變型以及重建變窄和塌陷性的內鼻閥角。本文我們報告一位 25 歲女性，因為之前兒童期的臉部外傷後造成內鼻閥部變形狹窄。一年前經由鼻內 Z- 字型成型術來矯治此一疾病。因而成功地阻止鼻閥變窄之復發，也使得鼻翼和鼻孔有達到容貌上對稱性。

關鍵詞：鼻閥（nasal valve）、鼻內 Z- 字型成型術（intranasal Z-plasty）

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Case Report

Schwannoma of the Stomach and Esophagus: A Case Report

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Abstract

Schwannomas of the gastrointestinal (GI) tract are generally benign and slow-growing tumors that originate from the mesenchymal stem cells of the GI wall. These tumors are quite rare and must be differentiated from other submucosal tumors, such as the more common gastrointestinal stromal tumors, that have malignant behavior. We report a case of schwannoma of the esophagus and stomach in a 75-year-old man who presented with symptoms of upper GI bleeding. Upper GI endoscopy revealed an ulcerated mass in the cardiac region of the stomach. A computed tomography scan showed a large mass at the distal esophagus and cardia of the stomach. Endoscopic ultrasound-guided trucut biopsy was performed for histological diagnosis. Immunohistochemical analysis of the biopsy specimen revealed positivity for S-100 protein and negativity for c-kit and smooth muscle actin. These findings were consistent with the diagnosis of schwannoma.

Key words: schwannoma, stomach, esophagus

Introduction

Gastrointestinal (GI) schwannomas are rare mesenchymal tumors that originate from the mesenchymal stem cells of the GI wall. They are part of a heterogeneous group of neoplasms that includes gastrointestinal stromal tumors (GISTs), leiomyomas, leiomyosarcomas, neurofibromas, ganglioneuromas, paragangliomas, lipomas, granular cell tumors, and glomus tumors. Schwannomas most commonly occur in the stomach, representing 0.2% of all gastric tumors, followed by the colon and rectum. Esophageal and small intestinal schwannomas have rarely been reported[1-3]. Immunohistochemically, the diagnosis of schwannoma is confirmed by the presence of S-100 and vimentin and the absence of smooth muscle actin and c-kit[2]. Because most schwannomas are usually benign and slow growing with excellent prognosis, complete surgical removal is sufficient for treatment. However, malignant transformations, although exceedingly rare, have been reported[4,5]. Here we present a case of schwannoma of the stomach and esophagus with upper GI bleeding.

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Case Report

The patient was a 75-year-old male who presented to our ER with passage of tarry stools for approximately 10 days, along with dizziness. He denied a history of weight loss, fever, hemoptysis, or hematemesis. His vital signs were stable and his hemoglobin levels and hematocrit were 10.6 g/dl and 35.5%, respectively. A chest X-ray revealed a prominent round mass opacity at the lower mediastinum (Fig. 1). An upper GI endoscopy was performed, which revealed external compression of the esophageal wall with normal overlying mucosa. A large ulcerated submucosal mass approximately 5–6 cm in size was noted at the cardia of the stomach (Fig. 2). A biopsy of the mass revealed a gastric ulcer with granulation tissue. A CT scan was performed, which revealed a

large fusiform mass (12 × 10 × 6.5 cm) in the posterior aspect of the distal esophagus, displacing the esophagus anteriorly (Fig. 3). A 5.3-cm tumor at the cardia of the stomach was also noted. GIST arising from the distal esophagus and cardia of the stomach was strongly suspected. Endoscopic ultrasound (EUS) was performed, which revealed a hypoechoic mass arising from the muscularis propria of the stomach wall. The patient then underwent an EUS-guided trucut biopsy. Histological and immunohistochemical findings of the biopsy specimen were consistent with the diagnosis of schwannoma, showing positivity for S-100 and vimentin and negativity for CD117, CD34, and desmin (Fig. 4, 5). The patient was referred for surgery but was advised to receive conservative management because of the high risk of a difficult surgery.

Discussion

GI schwannoma was first described by Daimaru et al. in 1988 with a series of 24 cases[2]. The tumors arise from the Schwann cells of the neural plexus of the GI wall, tend to occur during the fifth to sixth decades of life, and are more common in women[1,6]. Schwannomas occur predominantly in the stomach and rarely in the colon and esophagus, and can range from 0.5 to 11 cm in the greatest dimension (mean: 2.8–4.5 cm). The upper and middle thirds of the stomach are more frequently involved than the distal third[7]. They principally involve the submucosa and muscularis propria and are usually covered by an intact mucosa[2,8].

The clinical presentation varies and can be site-specific. Patients are usually asymptomatic, although

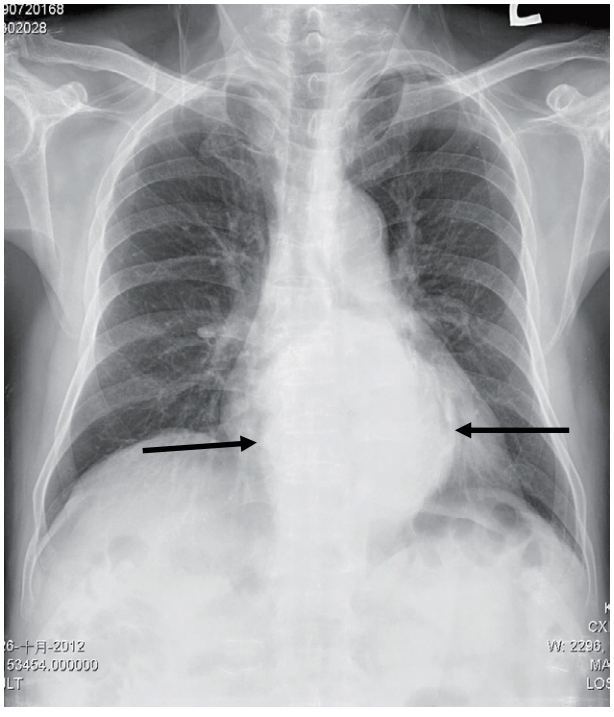

Fig. 1 Chest x-ray revealed a prominent round mass opacity at the lower mediastinum (arrows).

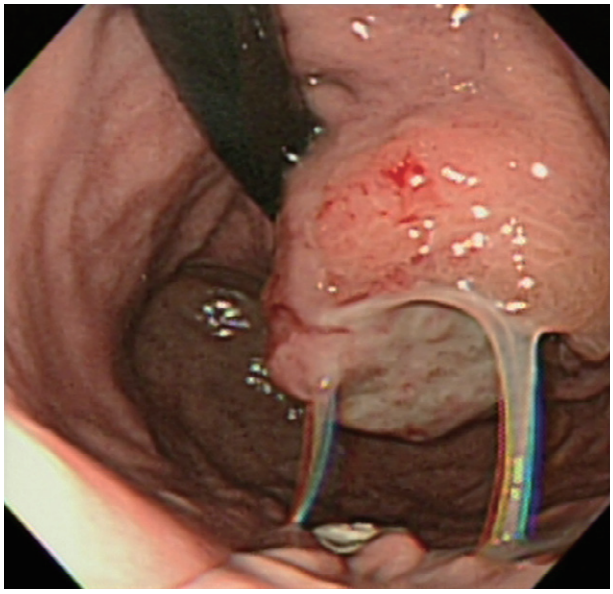

Fig. 2 Upper GI endoscopy revealed a large ulcerated submucosal mass at the cardia of the stomach.

