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IMAGE

PATHOLOGY

Editorial

Biomarkers for Spinal Muscular Atrophy

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Abstract

Spinal muscle atrophy (SMA) biomarkers are used to measure and evaluate the disease, and changes in the biomarkers may predict biological, physiological, or pharmacological changes before clinical detection. Biomarkers may also provide insight into disease progression that may allow personalized therapies for individuals with SMA, which can also be monitored by biomarkers.

Several methods have been used to monitor SMA. These include molecular and physiological biomarkers, such as *SMN2* copy number; SMN mRNA and protein levels; neurofilament proteins; plasma protein analytes like creatine kinase (CK) and creatinine (Crn); electrophysiological methods, such as compound muscle action potential (CMAP), motor unit number estimation (MUNE), motor unit number index (MUNIX), electrical impedance myography (EIM); and imaging techniques such as quantitative magnetic resonance imaging (qMRI) and muscle ultrasonography.

Biomarkers provide information regarding the underlying mechanisms of disease, reveal subclinical disease progression, and allow for more precise timing and treatment dose in patients with SMA.

Further research is necessary to elucidate the influence of biomarkers in modulating disease onset and progression as well as in therapeutic efficacy and treatment optimization.

Key words: spinal muscular atrophy, biomarker, molecular biomarkers, electrophysiology

Introduction

Spinal muscular atrophy (SMA) is a degenerative autosomal recessive motor neuron disorder. It is the primary cause of infant mortality and it has an incidence of 1 in 6,000 to 10,000 with a carrier rate of 1/54.

Homozygous deletion or mutation of the survival motor neuron 1 (*SMN1*) gene causes SMA. A nearly identical gene, *SMN2*, has a C to T substitution transcript mainly SMNΔ7 mRNA, which resulted in the production of truncated nonfunctional proteins that are unable to compensate for the full-length SMN normally produced by *SMN1*.

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SMA is divided into four subtypes according to the age of onset and maximal motor function. Type I, which is the most common and found in about 50% of patients with SMA, is also the most severe. Its onset is before 6 months of age and manifests with severe generalized weakness, hypotonia, impaired respiratory function, never sits unsupported, and death before 2 years due to respiratory infections or pneumothorax. Type II SMA manifests between 7 and 18 months, and patients can usually sit unsupported but cannot walk independently, have respiratory difficulties and progressive scoliosis, and develop problems with chewing and swallowing. Type III SMA manifests after childhood, and although patients have a normal life expectancy and achieve all major motor milestones, including standing and walking independently, some may be wheelchair-confined during adulthood. Type IV SMA manifests in early adulthood

(>18 years), and patients have normal life expectancy albeit mild to moderate muscle weakness, tremors, and mild breathing problems [1,2].

The current FDA-approved treatments for SMA are SMN-based or SMN-enhancing by either increasing exon seven inclusion in the mature mRNA (Evrysdi and Spinraza) or AAV-9 mediated gene therapy (Zolgensma). However, treatment of SMA is not only limited to increasing the levels of SMN protein in the body as the loss of SMN proteins also impacts other systems, pathways, and processes. Thus, non-SMN approaches supplement SAM treatment and often act on muscles or nerves. Since phenotypic heterogeneously of SMA, indicators (biomarkers) are necessary to detect and clinically manage the disease in addition to understanding variability between patients after therapy [3,4].

Biomarkers are medical indicators that provide information regarding disease progression and can be classified into five types: diagnostic, prognostic, predictive, disease progression, and pharmacodynamic. Diagnostic markers facilitate the detection of disease states compared to healthy populations. Prognostic markers provide health outcome information and facilitate stratification of the disease phenotype. Disease Progression markers monitor disease phenotype after treatment initiation. Predictive markers "predict" treatment response prior to treatment initiation. Pharmacodynamic markers confirm and monitor treatment.

The number of *SMN2* copies is inversely correlated with disease severity. Hence, its measurement best predicts clinical outcomes in untreated patients. However, the number does not change with treatment; thus, it cannot be used to gauge disease progression or treatment response.

Although blood levels of SMN mRNA and protein provide information on the current disease state, they are not effective for monitoring disease progression and response to therapy as they may not be reflective of the levels in motor neurons or the central nervous system.

Compared to healthy individuals, neurofilaments (NFs) in both blood and cerebrospinal fluid (CSF) are elevated in patients with SMA. The decline of NFs offers insight into the axonal changes after treatment in infants; however, it is less useful in adult patients.

Elevated creatine kinase (CK) activity has been observed in patients with SMA, especially in milder forms; creatinine (Crn) is a metabolic waste product of CK that is inversely correlated with disease severity. CK and Crn baseline levels in serum can distinguish responders from nonresponders with nusinersen treatment in adults.

Electrophysiology has been used to quantify neuromuscular function in motor neuron diseases

Table 1 SMA biomarkers and types in use

Type of Biomarker	Diagnostic	Prognostic	Disease Progression	Pharmacodynamic	Predictive
Genetic testing	Yes				
SMN2 copy number		Yes			
SMN mRNA and protein levels		Yes (in some cases)		Yes (for systemic therapies)	
Neurofilament proteins (NFs)		Yes	Yes	Yes	
Creatinine			Yes (infants with 3 copies *SMN2*)		
Creatine kinase and creatinine				Yes	Yes
Compound muscle action potential (CMAP)		Yes	Yes		Yes
Motor unit number estimation (MUNE)		Yes	Yes		Yes
Motor unit number index (MUNIX) and motor unit size index (MUSIX)			Yes		
Electrical impedance myography (EIM)			Yes	Yes	Yes
Magnetic resonance imaging (MRI)	Yes		Yes (in some cases)		
Muscle ultrasonography	Yes				

and in vivo assessment of motor unit connectivity and has provided insight into the relationship between muscle connectivity and function to monitor disease progression. Compound muscle action potential (CMAP) represents the total electrical output of the motor units innervating a single or groups of muscles after supramaximal nerve stimulation. Motor unit number estimation (MUNE) quantifies the number of motor units innervating a muscle, equivalent to CMAP divided by single motor unit potential (SMUP), which is the ratio of the output of all motor units to a single motor unit. The noninvasive electrophysiology motor unit number index (MUNIX) estimates the number of functional motor units within a muscle, whereas the motor unit size index (MUSIX) provides information regarding the size of individual motor units; MUNIX and MUSIX are used to monitor functional changes in hand muscles of patients with SMA. Electrical impedance myography (EIM) is increased in healthy children compared to patients with SMA type II and III.

Quantitative magnetic resonance imaging (qMRI) is a noninvasive, sensitive, and less biased method to measure muscle physiology. Generally, longer disease duration correlates with worse MRI scores in proximal muscles. Muscle ultrasonography is another noninvasive imaging technique that can distinguish between healthy individuals from patients with SMA based on the muscle ultrasound results of the biceps, wrist extension, femurs, and anterior leg muscles. qMRI and muscle ultrasonography show promise as complementary methods to determine SMA phenotype and disease course [5,6,7].

Conclusion

The most accurate method to diagnose SMA is genetic confirmation of the *SMN1* gene and *SMN2* copy number. *SMN2* copies are the strongest prognostic biomarker in patients with SMA without treatment. Although SMN mRNA and protein levels in blood and CSF samples differ, they are useful in monitoring systemic response to CNS-targeting therapies. NFs are used to assess prognosis, disease progression, and treatment response especially in treated SMA infants but not in adults. Serum Crn is a sensitive marker of disease progression in presymptomatic infants, and *SMN2*, CK, and Crn can be used as predictive and pharmacodynamic biomarkers in treated patients. CAMP, MUNE, and EIM monitor motor function and predict treatment effects in all age groups, and they can also detect neuromuscular changes before clinical symptoms appear. qMRI and muscle ultrasonography may reflect anatomic and functional changes to distinguish patients with SMA from healthy individuals; however, lack of equipment and evaluator reliability limits their applicability.

Although a single biomarker cannot monitor disease progression and treatment efficacy, monitoring patients with SMA using several biomarkers can provide a more accurate clinical assessment. Continued research in motor neuron disease processes will result in the addition of novel biomarkers that can more accurately assess and monitor patients with SMA.

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脊髓肌肉萎縮症的生物標誌

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摘要

脊髓肌肉萎縮症的生物標誌用於測量和評估疾病，生物標誌的變化可能會在臨床檢測前披露生物、生理或藥理學中出現的現象，提供疾病進展的見解，並允許對脊髓肌肉萎縮症患者進行更適當的治療。生物標誌也有助於描述脊髓肌肉萎縮症治療的有效性。目前已有越來越多的分子和生理生物標誌物，如 *SMN2* 基因數，SMN mRNA 和蛋白質量、神經膠體蛋白（NFs）、血漿蛋白分析物如肌酸激酶（CK）和肌氨酸（Crn），以及各種電生理學如複合肌肉動作電位（CAMP）、運動單位數估計（MUNE)）、運動單位數指數（MUNISX）、電阻抗肌電圖（EIM）、成像測量如定量磁共振成像（qMRI）和肌肉超聲波檢查等。生物標誌物為潛在的疾病機制提供資訊，揭示亞臨床疾病的進展，允許脊髓肌肉萎縮症患者在時機和劑量上進行更精確的治療。目前生物標誌在疾病發病、疾病進展、治療療效以及優化治療方面的研究仍在進行中。

關鍵詞：脊髓肌肉萎縮症，生物標誌，分子生物標誌，電生理學

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Review Article

The Role of Physical Activity in Delaying Cognitive Function Decline in the Elderly

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Abstract

The global elderly population has continued to grow faster than expected, with estimates showing that Taiwan will have become an aged society by 2018. Accordingly, mild cognitive impairment, one of the health issues associated with an aging population, has been increasing. Patient care may place a considerable burden on the national economy, society, family, medical resources, and drug availability. This article reviews the perspectives of literature obtained from the Cochrane library, PubMed (Medline), UpToDate, and Google scholar using three main methods: searching for keywords containing cognitive dysfunction, physical fitness, exercise prescription intervention, quality of life, etc.; searching for related articles on physical activity and cognitive function, neuroendocrine, molecular biology, etc.; and combining case–control studies, systematic reviews and meta-analyses, analytical research, and randomized control studies to explore the effects of physical activity intervention and fitness level of the elderly on the epidemiology of dementia, prevention of cognitive function decline, improvement of cognitive function, and quality of life. Understanding which types of exercise intervention helps improve quality of life among patients with mild cognitive impairment and Alzheimer's disease is imperative. This review aims to identify physical fitness exercises that is specifically geared toward improving cognitive function, can used as a reference for health promotion in Taiwan, provides guidance on dementia prevention and cognitive dysfunction care for the elderly, and helps construct guidelines on physical fitness and exercise prescriptions in Taiwan.