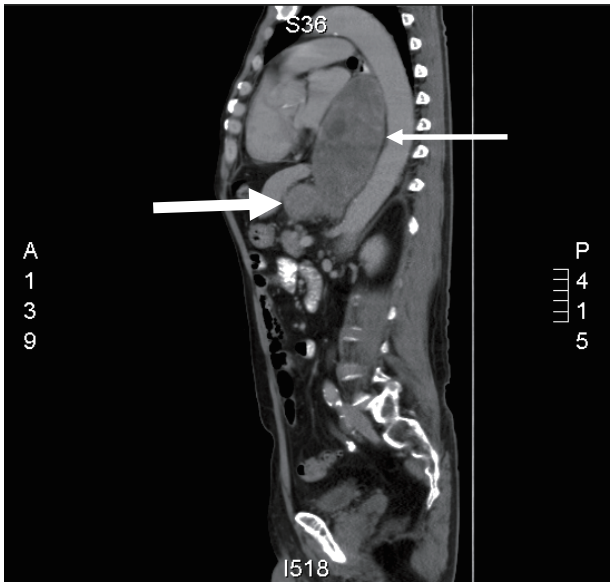

Fig. 3 CT scan (sagittal view) with contrast revealed a large fusiform mass in the posterior aspect of the distal esophagus (thin arrow) and cardia of the stomach (thick arrow).

the tumors may cause upper GI bleeding, abdominal pain and discomfort, or appear as a palpable mass[1,3,8]. Bleeding usually results from ulceration of the tumor, similar to the case in our patient. In esophageal schwannoma, patients may present with symptoms of dysphagia and chest pain.

GI schwannomas can vary from small dome-shaped submucosal tumors to large fungating tumors with central ulceration. The tumors are well-circumscribed but not encapsulated and may show rubbery to firm consistency with yellow–white to tan color, glistening, and trabeculated cut surfaces[7].

On computed tomography, schwannomas are often homogeneous, with minimal to marked enhancement after contrast. The tumors do not exhibit cystic change, cavitary formation, necrosis, or calcification. These features distinguish schwannomas from GISTs, which have a much more heterogeneous appearance because of the presence of hemorrhage, necrosis, and cystic change[3]. Sonographic findings include a homogeneous hypoechoic mass with low internal echoes and the presence of marginal haloes[9]. Magnetic resonance imaging (MRI) can be important in defining the exact location and extent of the tumor with displacement of surrounding organs or vessels. Typical MRI findings are sharply demarcated, strongly enhancing tumors with low to medium signal intensity on T1-weighted images and high signal intensity on T2-weighted images[10].

The definitive diagnosis of schwannomas is determined by microscopic examination and immunohistochemical staining. Histologically, schwannomas are spindle cell tumors without epithelioid features, with a peripheral cuff of lymphoid tissue[8]. Prominent lymphoid cuffs surrounding the tumor are pathognomonic of GI schwannomas, although immunohistochemical examination is needed for confirmation[7]. Immunohistochemically, the tumor cells are positive for S-100 and vimentin, and negative for CD117 (c-kit protein), CD34, desmin, and smooth muscle actin[11,12]. This immunohistochemical staining is necessary to differentiate schwannomas from other mesenchymal tumors, specifically GISTs, which are positive for CD117 and CD34. It is important to differentiate schwannomas from GISTs because the latter may be malignant or have malignant potential.

The prognosis for patients with schwannomas of the GI tract is generally excellent because the majority of them follow a benign clinical course. Surgical excision is recommended because of uncertainty of preoperative diagnosis and the possibility of malignancy[13]. However, for patients with benign,

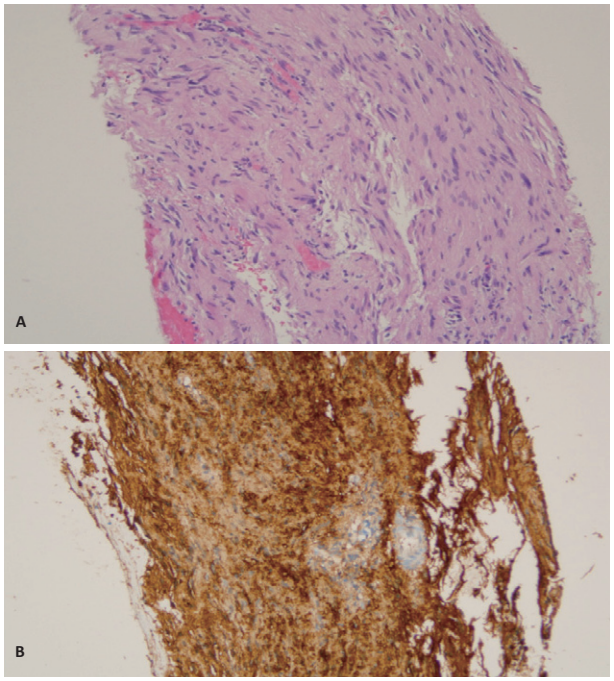

Fig. 4 (A) Hematoxylin-eosin staining showing broad bundle of spindle cells (200X). (B) Immunohistochemical analysis showed the tumor cells were positive for S-100 protein (200X).

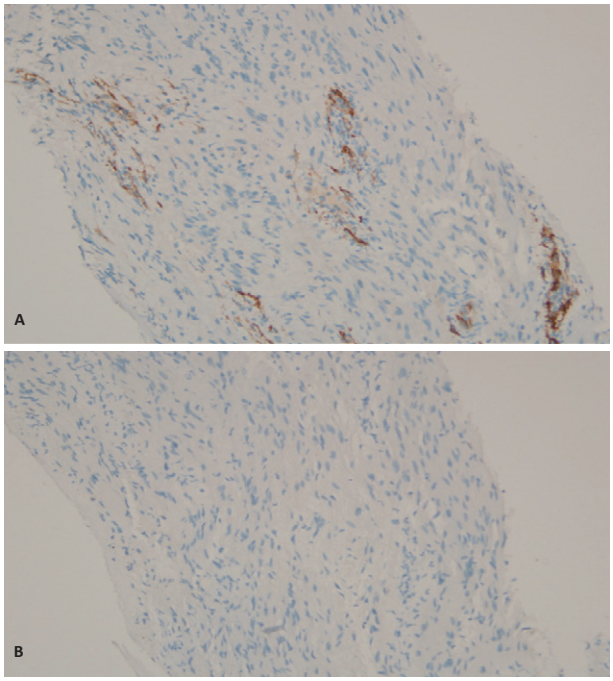

Fig. 5 (A) Immunohistochemical analysis showed the tumor cells were negative for CD34 (200X). (B) Negative c-Kit marker for GIST (200X).

asymptomatic schwannomas, conservative management is suggested[14].

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胃食道的 Schwannoma：病例報告

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摘要

胃腸道的許旺氏細胞瘤（schwannoma）通常為良性，且源自於胃腸道壁間質層的幹細胞緩慢生長。此類的腫瘤臨床上相當少見，且在診斷時需與臨床上較常見的惡性胃腸道基質瘤做鑑別診斷。

病例報告：75 歲男性，求診時主訴症狀為上消化道出血，最終診斷為食道與胃部的許旺氏細胞瘤。行胃鏡檢查，在胃體發現一潰瘍性的病灶；電腦斷層檢查則發現在遠端食道與胃體有一巨大腫瘤；之後行內視鏡超音波引導下切割針穿刺活檢，其免疫組織化學分析結果顯示 s-100 蛋白陽性以及 c-kit 、平滑肌肌動蛋白陰性。這些證據與最終診斷為許旺氏細胞瘤的結果相符。

關鍵詞：胃食道 schwannoma

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Case Report

Bone Cement Implantation Syndrome: A Case Report and Literature Review

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Abstract

Cardiopulmonary dysfunction resulting from cement arthroplasty procedures is known as bone cement implantation syndrome (BCIS). Here we report the case of an 82-year-old woman who suffered from lethal progression of heart block after application of bone cement into the intertrochanteric area. The possible etiology, associated risk factors, and preventive measures for BCIS have been reviewed.

Key words: Bone cement, Intraoperative complications, BCIS, Implantation syndrome

Introduction

Bone cement implantation syndrome (BCIS) is a rare but potentially life-threatening intraoperative complication that occurs during cemented orthopedic surgery. It is characterized by hypoxia, hypotension, or both, and/or unexpected loss of consciousness in conjunction with cementation, prosthesis insertion, joint reduction, or occasionally during limb tourniquet deflation maneuvers. Cardiovascular collapse following the use of bone cement (methyl methacrylate) in bone surgery has been reported previously; however, reports of reactions to PRO-DENSE® (a bioceramic $CaSO_4/Ca(PO_3)_2$ composite bone cement) following arthroplasty have been rare. Here we report the case of an 82-year-old woman hospitalized for elective orthopedic surgery complicated by intraoperative cardiac arrest during cemented hemiarthroplasty performed using the PRO-DENSE® bone graft substitute.