Key words: Cognitive impairment, physical performance, activity intervention, quality of life, exercise prescription

Epidemiology of dementia in Taiwan

Estimates have shown that by 2021, over 50 million people worldwide will have dementia and that approximately 10 million new cases would occur each year, with Alzheimer's disease (AD) accounting for 60%–70% of the total population with dementia. Another type of early-onset dementia can be inherited from the family and has been associated with abnormal aging. According to statistics, the proportion of the elderly population in Taiwan reached 14% in 2018 and is expected to reach 20.3% by the end of 2025. Based on data from the Taiwan Dementia Association in 2019, the prevalence of dementia in the elderly community is 120,000 cases, accounting for approximately 4.8% of the elderly population. Over 30,000 elderly with dementia are admitted in long-term care institutions and over 20,000 people with dementia have been estimated to be under the age of 65. The total Taiwanese population with dementia exceeds 180,000. Older age has been associated with increased risk for dementia. According to available research, dementia has a prevalence of 1.2%, 2.2%, 4.3%, 8.4%, 6.3%, and 30.9% among those aged 65–69, 70–74, 75–79, 80–84, 85–89, and over 90 years old, respectively. Taiwan's demographic data in 2019 and the aforementioned prevalence of dementia per

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five-year age group suggest that 269,725 people over the age of 65 should have had dementia at the end of 2018. The prevalence of dementia among those aged 30–64 years old is around one in a thousand, and Taiwan has around 12,638 people within this young-onset dementia age bracket. Estimates show that approximately 282,364 people over the age of 65 (one in every 65 people in Taiwan) will have developed dementia in 2021, a number that is expected to exceed 460,000 (one in every 50 Taiwanese) by 2031 and 670,000 (3 in every 100 Taiwanese) by 2041. By the year 2051, more than 830,000 Taiwanese people (1 in every 25 Taiwanese) are expected to have dementia, a figure expected to reach over 880,000 by 2061, accounting for one in every 20 Taiwanese. Over the next 30 years, the number of people with dementia in Taiwan will grow at an average rate of one patient with dementia every 40 min.

Factors causing dementia

Dementia is a progressive neurodegenerative syndrome that mainly affects short-term memory. People exhibit varying symptom severity ranging from mild to moderate, as well a different terminal symptoms and timing of degeneration. Such symptoms often involve short-term memory deterioration, poor judgment, mood and personality changes, confusion regarding time and place, difficulty in language expression or writing, social deterioration, etc., which can affect activities of daily living and cause disability or dependence. Age is the most relevant risk factor for dementia given that the incidence and prevalence of dementia increase with age. Accordingly, the prevalence rate of dementia doubles every five years over the age of 65. Brain injury, hypoglycemia, comatose status, and ischemic cerebral infarction have also been identified as possible risk factors for dementia. Given that brain injury is a significant risk factor for dementia, preventing accidents that cause brain injury, such as falls, can also reduce its risk. Dementia can be classified into Alzheimer disease (AD), Dementia with Lewy Bodies, frontal-temporal dementia, vascular dementia (VaD), Alzheimer and VaD (Alzheimer and VaD), and dementia related to other factors. Among them, Alzheimer's dementia is the most common, accounting for 42%–65% of all dementias[1], followed by VaD, Alzheimer and vascular mixed dementia, or Lewy body dementia[1]. Studies in Europe and the United States have shown that increasing physical activity can delay the progression of AD and related dementia, as well as the rate of cognitive decline in patients[2].

Molecular mechanism by which exercise prevents dementia

The effects of exercise on the structure and function of the brain nerves may involve the promotion of the secretion of brain-derived neurotrophic factor, which promotes the proliferation, differentiation, maturation, and survival of neural stem cells in the brain while simultaneously increasing brain concentrations of insulin like growth factor-1 (IGF-1) and vascular endothelial growth factor, increasing brain angiogenesis, providing nutrition for new brain nerve cells, and promoting the formation of long-term potentiation between brain nerve cells, which enhances the performance of brain spatial learning and memory function. Thus far, however, limited research has been available on the effects and mechanisms of exercise on the brain nerve structure and function[3-5]. Studies have suggested that the E4 protein increases the likelihood of suffering from AD by 3–5 times and that the homogenous genotype E4/E4 increases this probability by 5–15 times. However, those with the E2 protein may be resistant to AD. Clinical results found that over 50% of patients with AD had the ApoE4 gene, the detection of which indicates a genotype with a higher risk of AD, such as E3/E4 or E4/E4 (Alzheimer's Association, 2019). Although the genotype may increase the likelihood of suffering from AD, lifestyle still remains an essential factor. While physical activity measurements have been successfully utilized in older adults without cognitive impairment, further research is needed on the differences between healthy people and patients with AD. Clinically, using various scales to measure the performance of patients with AD is challenging. A major neurocognitive disorder is characterized by a decline in at least one of the cognitive domains, including complex attention, executive function, learning and memory, language, perceptual-motor-visual perception, or social interpersonal cognition (Blazer D. (2013), DSM-5.) An integrated analysis confirmed that the effects of exercise in preventing various types of dementia and AD showed a dose–response trend, suggesting that greater amounts of physical activity

promote better preventive effects[6]. The same result was confirmed in another integrated analysis examining 21 studies containing 97,557 research subjects and conducted follow-up for 3–31.6 years (prospective studies). Dose–response analysis found that all dementia and AD cases showed a linear relationship when the amount of physical activity was between 0–2,000 kcal/week or 0–45 metabolic equivalents (MET)/week, especially for every 500 kcal or 10 MET increase in physical activity per week. One MET is defined as the consumption of 3.5 mL of oxygen per kilogram of body weight per minute, equivalent to the oxygen consumption per minute at rest without any activity (Jetté M, 1990). MET, which have been used in exercise testing, exercise prescription, and evaluation of functional capacity, indicate the relative energy metabolism level of various activities and is an alternative method for expressing exercise intensity and the number of heartbeats and conscious exercise intensity, which can reduce the incidence of dementia and AD by 10% and 13%, respectively. Research on physical activity and dementia found that in six generational follow-up studies, participants aged between 65 and 93 accounted for approximately 749–4,615 people. The follow-up period was between 3.9 and 7 years, with only one follow-up reaching 21 years[7]. Some methods for assessing the amount of physical activity included maximum or minimum amount of physical activity, the number of exercises per week, the number of calories burned by physical activity, and the amount of walking as comparative indicators. One of the studies[8] found that the subjects who walked the least (25% percentile) had an 80% higher risk of overall dementia than those who walked the most. Other studies have shown show that subjects with considerable physical activity, frequent exercise sessions, or high-intensity physical activities had reduced overall dementia risk odds ratio (OR) ranging between 0.48 and 0.63[9]. Three other studies[8,10-11] confirmed that high physical activity or exercising more than twice a week can reduce the risk of AD, with an OR ranging from 0.38–0.5[12]. Overall, the results of the generational follow-up study confirmed that increasing the amount of physical activity of the middle-aged and elderly can effectively reduce the risk of cognitive dysfunction, AD, and VaD. Case–control studies, such as that by Podewils (2005)[13], included physical fitness as a comparative indicator. The study showed that those in the top 25% of physical fitness had a reduced risk of AD, with a relative risk (RR) of 0.85, compared to those within the 25–50% range. Exercising over four times/week can better improve physical fitness within 2 weeks and lower RR of dementia to 0.51 compared to exercising <2 times/week. In their study, Sumic (2007)[14] used older women with an average age of >88.5 years as the research subjects. Those who exercised ≥4 hours a week had a HR for cognitive impairment of only 0.12 compared to those who exercised <4 hours a week. Compared to women with the highest physical activity, women and men with the lowest physical activity had 5 and 2 times the risk of suffering from dementia, respectively. Andel (2008)[15] studied the physical activity in middle-aged subjects (average 48.1 years old). By comparing those engaged in a routine of physical activities with those who exercise irregularly, the study found that after the age of 31, the OR for dementia risk among those who participated in low-intensity physical activities and high-intensity physical activities was 0.63 and 0.34 respectively. The results of three case–control studies also confirmed that increasing physical activity of middle-aged and older people can effectively prevent the risk of cognitive function impairment, AD, and VaD. Systematic analysis and retrospective research reports in nine generational follow-up studies and case–control studies, as well as a systematic analysis of past research reports, all provided significant insights into the relationship between physical activity and dementia. The results of Hamer (2009)[16] showed that subjects with the highest physical activity had a RR of 0.72 for dementia, 0.55 for AD, and 0.82 for Parkinson's dementia. A study by Aarsland (2010)[17] showed that physical activity could significantly reduce the risk of VaD with an OR of 0.62. Weih M (2010)[18], who analyzed the relationship between physical activity and AD using dichotomy, showed that those who answered yes or high on physical activity had a lower chance of AD than those who answered no or low on physical activity, with OR for the risk of AD of 0.59. A systematic review and analysis of research reports once again confirmed that increasing the physical activity of the elderly can effectively reduce the risk of Parkinson's dementia, AD, and blood vessel type of dementia[18]. The study by Larson et al. (2006)[19] also found that the likelihood of dementia was 13.0 and 19.7 (per 1,000 people/year) for those who exercised

≥3 and <3 times a week, respectively. Compared to those who exercised <3 times a week, those who exercise more than three times a week had a 38% reduction in the risk of dementia. Rovio et al.'s (2005) [12] research found that those who engaged in leisure activities more than twice a week had reduced risk of dementia by 52% compared to those who were physically active less than twice a week. Podewils et al. (2005)[13], who compared the effects between engaging in physical activities ≥4 times/week and only 0–1 time/week, showed a 49% reduction in the likelihood of dementia in the former. Analysis of the research as mentioned earlier found that all exercise types were aerobic exercises. A study on 400,000 people in Taiwan found that 100 min of moderate-intensity exercise per day had the highest health benefits (CP Wen, 2003). Meanwhile, Nigam (2011)[20] recommended that reaching 700 min of physical exercise a week can provide significant health benefits. Available evidence strongly suggests that recreational physical activities of more than 4 h per week or at least twice a week can reduce the risk of dementia. Completing 100 min of moderate-intensity aerobic exercise every day may be the best recommended amount of exercise for preventing dementia. Studies have confirmed that high-intensity physical activities or exercising more than twice a week reduces the risk of AD, with an OR between 0.38 and 0.5[12, 21-22]. Results from a randomly distributed experimental design research confirmed that exercise has positive effects on the patients' cognitive function, among which aerobic exercises combined with non-aerobic exercises and aerobic exercises alone were effective, whereas non-aerobic exercises alone were not effective[23].

A systematic retrospective study analyzed 32 types of physical activities used in intervention studies. Most of the studies lasted 6 months, with a few conducting follow-up for 1–2 years. Notably, insufficient evidence was available to suggest that short-term single-item exercise intervention (aerobic exercise, resistance exercise, or Tai-Chi) prevented cognitive decline or occurrence of dementia in the elderly. However, multi-sport interventions did, in fact, delay cognitive decline[24]. Aerobic exercises, resistance exercises, Tai-Chi exercises, and multiple combinations of exercises are beneficial for cognitive function among to adults over 50 years old (except for yoga, which has not been proven effective). To obtained the best effect, each exercise session should last for at least 45–60 min with medium to high-intensity, alternate between aerobic and resistance exercises, and be divided into multiple sessions spread throughout the week.

Discussion

The results of epidemiological generational follow-up studies, case–control studies, and systematic reviews have shown that maintaining a healthy level of physical exercise reduces the risk of AD, VaD, or overall dementia. Increasing the amount of physical activity in the elderly can indeed prevent dementia. Suggestions for exercise regimens are as follows[25]:

1. Balance exercise: 10 min to help maintain the stability of the body in daily life or exercise. An example of a balance exercise is to stand on one foot. However, the elderly may require something to hold onto to avoid falling.