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Case Report

An 82-year-old woman was admitted to our hospital with a history of right intertrochanteric fracture due to a fall 3 days before admission and chronic renal failure treated by regular hemodialysis three times per week. Other medical history included hypertension and diabetes mellitus treated by a regular medication regimen. She also had a history of ocular myasthenia, which was controlled by pyridostigmine administration, and coronary artery disease treated twice previously by percutaneous transluminal coronary angioplasty. Echocardiography revealed inferior and lateral wall hypokinesis with mild left ventricular dysfunction, confirmed by an ejection fraction of 56%. All preoperative biochemical and hematological profiles were within acceptable limits. On admission, our patient was stabilized with anti-hypertensive medications and blood sugar control. After 3 days of treatment, most of the patient's symptoms resolved; thus, we decided to operate via open reduction and internal fixation using a Knowles pin and Pro-Dense bone substitute augmentation. Because most of the patient's daily life was spent being bedridden and considering the patient's poor physical condition, we

predetermined a suitable Knowels pin for fixation in order to shorten the surgical duration. On the day of surgery, the patient was conscious and coherent, with a pulse rate of 79 beats/min and a blood pressure of 152/70 mmHg in the supine position. The right internal jugular vein was cannulated to assess central venous pressure (CVP), and spinal anesthesia was administered at 10 mg of 0.5% heavy bupivacaine with the paresthesia level reaching T10. The patient was hemodynamically stable with a systolic pressure of 120 mmHg, heart rate of approximately 75 beats/min, and SaO_2 saturation of about 99% with 100% oxygen under a face mask. Surgery was performed in the supine position on a fracture table. Her general condition was satisfactory during the first 50 min of anesthesia as her systolic blood pressure remained above 110 mmHg. Normal saline (350 ml) was administered intravenously and the estimated blood loss was 10 ml within the first hour. A standard posterior approach was adopted, in which we made a small hole over the greater trochanter area and injected 10 ml of PRO-DENSE® bone substitute into the intertrochanteric area. Approximately 30 s later, sudden and progressive bradycardia of 30–40 beats/min developed and the patient's blood pressure decreased to a level that was not detectable using a non-invasive blood pressure monitor. Adrenaline (1 mg) was then injected intravenously but was not useful. Emergency endotracheal intubation and ventilation with 100% oxygen and external cardiac massage was started. Rapid infusion of a total of 1000 ml of normal saline and 1 mg of adrenaline was administered intravenously, and this was repeated every 3 min for a total dosage of 10 mg. CVP was maintained at about 12 cm throughout the treatment period. During the following one hour of resuscitation, ventricular fibrillation persisted even after defibrillation with 360 J of direct current and acidosis correction by administration of bicarbonate. After five cycles of cardiopulmonary resuscitation, the patient exhibited pulseless electric activity and could not be revived after one hour of attempting resuscitation, and was thus pronounced dead in the intensive care unit. The patient's relatives did not consent to an autopsy.

Discussion

PRO-DENSE® is a bioceramic calcium sulfate/calcium phosphate composite bone cement. However, injection of calcium-based cement reportedly presents a risk of adverse reactions. For example, Krebs et al.[1] demonstrated in an animal model that intravascular injection of calcium phosphate cement can induce pulmonary embolism. A previous animal study demonstrated that injection of calcium chloride into sheep caused "labored respiration" and tachycardia[2] In addition, there are case reports of vasoconstriction and death following intravascular calcium infusion.[3] An allergic reaction to calcium phosphate cements has also been reported.[4] As a final consideration, it is possible that injection pressure causes vascular dissemination. Cement placement in sealing and prosthesis insertion may result in pressurization of the intramedullary canal as increased intramedullary pressure can force medullary fat into the blood vessels, resulting in cardiovascular and pulmonary complications.[5]

Although BCIS is an established entity, there is no widely accepted definition of this disorder because cases range from mild transient hypoxemia to more severe presentations resulting in death.

BCIS severity is classified as follows:[6]

Grade 1: moderate hypoxia (SpO_2 < 94%) or hypotension (decrease in systolic blood pressure (SBP) of >20%).

Grade 2: severe hypoxia (SpO_2 < 88%) or hypotension (decrease in SBP of >40%) or unexpected loss of consciousness.

Grade 3: cardiovascular collapse requiring cardiopulmonary resuscitation.

All clinical features were found to be temporary and related to one of the following steps: femoral reaming, cement and prosthesis implantation, or joint reduction.[7–11] The most frequent signs and symptoms were as follows:

- Decrease in arterial oxygen saturation[7,8,11–14]
- Decrease in systemic blood pressure[8,9,13–15]
- Increase in pulmonary vascular resistance[14,16–19]
- Decrease in right ventricular (RV) ejection fraction, stroke volume, and/or cardiac output[9,18,21]
- Bradycardia[8,14,23]
- Cardiac arrest[8,13,15,17,24]

The incidence of BCIS varies widely among reports in the literature, and fatalities are seemingly rare. The etiology and pathophysiology of BCIS have not been completely elucidated, although various theories have been proposed, including the following:

- Systemic toxicity of polymethyl methacrylate

monomers into the circulation during cementation[26–28]

· Immunological mechanisms, i.e., a type I hypersensitivity/anaphylactic reaction to the acrylic monomer or calcium phosphate, which may be a causative factor of acute events because BCIS shares many clinical features with anaphylactic shock.[4] Patients who develop hypotension during cementing procedures were shown to have significantly increased histamine levels, and antihistamines seemed to convey a protective effect against the development of hypotension.[29]

· Showers of emboli, named "snow flurry" by Lafont et al.,[30] have been observed by transesophageal echocardiography during both cemented and non-cemented procedures. Suspected constituents of these emboli include cement particles, bone particles, air generated from mono-to-poly methacrylate conversion, and bone marrow tissue.[12,20,31–33] Many studies have reported the nature and effect of these emboli, but with different and often contradictory results. For example, Hayakawa et al.[40] reported that these "snow flurries" do not arise from cement material, but rather are produced by both cemented and non-cemented procedures. Using inert bone wax under high intramedullary pressure, Orsini et al.[31] demonstrated that generation of higher intramedullary pressure in a cemented procedure as opposed to the cement material itself results in the generation of a greater number of microemboli and more significant cardiorespiratory changes than those by non-cemented procedures;[41] this is in accordance with the most accepted current theory of BCIS pathogenesis.[42,43]

Risk factors for the development of BCIS include the following:

· Underlying cardiovascular disease: RV dysfunction, coronary artery disease, and/or preexisting pulmonary arterial hypertension[14,32]
· Advanced age[13–15]
· Osteoporosis by an increased risk of emboli generation due to enlarged porous cavities[13–15]
· Fracture diagnosis as an indication for surgery, especially intertrochanteric in type or those associated with underlying malignancy[14,34,35]
· Metastatic bone disease[32,36]
· Femoral canal diameter of >21 mm[37]
· Previously noninstrumented femoral canal[13,36]
· Patent foramen ovale (paradoxical embolus)[30]

Anesthetic risk for BCIS can be reduced by meticulous preoperative examination to rule out significant cardiac, pulmonary, or metastatic bone diseases during complete investigation of comorbid diseases and careful pre-optimization of patients. Increasing the inspired concentration of oxygen should be considered at the time of cementation.[19] Furthermore, hemodynamic monitoring should be considered for all cases that are particularly at risk for BCIS.[19]

Surgical risk reduction strategies for BCIS include medullary lavage, restoration of hemostasis before cement insertion, minimization of prosthesis length, use non-cemented prosthesis, and ventilation of the medulla,[39] as venting the medulla permits air to escape from the end of the cement plug and reduces the risk of air embolus.