2. Flexibility or stretching activity: use muscle stretching activities to increase the range of motion, including dynamic, and static stretching. Warm up or stretching is recommended before any exercise to avoid injuries.

3. Aerobic activity: 150 min/week divided into 7 days, 20–30 minutes per day.

4. Muscle strengthening activity: also known as resistance activities or weight training. 60–100 min a week is recommended performed 2–3 times a week every other day after aerobic exercises.

Past research reports provide favorable evidence that increasing physical activity can prevent cognitive decline in the elderly by affecting nerve cell physiology and molecular biology. Based on this evidence, we can conclude that exercising more than 150 min a week or at least three times a week in addition to usual leisure and physical activities can reduce the risk of dementia. Achieving 100 min of moderate-intensity aerobic exercise every week can aid in the prevention of dementia. Studies recommend exercising at least 2–3 times a week with more than 4 h of moderate to high-intensity physical activity or 5 days a week with moderate-intensity aerobic exercise for 100 min. The duration, frequency, and intensity of these two exercise models may be an effective way to reduce dementia. Studies recommend that individuals begin increasing the amount of physical exercise

once they reach middle age to prevent the onset of dementia in the elderly.

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身體活動在延緩老年認知功能下降中扮演之角色

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摘要

全世界老年人口正迅速增長，台灣已在 2018 年成為高齡化社會，老年人口增加速度超出一般預期；與老化相關的健康問題，例如輕度認知功能障礙的人口增加；長期病人照護可能會增加經濟，社會，家庭照護，醫療資源和藥物方面的巨額支出。本文獻回顧主要透過 Cochrane library，PubMed（Medline），Uptodate 和 Google scholar 等，從文獻搜尋關鍵字：認知功能障礙，運動介入，生活品質，身體活動等相關文章，結合病例對照研究，系統性文獻回顧及統合分析，各研究的結論及隨機對照試驗結果，探討體適能介入和老年人的健康程度對失智症流行病學的影響；透過認知功能和生活品質，了解哪一類型的運動介入有助於改善輕度認知障礙和阿茲海默症患者的生活品質；目的為改善大腦的認知功能方面提出身體活動的益處，可作為台灣健康促進的參考，為老年預防認知功能下降和失智症提供指引，並給予台灣運動處方的指引。

關鍵詞：認知障礙，體能，活動介入，生活品質，運動處方

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Original Article

Intellectual Disability Not as An Obstacle for 1-more-year Early Interventional Therapy in Developmentally Delayed Children: A Retrospective Analysis in A Local Hospital

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Abstract

Children with developmental delay (DD) typically exhibit impairments in gross motor, fine motor, language, cognitive, sensory, psychological, behavioral, auditory, and/or visual development in one or more developmental domains. There are a several causes for DD, and many cases of DD may have multiple causes. Additionally, while intellectual disability (ID) is among the major causes of DD, not all children with DD have ID;furthermore, since children with ID typically have underlying neurological or functional impairments, there is uncertainty regarding whether ID limits the degree of improvement that a given rehabilitation can provide and, if so, should the progress of gross and fine motor skill development differ between children with concurrent DD + ID and children with DD only after receiving the same therapy.To answer this question, a retrospective study was designed to analyze the outcome of gross and fine motor skill treatment for children with concurrent ID + DD and children with DD only who received at least 12 months of physical and occupational rehabilitation at the child development center of the Tungs' Taichung Metroharbor Hospital.

No significant differences were found between the progress of gross and fine motor skill development of the children with concurrent DD + ID and children with DD only after therapy. It is concluded that the physical and occupational therapy used in this study is appropriate for both children with concurrent DD + ID and children with DD only and that both types of children should actively continue their rehabilitation to achieve the greatest possible levels of self-reliance and independence in their daily lives.

Key words: developmental delay, intellectual disability, rehabilitation, gross motor skills, fine motor skills

Introduction

Developmental delay (DD) is defined as any nonattainment of an expected milestone for a child's age in the areas of speech/language, physical, cognitive, self-help, or social/emotional development in one or more developmental domains [1]. DD may become evident during infancy or early childhood, but it becomes more apparent and therefore more frequently diagnosed in early school years [2]. There are a wide range of causes for DD, including genetic, metabolic, endocrine, vascular, malformation syndromes, traumatic, infections, toxins, and environmental etiologies; however, despite careful evaluation and investigation, the cause of a given DD is often unknown [3]. Due to a lack of standardized diagnostic criteria, differences in the definitions, the use of new techniques, or subjects selected only for clinical characteristics [4], the estimated prevalence of DD ranges widely from as few as 1% to as many as 17.8% [1, 5-7].

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Intellectual disability (ID) is one of the causes of DD and is characterized by notable deficits in cognitive functioning and adaptive behavior that originates before 18 years of age (i.e., during the developmental period).[8] The prevalence of ID is estimated to be between 1% and 3% due to different diagnostic criteria and subject selection [9, 10]. As with DD, ID also has causes that are heterogeneous and, in most cases, multifactorial, with risk factors including genetic abnormalities, prenatal exposure to alcohol or infection, trauma during birth, early childhood infections, exposure to heavy metals, and severe malnutrition that can affect children both before birth and during childhood [11].

Motor skills are classified as gross and fine motor abilities. Gross motor skills require the coordination of arms, legs, and other large body parts for actions such as running, jumping, and throwing. [12] Fine motor skills require coordination of delicate movements between the fingers, hands, and feet for actions such as picking up and grasping small objects [12]. Development of these gross and fine motor skills begins in infancy, and throughout childhood, tremendous physical and developmental growth occurs that typically progresses in a predictable sequence [13]; as such, tracking of developmental milestones facilitates the assessment of a child's developmental functioning, and monitoring the development of motor skills in children is important when identifying children who may be at risk for various developmental delays.

Early interventions consisting of physical therapy and other forms of treatment are critical for children with DD only or DD + ID [14]. Additionally, such children can benefit substantially if pediatric doctors, physiatrists, therapists, social workers, and special education teachers work together, and to achieve optimal development and achievement in school, work, and daily life, they need to ensure early identification and treatment of these children [15].

By addressing their skill deficits in various areas, rehabilitation is regarded as a comprehensive means to improve and optimize the competencies and functioning of individuals with DD and ID and, in turn, provide them with the greatest possible degree of self-reliance and independence, as well as facilitating social and economic participation [15]. However, since children with ID typically exhibit underlying neurological or functional impairments, rehabilitation interventions may result in different outcomes in children with ID + DD compared with children with DD only. Moreover, if such outcomes are substantially different, it would challenge the appropriateness of applying the same rehabilitation programs both to children with ID + DD and children with DD only. In other words, there is some uncertainty regarding whether ID limits the degree of improvement that rehabilitation can provide and, if this is the case, whether children with ID + DD should receive different forms of treatment to those with DD only.

To answer this question, a retrospective study was conducted to analyze the outcomes of the effect of rehabilitation on children with ID + DD and on children with only DD who participated in the same rehabilitation program for at least 12 months at the child development center of the Tungs' Taichung Metroharbor Hospital.

Method

Subjects

The research period spanned from January 2014 to December 2017. The study subjects were children with DD (ICD-10 E88.41) who received a rehabilitation intervention consisting of physical and occupational therapy at the child development center of Tungs' Taichung Metro Harbor Hospital, a local teaching hospital. After analyzing and collecting data, those with an IQ score of 69 or below were confirmed to have ID, whereas those with higher scores did not have ID. The hospital's EA01 electronic resources system was used to screen the results of the children with DD in terms for their first gross motor assessment, and assessments pre-rehabilitation and post-rehabilitation for gross and fine motor skills. Each child received at least 12 months of physical and occupational therapy, with the first assessment of their gross and fine motor skills conducted before therapy and the second conducted after therapy. Each child was evaluated by the same therapist for the first and subsequent assessments. The assessment results were based on Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT) scores, which, is commonly used to assess five important developmental areas: cognition, language, motor, social, and self-care skills in Taiwan [16]. The CDIIT comprehensively covers pediatric development, concrete and interesting materials, complete norm establishment, and

clinical applicability, good internal consistency, test–retest and inter-rater reliabilities, construct validity, concurrent validity, predictive validity, diagnostic accuracy, outcome measure for assessing and monitoring developmental skills in children with DD;[17] therefore, this tool is adopted to access children with developmental delay in this child developmental center.

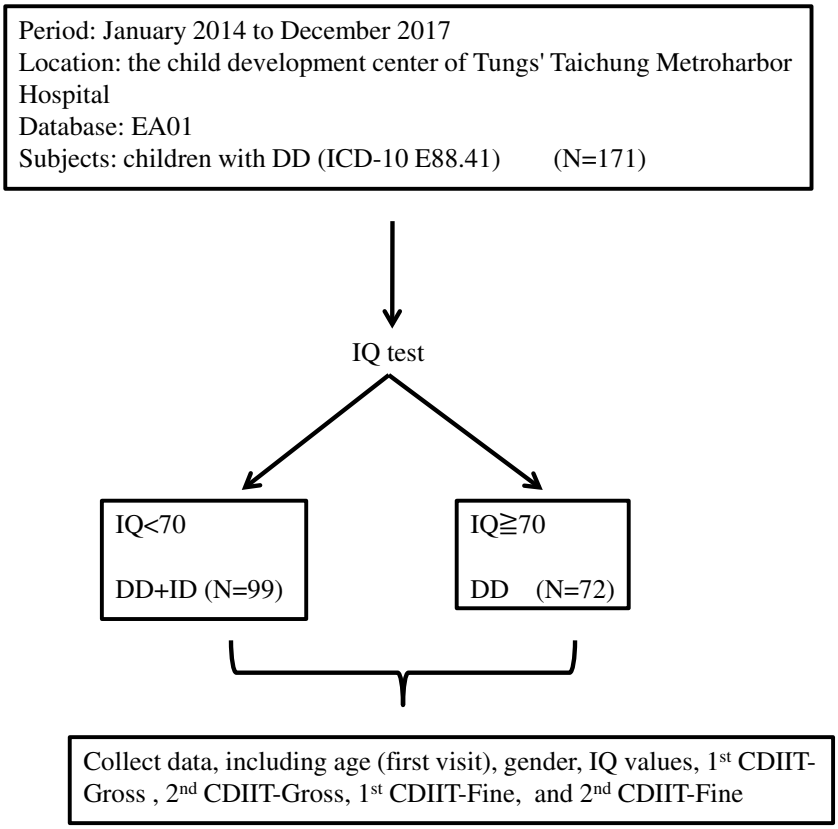
The flow chart of the patient selection process for this study is summarized in Figure 1.

Consent and ethical approval

The study was approved by the institutional review board (IRB) of Tungs' Taichung Metro Harbor Hospital, Taichung, Taiwan (approval number 106054). The IRB issued consent for waiver of informed consent for this retrospective chart review study.

Statistical analysis

A statistical analysis was performed on the presence of ID in the children using the Statistical Package for the Social Sciences (SPSS), version22 (SPSS Inc., Chicago, IL, USA). A preliminary descriptive analysis was performed on the basic data of the subjects (including their gender and age) as well as on their development of gross and fine motor skills before and after rehabilitation. Differences in the post-rehabilitation assessment results of the children with and without ID were compared. Categorical variables are reported as numbers and percentages, whereas continuous data are presented as means and standard deviations. The chi-square test was used to compare the categorical data, and a one-way analysis of variance was used to compare the continuous data. A p value <0.05 was considered statistically significant.