A fall in end-tidal carbon dioxide concentration can be the first sign of embolism and should alert the anesthesiologist. In awake patients, initial symptoms can include dyspnea and altered sensorium.[25] If there is evidence of BCIS, inspired oxygen concentration should be administered at 100% and continued to the postoperative period. Furthermore, hemodynamic collapse in BCIS should be treated in accordance with that for right ventricular failure[43] and aggressive resuscitation by intravenous therapy should be initiated, as previously recommended.[44]

In the present case, our patient was a high-risk candidate for BCIS because she was an elderly with cardiovascular disease and decreased functional reserve due to many predisposing factors (i.e., age of 82 years, chronic renal failure, diabetes mellitus, hypertension, and coronary artery disease). The manifestation of cardiac arrest in our patient was closely related to the injection of PRO-DENSE^{R} bone cement into the intertrochanteric area during a period of hemodynamic stability. Although there was no direct pathological or autopsy evidence available in this case, we speculated that the bone cement was the leading cause of cardiac arrest, which may have been due initial cement-induced sudden and severe hypotension that remained undetected using a non-invasive blood pressure monitor. Secondly, an anaphylactic reaction to the injected calcium phosphate may have occurred;[2,4] thirdly, an acute massive cement-induced pulmonary embolism may be a cause.[1,30,31] Fourthly, a combination of the aforementioned factors may be responsible. The timing of the onset of intraoperative cardiovascular

collapse may have occurred immediately after administration of bone cement or 2–15 min afterward.[25,45] Nonetheless, our patient developed sudden bradycardia and hypotension, resulting in unconsciousness and was classified as grade III BCIS. Despite our best efforts, we were unable to revive the patient.

In conclusion, extra precaution is necessary while using bone cement in patients with comorbid diseases, and inspired oxygen concentration should be increased while using bone cement. Furthermore, the patient's hemodynamic status should be closely monitored during and after use of bone cement to prevent unexpected fatalities. Early and aggressive resuscitation with the use of vasopressors, establishment of invasive hemodynamic monitoring (e.g., intra-arterial blood pressure monitoring), and surgical modifications are key for preventing catastrophic outcomes.

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骨水泥植入症侯群：一病例報告及文獻回顧

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摘要

關節整形術使用骨水泥的過程中造成病患的心肺功能喪失被稱為骨水泥植入症侯群。我們報告一位八十二歲的女性病患在接受股骨部位的骨水泥植入時發生致命性心臟功能喪失。它的可能發生原因，危險因子和預防方法，我們作一文獻回顧。

關鍵詞：骨水泥、術中併發症、植入症侯群

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Case Report

Epidural Blood Patch for Spontaneous Intracranial Hypotension Performed in Neurology Practice

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Abstract

An epidural blood patch is a primary treatment for spontaneous intracranial hypotension. The traditional epidural blood patch is not readily available in some institutions, including referral centers. Here, we report an alternative method for performing epidural blood patch that is based on the experience in neurology practice. In this method, the epidural space is located by checking the tissue resistance in a stepwise manner using a spinal needle and tuberculin syringe. The procedures are described here in detail. Six consecutive cases of spontaneous intracranial hypotension were successfully treated with this alternative method for performing an epidural blood patch.

Key words: Epidural blood patch, Loss of resistance, Myelography, Pachymeningeal enhancement, Spontaneous intracranial hypotension.

Introduction

An epidural blood patch (EBP) is the treatment of choice for spontaneous intracranial hypotension (SIH). EBP is usually performed with the loss-of-resistance (LoR) technique using a 16/18 gauge(G) Tuohy needle and a low resistance syringe. However, this procedure is not readily available in all institutions; hence, an alternative method used in neurology practice might be useful. Here, we describe this alternative method for performing EBP, which uses a 22/24 G spinal needle and a 1-ml tuberculin syringe. EBPs performed with this method have successfully eliminated headache in five cases of SIH and one case of spontaneous cerebrospinal fluid (CSF) leakage related to cervical vertebrate dysplasia.

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Case Report

Between 2008 and 2012, we examined five consecutive cases that fulfilled the criteria for SIH established by International Classification of Headache Disorders, Second Edition, and one case of spontaneous CSF leakage related to cervical vertebrate dysplasia (age range: 29-66, female:male = 5:1). Clinical presentations of these six patients included different degrees of postural diffuse headache and dizziness occurring daily during casual activities. Most of the patients reported experiencing persistent tightness in the neck. Case 6 experienced double vision and tinnitus. Except for case 5, no patients had history of lumbar puncture or spinal trauma. Case 5 had previously received two EBPs at other hospitals and suffered from a relapsing headache with vomiting and photophobia. All six cases showed diffuse pachymeningeal enhancement on cranial magnetic resonance imaging (MRI). Five cases underwent MR myelography (MRM), and four of these cases showed epidural fluid collection. Conservative treatments, including restrictive bed rest,

prednisolone, ergotamine tartrate, non-steroidal anti-inflammatory drugs, and intravenous crystalloid fluids, failed to permanently relieve the postural headache. All six patients eventually received EBPs that were performed with the alternative method described here.

To assure adequate CSF replenishment, the patients received a bolus intravenous fluid infusion, and were confined to complete bed rest at least 24 h before undergoing the EBP procedure. The depth of the epidural space was estimated using a lateral spinal X-ray or sagittal spinal MRI. Local anesthesia was administered subcutaneously, rather than deeply, to retain pain sensitivity in the paraspinal tissue. With the patient in the lateral knee–chest position, a 22/24 G spinal needle was inserted via the midline approach. At approximately two-thirds of the estimated depth, the stylet was removed from the needle and a tuberculin syringe preloaded with 0.5 ml saline was connected. The tip of the needle remained positioned in the ligament interspinous, and the tuberculin syringe plunger was pushed slightly to determine the amount of tissue resistance. The syringe was then disconnected, the stylet was replaced, and the needle was advanced approximately 3 mm. After advancing the needle, the stylet was again removed to determine the tissue resistance using the same saline-primed tuberculin syringe. These steps were repeated until a change in the tissue resistance was noted. The resistance became distinctively higher when the needle tip entered the ligamentum flavum, which indicated further caution was required in subsequent needle advancements. When the needle tip entered the epidural space, the tissue resistance decreased dramatically. The syringe was then briefly disconnected to ensure there was no persistent CSF return. Approximately 3 ml of saline was injected to confirm the tip was located in the epidural space; this injection was typically painless and free of resistance. Case 6 experienced panic and agitation during the needle puncture, and therefore was sedated and received a contrast medium injection under a fluoroscope to confirm the final tip location after pressure-checks had been completed.

For blood patching, autologous blood of each patient was withdrawn and injected under sterile conditions. The injection was stopped if the patient experienced discomfort in the back or an extremity. In case 6, who was sedated, the blood volume injected was limited to 15 ml. Throughout the procedure, the bevel of the spinal needle was kept in a cephalad-to-caudal direction. Finally, the patient was placed in the Trendelenburg position for at least 1 h. Cases 1 and 2 required two EBPs to relieve their symptoms, whereas symptoms of the remaining patients improved with a single lumbar patch. Only case 2 reported neck and shoulder soreness, which improved after several days without intervention. There were no major complications or recurrences of postural headache between the procedure and the outpatient follow-up. The clinical findings and treatment results for all cases are listed in Table 1. MRM for case 1 before and after the EBP treatment are presented in Figure 1.

Table 1. Patient characters, image finding, management and outcome.

	Case 1 F	Case 2 F	Case 3 M	Case 4 F	Case 5 F	Case 6 F
Height/weight and BMI	165cm / 55kg / 21.2	164cm / 57kg / 21.1	167cm / 62kg / 22.2	158cm / 60kg / 24	166cm / 55kg / 20	150cm / 56kg / 24.9
Days of symptoms before our patch	8 days	60 days	10 days	30 days	21 days	90 days
Pachymeningeal enhancement	Yes	Yes	Yes	Yes	Yes	Yes
MR myelography	Positive	Positive	Positive	Not performed	Negative	Positive
Estimated location of leak	Upper thoracic	Lower cervical	Lower thoracic	-	-	Upper cervical
Location of first patch	T3/4	C6/7	L4/5	L4/5	L4/5	L4/5
Location of second patch	T12/L1	L1/2	-	-	-	-
Dural puncture	No	No	No	No	No	No
Complication	No	Neck soreness	No	No	No	No
Volume of injected blood	8 ml / 5 ml(clot)	6 ml / 9 ml	17.5 ml	21ml	21 ml	15ml
Follow up	12 months	26 months	3 months	2 months	3 months	6 months

Discussion

The traditional EBP is not generally available in Taiwan, chiefly because of institutional policies, limited experience with this rare disease (SIH), and a lack of understanding of the potentially serious complications in delayed SIH. Most of the cases in our series suffered for a prolonged period. Three of the patients transferred from other hospitals and refused another transfer. However, the alternative EBP method described here successfully eliminated their symptoms.

There are three major differences for this method: the method of needle advancement, needle size, and syringe. With the LoR technique, the operator uses one hand to continuously apply pressure to the syringe plunger to advance the entire set while the other hand controls the hub. This technique relies heavily on the clinician's perception of the resistance gradient between the ligamentum flavum and epidural space, and the clinician focusing his or her attention on maintaining steady needle advancement and determining the needle depth. Performing these coordinated actions is a difficult task. Although Loss-of-Resistance sets were developed in the 1970s, inadvertent dura punctures are not uncommon and remain a risk. The 2008 Nordic study reported more than 900 cases of inadvertent puncture in a single year (1) and concluded that formal training courses were needed. Since then, new strategies have been developed and new equipment has been invented (e.g., ultrasound guidance, Epidrum®) (2), but the technique barrier for neurologists remains. The core idea of our systematic resistance/pressure-checking method is not new. Delineating the procedure based on the lumbar puncture technique, however, might assume a short learning curve for neurologists. The key concept is to advance the needle and check the tissue resistance separately, rather than simultaneously.

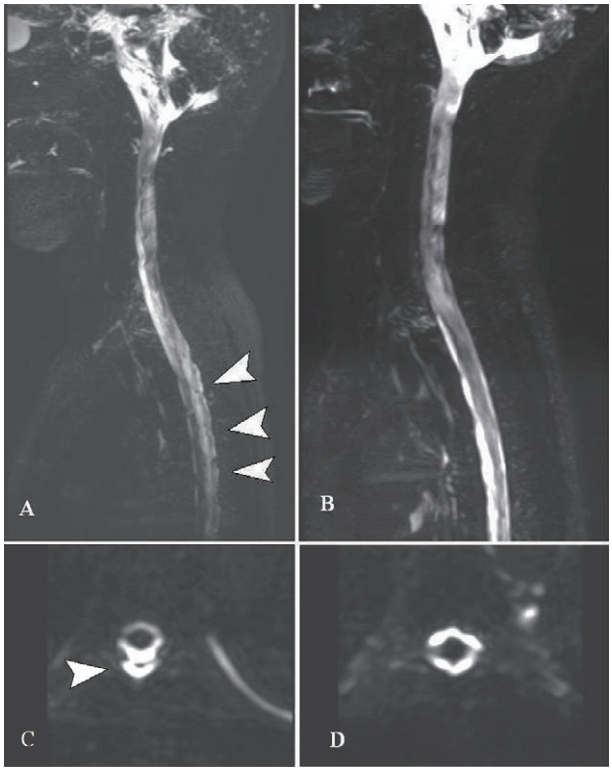

Fig. 1 MR myelography of case 1, performed 3 days before (A/C) and 30 days after (B/D) epidural blood patches. The epidural fluid collection (arrowheads) disappeared in the follow-up study.

If the clinical situation of miscellaneous diseases that require epidural procedures are compared, EBP appears distinctive. First, SIH patients who fail to respond to conservative management showed a refractory intracranial hypotension. These patients might have a higher risk for complications such as subdural hematoma or sinus thrombosis. Second, some patients of SIH have connective tissue disorders (3) and might experience delayed healing of the dura. Third, the literature published to date has not discussed the treatment following an unintentional dura puncture during EBP or the efficacy of an "immediately" placed EBP in such a situation. Lastly, operators tend to use large bore 16/18 G Tuohy needles during similar procedures for a clearer perception and to allow a catheter insertion, which are not absolutely necessary in EBP. The needle sizes described here are not obligatory: however, smaller needles cause less morbidity. For patients with a low intracranial pressure and possible connective tissue disorders, it is quite reasonable to use 22/24 G needles.

Smaller needles had been reported to be difficult in locating the epidural space by Liu et al. with traditional LoR technique (4). The result might be explained by that they used same size syringe (10 ml) which was originally bundled with large bore needles in commercially available sets. The low-resistance syringe was initially designed for withdrawing arterial blood. When it comes to identifying the epidural space, the applicability of a large barrel syringe with a small sized needle has not been challenged since

the barrel:needle diameter ratio increases in such a combination and generates an extra pressure gradient inside the syringe hub/neck. The use of tuberculin syringe provides a smaller barrel:needle diameter ratio and pertains a smoother move. Smaller diameter ratio can also bring a better perception with larger angle of fingers flexion when the plunger is pushed against the decreased resistance in epidural space. Moreover, a smaller barrel comes with a smaller contact area between the plunger and inner wall of the syringe, thus producing less friction. The initial resistance of low-resistance syringes marketed by different manufacturers is usually around 0.3 Newton (N; 1 N = 1 $kg \cdot m/s^2$). We studied the force required to overcome the initial resistance and resistance-in-proceed for the 1-ml Terumo® tuberculin syringe. According to the averages from our tests performed with LUTRON® force gauge, forces were less than 0.59 N and 0.33 N, respectively. Based on our experience, this difference is not noticeable with gloved fingers. Besides, with the same buffer distance, the tuberculin syringe uses much less saline and reduces the chance of a confusing fluid return. We look forward to using industrial sets bundled a small bore Tuohy needle and a small-barrel low-resistance syringe that can be used in future EBP procedures.

In conclusion, we found that the combination of small bore needles and small barrel syringes can be used for EBP. The systematic method presented here showed adequate responsiveness with no major adverse events. Confirming the location of the epidural space with contrast medium when the needle reaches the epidural space increases the safety of this alternative method. Further trials are required to assure patient safety and to refine the procedure. We look forward to future improvements and the extended availability of this alternative method for EBP.

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以硬膜外自體血液補片治療自發性顱內低壓，神經科醫師的經驗

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摘要

硬膜外自體血液補片是自發性顱內低壓的一個重要的治療選項，但是目前許多中型醫院仍無法提供傳統的硬膜外血液補片。我們在這裡報告一個由神經科醫師執行的替代性方法，詳細步驟在內文中陳述並加以討論。這個方法藉由在進針過程裡反覆偵測組織內壓力以定位針尖深度與位置，搭配使用一般常見的脊髓穿刺針與一毫升針筒，最終成功完成了六位顱內低壓患者的治療。

關鍵詞：硬膜外自體血液補片、脊髓腔攝影、廣泛腦膜顯影、自發性顱內低壓

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Case Report

A Case of Kikuchi–Fujimoto Disease Presenting with Shock

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Abstract

Kikuchi–Fujimoto's disease (KFD), also known as histiocytic necrotizing lymphadenitis (NHL), is a self-limiting disease that is commonly diagnosed in young women. It is characterized by cervical lymphadenitis and constitutional symptoms, including fever, weight loss, myalgia, and arthralgia. The etiology of KFD remains unknown, although viral infections and autoimmune diseases are suspected causes. The diagnosis is usually based on lymph node histology. We report the case of a patient presenting with cervical lymphadenopathy, lethargy, and high fever for 1 week. Her lymph node biopsy revealed histopathological features compatible with KFD. However, her disease was accompanied by episodes of shock and disseminated intravascular coagulation (DIC), which are unusual during the clinical course of KFD.

Key words: Kikuchi–Fujimoto's disease, Histiocytic necrotizing lymphadenitis, cervical lymphadenopathy, prolonged fever

Introduction

Kikuchi–Fujimoto's disease (KFD) is a benign disease that was first described by Kikuchi and Fujimoto *et al.*[1, 2]. This disease is rare and usually affects young women. There are no clearly defined diagnostic criteria of KFD and the etiology remains unclear[3]. Although viral infections and autoimmune diseases have been suggested, the triggering factors of KFD remain controversial. The disease is histologically diagnosed and the typical findings include paracortical areas of necrosis, karyorrhectic debris, and numerous histiocytes[4-5].