DD: developmental delay; ID: intellectual disability; IQ: intelligence quotient; CDIIT:Comprehensive Developmental Inventory for Infants and Toddlers; 1st CDIIT-Gross: pre-therapy gross motor skills assessment CDIIT scores; 2nd CDIIT-Gross: post-therapy gross motor skills assessment CDIIT scores; 1st CDIIT-Fine: pre-therapy fine motor skills assessment CDIIT scores; 2nd CDIIT-Fine: post-therapy fine motor skills assessment CDIIT scores.

Figure 1. A flow chart of the patient selection process for this study.

Results

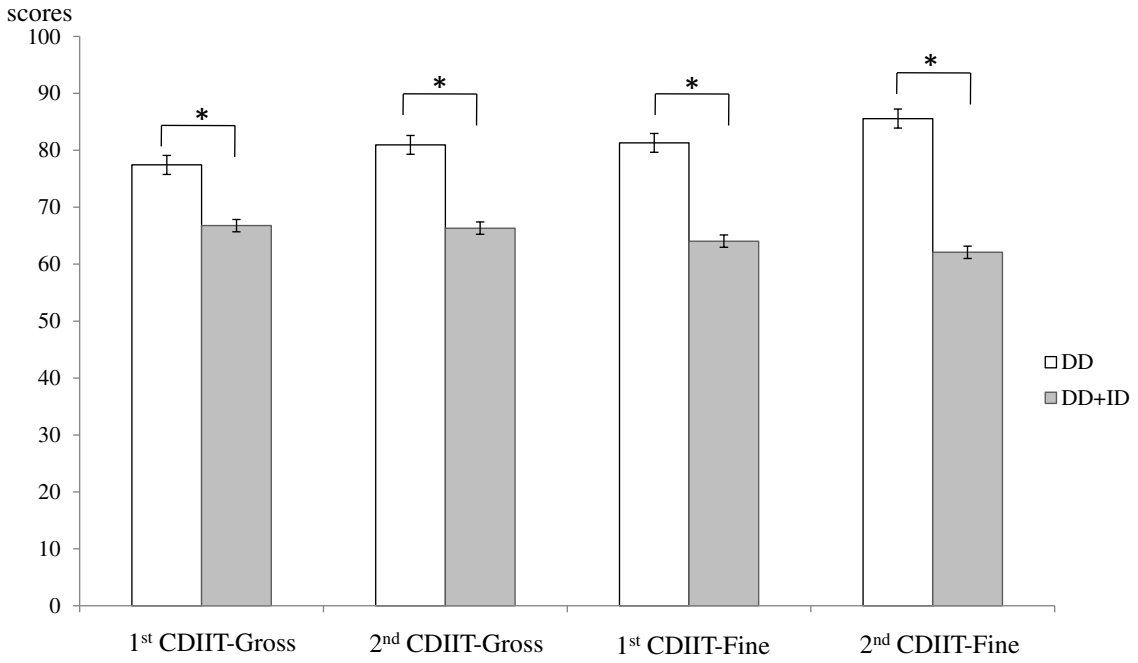
A total of 171 children (126 boys vs 45 girls) with DD who had received at least 12 months of physical and occupational therapy during the study period were identified in the medical records of the teaching hospital. Of all 171 children with DD, 99 (57.89%) were diagnosed with concurrent ID, as their IQ scores were lower than 70, whereas the remaining 72 (42.11%) children had IQ scores of ≥70. All the children sought assessment in this study after exhibiting signs of DD.

The age distribution ranged from 9–77 months. The average age was 40.17 ± 13.99 months. The average age of the children with DD only and DD +ID was 44.61 ± 13.79 and 36.94 ± 13.30, respectively. The average age of the DD + ID group was significantly younger than that of the DD-only group ($p<0.05$; Figure 1).

In the DD-only group, their average IQ was 83.74 ± 9.32. In the DD + ID group, their average IQ was 56.74 ± 9.54. The IQ values in the DD + ID group were significantly lower than those in the DD-only group ($p<0.05$; Figure 2).

The average pre-therapy CDIIT-Gross motor score for children diagnosed with concurrent DD+ID was 66.78 ± 10.58, whereas the average post-therapy CDIIT-Gross motor score measured 1 year later was 66.32 ± 10.73. Their average pre-therapy CDIIT-Fine motor score was 64.05 ± 10.57, whereas their average post-therapy CDIIT-Fine motor score measured 1 year later was 62.10 ± 11.30.

For the children diagnosed with DD only, the average pre-therapy CDIIT-Gross motor score was 77.44 ± 11.25, whereas the average post-therapy CDIIT-Gross motor scores measured one year later was 80.96 ± 11.07. Their average pre-therapy CDIIT-Fine motor score was 81.32 ± 11.95, whereas the average for their post-therapy CDIIT-Fine motor score measured one year later was 85.58 ± 14.91. Table 1 and Figure 2 show the distributions of the pre-therapy CDIIT-Gross motor and Fine motor scores ("1st CDIIT-Gross motor" and "1st CDIIT-Fine motor," respectively) and the post-therapy CDIIT-Gross motor and CDIIT-Fine motor scores ("2nd CDIIT-Gross motor" and "2nd CDIIT-Fine motor," respectively) for the children with concurrent DD + ID and the children



DD: developmental delay; ID: intellectual disability; CDIIT:Comprehensive Developmental Inventory for Infants and Toddlers; 1st CDIIT-Gross: pre-therapy gross motor skills assessment CDIIT scores; 2nd CDIIT-Gross: post-therapy gross motor skills assessment CDIIT scores; 1st CDIIT-Fine: pre-therapy fine motor skills assessment CDIIT scores; 2nd CDIIT-Fine: post-therapy fine motor skills assessment CDIIT scores

Figure 2. Analysis of the assessment results for children with DD only and children with DD+ID before and after receiving at least 12 months of early interventional therapy. * $p<0.05$.