We present a case of KFD. The patient had high spiking fever, anemia, cervical lymphadenopathy, elevated liver enzyme, positive anti-dsDNA antibody test results, and cervical lymphadenopathy.

Case Report

A 6-year-old female without a relevant history presented right cervical lymphadenopathy and general malaise after 7 days of spiking fever. On examination, her body temperature was 40.8°C, blood pressure was 111/71 mmHg, pulse was 136 beats per min, and respiratory rate was 30 breaths per min. Other physical examinations revealed slightly injected tonsils, no hepatosplenomegaly, and no skin rash but her right cervical lymph nodes (size, 1–2 cm) were palpable with mild tenderness. Laboratory test

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results showed a white blood cell count of $8.8 \times 10^3/\mu L$ [reference range (RR), $4.8–10.8 \times 10^3/\mu L$) with 66.4% neutrophil cells and 20.8% lymphocytes, hemoglobin of 10.5 g/dL (RR, 12–16 g/dL), platelets of 408,000/μL (RR, $140–500 \times 10^3/\mu L$), alanine aminotransferase of 93 IU/L (RR, 3–34 IU/L), and C-reactive protein (CRP) of 75.5 mg/L (RR, 0–5 mg/L). An acute systemic viral infection was initially suspected. However, there was no serological evidence of a viral infection. Serological test results were negative for Epstein–Barr virus (EBV), cytomegalovirus, adenovirus, toxoplasma gondii, and mycoplasma pneumonia. Empiric antibiotics were used after admission. However, the patient's symptoms progressed with spiking fever and gradually elevated CRP level. Hypovolemic shock with disseminated intravascular coagulation (DIC) was observed on the 10^{th} day of admission and the patient was transferred to the intensive care unit. Her vital signs stabilized after fluid challenge and blood-product transfusion. Broad spectrum antibiotics, such as vancomycin and meropenem, were prescribed but her fever persisted. Her urine, blood, and throat cultures were unremarkable. A cervical computed tomography scan demonstrated multiple, heterogenously enhanced nodular lesions with central low density in the right supraclavicular and posterior cervical spaces. Neck magnetic resonance imaging revealed necrolytic lymphadenopathy. Her Well–Felix test was sensitive, and doxycyclin was administered because rickettsia infection was suspected; however, fever and cervical lymphadenopathy persisted. Her serum antinuclear antibody (ANA), antiphospholipid, and anti-Smith antibodies were all negative but her anti-dsDNA antibody was positive. Her serum C3 and C4 levels were normal. The patient's clinical features did not match the diagnostic criteria for any autoimmune disease. The patient agreed to have a cervical lymph node biopsy. Histopathological examination of the right cervical lymph node biopsy specimen showed paracortical necrosis, karyorrhectic debris, proliferation of lymphocytes, and histiocytes. Polymorphic neutrophils were deficient. Immunohistochemical staining was positive for CD8+ in cytotoxic T lymphocytes and for CD68+ in histiocytes. On the basis of the pathological results, a final diagnosis of Kikuchi–Fujimoto disease was made. The patient's symptoms gradually improved after taking prednisolone 1 mg/kg/day.

Discussion

Kikuchi–Fujimoto disease (KFD) is a benign, self-limiting disease of unknown origin. It is characterized by tender cervical lymphadenopathy and constitutional conditions, including fever, leucopenia, weight loss, and other upper respiratory tract symptoms[1]. KFD, also known as histiocytic necrotizing lymphadenitis, was first reported by Kikuchi and Fujimoto in 1972. It usually affects young females under 30 years of age[2-4]. The disease remains poorly defined, and its etiology and pathogenesis remain unclear. Infectious agents, such as EBV, human herpes virus 6 and 8, parvovirus B19, and autoimmune diseases, have been suggested as causes of KFD but their actual associations with KFD have not been determined[5-10]. The presentation of KFD is rather nonspecific. At present, no specific diagnostic criteria are available, and the diagnosis is usually made on the basis of the characteristic pathological findings of excisional lymph node biopsy specimens. Typical histological findings of KFD include paracortical necrosis with heterogeneous histiocytes and karyorrhectic debris around the necrotic foci. Immunochemical analysis typically reveals a predominance of T cells (CD45RO), mainly CD8+ T cells and histiocytes (CD68)[2, 11]. KFD has been reported to be associated with systemic lupus erythematosus (SLE) and can be previously diagnosed, simultaneously or after diagnosis of SLE. The pathogenic association of these two diseases is not well known[5], but they have several similar clinical symptoms and signs such as lymphadenopathy, unexplained fever, arthralgia, and skin rashes. Therefore, clinicians should always consider SLE and confirm the diagnosis of SLE by specific examinations and follow-up[5, 12, 13]. KFD is generally benign with rare fatal complications[4, 14]. In general, the prognosis of KFD is excellent. However, certain case reports have described dramatic clinical courses such as shock and coincident hemophagocytic syndrome[15, 16]. A few fatal KFD cases have been reported[17-19]. No specific treatment is available for Kikuchi's disease and current treatment is usually supportive. A low-dose corticosteroid is suggested for patients who suffer from persistent severe symptoms and recurrence[20].

一個合併休克表現的 Kikuchi-Fujimoto disease 之病例報告

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摘要

Kikuchi-Fujimoto's disease (KFD)，也被稱為 histiocytic necrotizing lymphadenitis (HNL)，是一種良性的自限性疾病。通常好發於年輕女性，以頸部淋巴腺腫大，以及全身性症狀例如發燒、體重下降、肌肉及關節疼痛來表現。發病原因至今未明，可能與感染或自體免疫疾病有關。KFD 的診斷要靠淋巴腺病理組織分析。我們提出一個以頸部淋巴腺腫大，倦怠以及高燒一星期的病例報告，這位病人的淋巴腺組織型態與典型的 KFD 組織相符合。特別的是，這位病人臨床病程卻合併罕見的休克以及瀰漫性血管內凝血，這在 KFD 的表現中是很罕見的。

關鍵詞：Kikuchi-Fujimoto's disease (KFD)、Histiocytic necrotizing lymphadenitis、頸部淋巴腺腫大、長期發燒

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Case Report

失智症與假性失智

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摘要

84 歲退休男性第一次心身科求診因憂鬱情緒、活動量下降、失眠、無胃口、社交退縮、不愛講話、活動量變少、反應變遲鈍、以及記憶力變差。初步診斷憂鬱症合併假性失智並給予抗憂鬱劑適當療程，個案憂鬱情緒改善但仍存明顯記憶與認知功能障礙，日常生活功能受影響的程度擴大且出現被偷竊想法。後由病程澄清個案的記憶力狀況與日常生活功能，早在憂鬱情緒前即出現缺損，加上臨床治療過程、心理測驗結果以及症狀變化，鑑別診斷憂鬱症合併假性失智或失智症合併憂鬱，重新診斷為失智症合併憂鬱並給予適切的治療。

關鍵詞：老年憂鬱症、假性失智、失智症

前言

隨著醫療的進步，社會高齡化的影響，老化的議題日益重要。除正常老化現象外，如何鑑別失智症合併憂鬱或憂鬱症合併假性失智一直是老年精神科的挑戰，準確的診斷更能給予適當的治療，此處提供一病例分享。

病例

84 歲喪偶男性，高中畢，警察退休約 20 年，因近半年來，在太太過世之後，記憶力變差、不愛講話、活動量變少、與家人朋友互動變少、悶悶不樂、反應變遲鈍，由女兒帶至高齡精神科門診就診。

個案有高血壓與胃潰瘍病史，但都在藥物治療良好控制中。以往無明顯精神症狀、無精神疾病病史，個性健談、外向，社交活動活躍。當警官退休後，與太太、大兒子、媳婦與孫子同住，與家人互動良好，且參與社區活動，如：國內外旅遊、攝影與唱歌。99 年年初，太太過世，個案明顯情緒低落、食慾不佳、入眠困難與話量變少；但於 1~2 月後，低落情緒較有改善且睡眠與食慾回復正常狀態。然而之後，家人發現個案記憶力減退（煮飯的時候會忘記關火、東西放在哪裡經常會忘記、問過的話重複再問）、較無笑容、經常悶悶不樂、話量與活動量明顯減少、也較無動機參加休閒活動與家庭聚會（之前喜歡參加社區的旅遊活動都不參加了、看報紙剪報的習慣也沒有了）、經常有失神與對話反應變慢的情形。個案自述記憶力變差、對記憶力變差感覺到很煩悶、心情低落、生活很空虛、孤單無趣、擔心造成兒女的困擾、對兒女擔心自己日常生活處理不來且會干涉感到憤怒、不想與人講話且不想活動與外出。睡眠狀況與食慾狀況良好。

回顧過去狀況，個案子女表示，在今年年初個案太太去世之前，並無明顯注意到個案記憶力減退，個案生活作息、社交活動與自我照顧能力都正常。

個人史：

菸酒藥物使用史：無

過去病史：(1) 高血壓 ，使用藥物血壓穩定控制；(2) 消化性潰瘍曾使用氫離子幫浦阻斷劑治療；(3) 攝護腺肥大；(4) 無糖尿病、無中風病史；無其他外科病史、無頭部外傷病史、無癲癇。

近半年藥物使用史：

心臟內科門診用藥：目前 – Inderal 10mg 1# BID、Bokey 1# QD；過去 – Moduretics 和 Isobide

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泌尿科門診用藥：目前 – Dutasteride 1# QD、Harnalidge 1# HS、Impramine 1# BID

藥物過敏史：無

家族史：

家族精神病史：無

家庭動力狀態：個案有兩個兒子、一個女兒。三名子女皆住在中部地區。退休後與太太跟大兒子一家人同住。平日與三個小孩和媳婦們互動良好，經常有家族的聚會，個案的社會活動獨立性良好，兒女們多鼓勵父母參與社交活動且有自己的生活，個案也不太獨斷、干涉小孩們的生活與決定。太太過世之前，生活瑣事的打理皆由太太包辦；個案太太過世之後，個案白天自己處理飲食與其他生活瑣事。

身體檢查：

身高：172 公分；體重：63 公斤；聽力：無明顯異常；視力：佩戴老花眼鏡；神經學檢查：正常。

精神狀態檢查：

外觀：衣著適宜整潔，偏瘦；態度：配合、有禮；注意力：容易分心；言語：少話、流暢、切題；表情：適切，但較少笑容；情緒：情緒低落、無喜樂感；行為：活動量少，輕微精神運動遲緩；想法：無動機、孤單、無意義感、對自己能力無自信、擔心給家人帶來麻煩、負面想法。無妄想、無死亡或自殺意念；知覺：無任何型式幻覺。

認知功能 JOMAC（judgment,orientation,memory,abstract thinking, concentration/calculation）：

Judgment 判斷力：正常；Orientation 定向力：時間中的「日」錯誤，其餘正常；Memory（3 item recall）記憶力（回憶 3 物件）：0/3；Abstract thinking 抽象思考能力：正常；Concentration/calculation（series of 7）注意力／計算能力（連續減七）：4/5。

個案同時合併有認知功能減退與憂鬱症狀，認知功能減退的情形，尚未達明顯失智程度，器質性原因的檢查顯示並無其他器質性因素導致目前認知功能減退與情緒低落的狀況；且由病史中來看，認知功能減退的時間是較突然的（非漸進性），且與情緒低落發生時間有高度相關性。綜合以上評估與檢查，診斷為：

第一軸：重度憂鬱症，單次發作合併假性失智 Major depressive disorder, single episode with pseudodementia；第二軸：無異常；第三軸：高血壓、消化性潰瘍、攝護腺肥大；第四軸：太太過世；第五軸：GAF（Global Assessment of Functioning scale 整體功能評估）：45（目前）、85（過去一年最佳水準）。

治療過程：

初期記憶力與認知功能減退情緒低落 MMSE（Mini-Mental State Examination 簡短智能測驗）：25；Hamilton Depression Rating Scale- 17 漢氏憂鬱量表（HAMD-17）：12，給予 Bupropion-150mg IR 1# QD，討論日常生活安排、活動參與

2. 對 Bupropion 無不良反應記憶力與認知功能減退情緒低落無改善，HAMD-17: 12；增加 Bupropion to 150mg 1# BID，鼓勵增加運動量與安排規律生活休閒活動 Bupropion 300 mg qd 治療六個星期後情緒低落較改善，活動量增多，但記憶力減退狀況無改善，安排腦部電腦斷層：無明顯異常除腦部萎縮，腦室擴大。維持 Buproprion 300 mg qd

3. 記憶力減退狀況持續，個案會忘記關瓦斯，忘記重要證件放在哪裡，所以把證件都包一包放在身上；擔心遙控器不見而把遙控器放在身上；懷疑家人把東西拿走，或擔心小偷來家中行竊，所以東西都藏地很隱密。吃藥會漏吃，家人擔心不敢讓他單獨開車出門。MMSE: 24；Montreal Cognitive Assessment（MoCA）蒙特利爾認知評估：16；HAMD-17: 8；Instrumental Activities of Daily Living 工具性日常生活活動（IADL）：5

經由治療療效發現個案情緒狀況有改善但記憶與認知功能持續退步、日常生活功能受影響的程度擴大且出現被偷竊想法（尚未到妄想程度）。再詢問個案病程：他的記憶力狀況與日常生活功能，在他太太還沒過世之前，就有退步情形，只是太太都照顧得很周到，於是並無顯現出明顯障礙。再者，由個案測驗結果可發現，個案的缺陷在於短期記憶與定向感多，與憂鬱症伴隨假性失智的缺陷多在“注意力”不同。個案也認真努力回答問題。

重新診斷為阿茲海默症合併精神行為症狀 Alzheimers dementia with behavioral and psychological symptoms of dementia（BPSD）：憂鬱和被偷想法。

針對 Alzheimer's dementia with BPSD 開始使用 Exelon-1.5 mg 1# BID，並將 Bupropion-150 mg IR 減至 1# QD。對 Exelon 無不良反應，持續六星期治療後，認知能力退化能力稍緩並能維持生活功能，藥物維持 Exelon 6 mg 和 Bupropion 150 mg，並衛教家屬失智症的照護。

討論

這個案在一開始很難鑑別失智症合併憂鬱或憂鬱症合併假性失智。一開始個案認知功能退步情形並不明顯（MMSE-25>24），雖個案在測驗過程中表現認真努力，但其憂鬱症狀明顯，且認知功能退步的狀況是突然

的（太太過世後傷慟反應與延續憂鬱症狀），所以一開始的診斷為 Major depressive disorder with pseudodementia 重度憂鬱症合併假性失智。但隨著使用抗憂鬱藥，憂鬱情緒有改善，但認知功能卻逐步退化，並且出現被偷竊想法；重新詢問評估病程後發現：他的記憶力狀況與日常生活功能，在他太太還沒過世之前，就有退步情形，只是太太都照顧得很周到，於是並無顯現出明顯障礙，但太太過世後這些認知功能缺損就明顯的被突顯出來。造成一開始評估時，認為個案的認知功能是在太太過世後，情緒低落後突然發生，於是在診斷上先做了 Major depressive disorder with pseudodementia 重度憂鬱症合併假性失智的診斷。

由於這兩個狀況很難區別，所以在治療過程中必須密切注意情緒狀態與認知功能狀態的改變，能夠給予適切的診斷跟治療。

個案的憂鬱症狀有退縮、無活力、無喜樂感、無動機與體力減退狀況，且無使用 bupropion 之禁忌症—癲癇，所以選擇使用 Bupropion 來治療憂鬱症狀。可以選擇使用 Dozepezil 或 Rivastigmine 來治療失智症狀，兩者的負作用都少且使用耐受性良好。但個案因認知功能退步速度快，於是選擇使用 Rivastigmine（exelon）來治療。

American Psychological Association guideline 美國心理協會治療指引 2007（APA 2007）「阿茲海默失智症合併憂鬱症」治療準則：

(1) 根據準則建議「藥物副作用與病患個別的考量仍是治療此類病患的首要考慮」

(2)「新一代血清素回收抑制的抗憂鬱藥 -SSRI- 較容易被接受」，而「其他非 SSRI 的新一代抗憂鬱藥如，Venlafaxine，Buproprion 或 mirtazapine 也可被建議」

(3) 但是學理上傳統的三環抗憂鬱藥（TCA）因有造成心臟血管和抗膽鹼副作用的危險，對老年病患影響較大不建議使用

(4) 和大部分其他藥物相同，開藥原則應從低起使劑量開始，緩慢增加劑量並拉長調整劑量所需時間

(5) 由於 Fluvoxamine 對肝臟 CYP 1A2、3A4 及 1D12 有壓抑作用使得藥物交互作用增加，需十分注意其用藥安全；

(6) 而三環抗憂鬱藥 imipramine 及 Paroxetine 40 mg 的 1 篇研究顯示在老人失智症合併憂鬱時的副作用不少而且也出現死亡個案，較不優先建議。

(7) 若是抗憂鬱藥對治療「阿茲海默失智症合併憂鬱症」無效時，電療（ECT）可以考慮使用。

(8) 整體的建議是抗憂鬱藥對治療阿茲海默失智症合併的憂鬱症有療效—不論是憂鬱症狀的減輕及憂鬱症治癒均有效，而且是安全的—對認知功能的減損或副作用報告與安慰劑組無統計差異。

(9) 根據專家共識意見其治療有效劑量可能跟一般治療成人憂鬱症的治療劑量相同，治療有效時間可能比一般成人憂鬱症 4-6 週長

(10) Paroxetine、Fluvoxamine、Escitalopram、Milnacipran、Duloxetine、Reboxetine、Mirtazepine 及 Bupropion 等藥物沒有針對阿茲海默失智症合併憂鬱的隨機分派雙盲安慰劑對照藥物研究

(11) 須排除藥物、身體疾病或譫妄的共病現象後。

(12) 應審慎地使用乙醯膽鹼代謝酵素的拮抗劑（AChEI）及新一代抗憂鬱藥或可逆性 MAOI。

(13) 抗憂鬱藥物的使用對失智症合併憂鬱症狀有積極正面的療效，並且可以減輕照顧者的負擔與改善病患的生活品質。

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3. Am J Psychiatry. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. APA Work Group on Alzheimer's Disease and other Dementias. 2007; Dec: 164(12 Suppl): 5-56.

A Case of Dementia with Depression Incorrectly Diagnosed as Pseudodementia

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Abstract

A retired 84-year-old male presented with depression, lack of energy, anhedonia, social withdrawal, poor sleep, poor memory, and cognitive impairment after the death of his wife. An antidepressant agent was administered after the provisional diagnosis of the first episode of major depressive disorder with pseudodementia. However, symptoms such as impaired cognitive function, poor memory, and impaired life function persisted after adequate antidepressant doses. The diagnosis was revised to dementia with depression because of the pattern of symptoms and signs, clinical response, and past history. Under the corrective diagnosis, he received appropriate treatment.

Key words: geriatric depression, pseudodementia, dementia

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2. Monographs:

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3. Monographs with multiple authors:

   Levinsky NG: Fluid and electrolytes. In: Thorn GW, Adams RD, Braunwald E, Isselbacher K, Petersdprf RG eds. Harrison's Principles of Internal Medicine, 8th ed. New York: Mcgraw-Hill, 1977:364-75.

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例：One of the first well documented reports of ECH poisoning with fatality in young children was reported by Miller et al. in 1970[2].

例：Boulet 等人 [3] 報告氣喘患者接受衛教後的知識改變量不受個人因素影響

3. 參考範例

A. 期刊：[作者姓名：題目。雜誌簡稱 年代；卷數（期數）：起迄頁數]

(1) 許吟姿、楊光道、張恆鴻：結締組織疾病併發間質性肺病變患者 99mTc-DTPA 肺廓清率之臨床研究。內科學誌 1992;3:79-83.

(2) Yang KTA, Chen HD: A semi-automated method for edge detection in the evaluation of left ventricular function using ECG-gated single-photon emission tomography. Eur J Nucl Med 1994;21:1206-11.

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(1) 楊志良：生物統計學新論，一版。台北；巨流圖書公司，1984：33-8.

(2) Plum F, Posner JB: Diagnosis of Stupor and Coma. 3rd ed. Philadelphia: Davis, 1980:132-3.

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(1) 蔣欣欣：護理與健康，編輯：顧乃平：護理專業導論，一版。台北；匯華出版公司，1991：83-121。

(2) Levinsky NG: Fluid and electrolytes. In: Thorn GW, Adams RD, Braunwald E, lsselbacher K, Petersdprf RG eds. Harrison’s Principles of Internal Medicine, 8th ed. New York: Mcgraw-Hill, 1977:364-75.

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4. 相同貢獻作者請加註說明，如研究主題的設定、參與決定研究設計、進行統計分析、詮釋研究結果、以及各章節撰稿等貢獻。
5. 請附兩份原稿（一份原稿和一份複印稿，但圖片應使用原圖），包括附表、附圖及照片。圖表應專業製作，一張紙僅一個附圖或附表，依引用順序以阿拉伯數字標出排列。附表須有標題及說明。照片須 5×7 吋光面黑白，背面以鉛筆編號，附圖須有簡單說明（Legend），並另頁撰寫。光學或電子顯微鏡照片，請註明擴大倍率或比例。

註：[1] 根據「生物醫學雜誌投稿之統一規定」第五版，刊載於 Annals of Internal Medicine 1997;126(1): 36-47.

肆、參考文獻

未經發表之論文或摘要不得列爲參考文獻，但可於本文中說明並註明「未發表」（unpublished observations）。博碩士論文可引用。已被任何雜誌接受刊發但仍未發表之著作，請列出雜誌名稱及年份，並註明「in press」。

原著論文、病例分析研究、病例報告等論述及特別約稿之綜論（review article）按下列格式撰寫：

1. 雜誌名稱之簡稱須按照 Index Medicus 型式，作者人數小於 6 位時，詳列所有作者姓名，超過 6 位時，只須列出前 6 位，其它以「等」（et al）代替。

   例：Bhasin S, Storer TW, Berman N, Callegari C, Clecenger B, Phillips J, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996; 335:1-7.
2. 本文內引用時，若兩名以下作者請列出姓氏。兩名以上則列出第一名之姓氏，其他以「等」（et al）代替，並以阿拉伯數字方括弧表示於引用之後。

   例：One of the first well documented reports of ECH poisoning with fatality in young children was reported by Miller et al. in 1970[2].
3. 參考範例

   A. 期刊：[作者姓名：題目。雜誌簡稱 年代；卷數（期數）：起迄頁數]

(1) 許吟姿、楊光道、張恆鴻：結締組織疾病併發間質性肺病變患者 99mTc-DTPA 肺廓清率之臨床研究。內科學誌 1992;3:79-83.

(2) Yang KTA, Chen HD: A semi-automated method for edge detection in the evaluation of left ventricular function using ECG-gated single-photon emission tomography. Eur J Nucl Med 1994;21:1206-11.

B. 單行本：[作者姓名：書名，版數（卷數）。發行地；出版公司，年代：引用部份頁數]。

(1) 楊志良：生物統計學新論，一版。台北；巨流圖書公司，1984：33-8.

(2) Plum F, Posner JB: Diagnosis of Stupor and Coma. 3rd ed. Philadelphia: Davis, 1980:132-3.

C. 多重作者之單行本：[有關文章作者姓名：書名，版數（卷數）。發行地；出版公司，年代：引用部份頁數]。

(1) 蔣欣欣：護理與健康，編輯：顧乃平：護理專業導論，一版。台北；匯華出版公司，1991：83-121。

(2) Levinsky NG: Fluid and electrolytes. In: Thorn GW, Adams RD, Braunwald E, lsselbacher K, Petersdprf RG eds. Harrison’s Principles of Internal Medicine, 8th ed. New York: Mcgraw-Hill, 1977:364-75.

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