Table 1. Clinical characteristics of children with DD+ID and children with DD only

	DD only	DD+ID	Total	*p*
N	72	99	171	
Gender (boy: girl)	52:20	74:25	126:45	0.711
Age	44.61 ± 13.79	36.94 ± 13.30	40.17 ± 13.99	<0.05
IQ	83.74 ± 9.32	56.74 ± 9.54	68.11 ± 16.36	<0.05
1st CDIIT-Gross	77.44 ± 11.25	66.78 ± 10.58	71.27 ± 12.05	<0.05
2nd CDIIT-Gross	80.96 ± 11.07	66.32 ± 10.73	72.48 ± 13.04	<0.05
1st CDIIT-Fine	81.32 ± 11.95	64.05 ± 10.57	71.32 ± 14.04	<0.05
2nd CDIIT-Fine	85.58 ± 14.91	62.10 ± 11.30	71.99 ± 17.37	<0.05

DD: developmental delay; ID: intellectual disability; CDIIT:Comprehensive Developmental Inventory for Infants and Toddlers; 1st CDIIT-Gross: pre-therapy gross motor skills assessment CDIIT scores; 2nd CDIIT-Gross: post-therapy gross motor skills assessment CDIIT scores; 1st CDIIT-Fine: pre-therapy fine motor skills assessment CDIIT scores; 2nd CDIIT-Fine: post-therapyfine motor skills assessment CDIIT scores

with DD only. Although the comparison between pre-therapy CDIIT-Gross and -Fine motor scores and post-therapy CDIIT-Gross and -Fine motor scores in children with DD and in children with DD+ID was significant, however, the comparison between the pre-therapy CDIIT-Gross motor scores and post-therapy CDIIT-Gross motor scores and -Fine motor scores in children with DD + ID and in children with DD was no statistical significance (Figure 2).

Table 2 shows the effects of rehabilitation on DD + ID and DD-only groups. Regress is defined as the values from the 2nd CDIIT scores minus the 1st CDIIT scores <0; progress is defined the values from 2nd CDIIT scores minus the 1st CDIIT scores ≥0. Multiple linear regression analysis showed the effects of rehabilitation on the subject numbers with DD + ID and DD-only groups were not significant (p> 0.05).

Table 2. The effects of rehabilitation on DD+ID and DD groups. Regress is defined as the values from the 2nd CDIIT scores minus the 1st CDIIT scores less than zero; Progress is defined the values from 2nd CDIIT scores minus the 1st CDIIT scores more than or equal to zero. N is defined as the subject numbers with DD only or with DD+ID.

	DD only	DD+ID	
N	72	99	
Gross motor			
regress	19	34	p=0.267
progress	53	65	
Fine motor			
regress	26	42	p=0.405
progress	46	57	

DD: developmental delay; ID: intellectual disability

Discussion

The aim of the study was to determine whether the gross and fine motor skills outcomes of the physical and occupational therapy provided in the teaching hospital were significantly different for children with concurrent DD + ID than for children with DD only. The results, however, showed no statistically significant differences in the treatment outcomes for the two groups. Arguably, this result was somewhat surprising. According to traditional perspectives as well as the results of some past studies[18-23] children with DD only can better develop gross and fine motor skills compared with children with DD + ID, but the results of this study suggest otherwise. More specifically, after receiving at least 12 months of rehabilitation therapy, both the children with concurrent DD + ID and the children with DD only exhibited progress in their gross and fine motor skill development. As motor development is directly linked to the development of cognitive, language, and social skills, a good and comprehensive rehabilitation enables the maximization of an individual's functional abilities and helps individuals with ID + DD and DD only learn to improve the skills needed for walking, eating, or self-care management.

Children with ID have complex needs and limitations in terms of bodily functions, personal factors, and activity skills, and they require specific forms of

health and social services [24]. However, the purpose of this study was whether children with or without ID should be treated equally. The primary goal of rehabilitation for children, regardless of whether they are in the DD + ID group of DD-only group, is to prevent or reduce impairment or, in other words, to empower the affected individual, rather than to cure the condition per se [14, 15, 24]. Rehabilitation is intended to optimize the functional abilities of children with DD + ID in various areas, including gross and fine motor skills, language skills, and cognitive and adaptive abilities, among others, so that they can achieve the greatest possible levels of self-reliance and independence in their daily lives [25, 26]. Furthermore, because previous literature has shown that children with DD + ID exhibit higher levels of emotional and behavioral problems [27-29], it is expected that therapies that mitigate their impairments will also serve to decrease the burdens that caring for them place on their parents, teachers, and society in general.

However, by placing the obvious virtues of that objective aside, it is important for therapists, parents, governmental authorities, and other interested parties to have a clear understanding of how effective rehabilitation can achieve the ultimate goal for these children, that is, to be self-reliant and independent in their daily lives. To that end, researchers have studied the outcomes of rehabilitation for individuals with DD and ID in various contexts. For example, in a 2019 review article aimed at summarizing the best evidence available with regard to the outcomes of rehabilitation for individuals with ID, Nevala et al. found that rehabilitation resulted in significant improvements in cognitive achievements, communication skills, self-care skills, and activities of daily living [15]. However, by placing those general findings aside, it is also reasonable to suspect that specific factors could affect the efficacy of rehabilitation efforts; hence, various studies have been conducted to determine how a range of factors influence rehabilitation outcomes [12, 15, 21].

A 2017 study by Hong et al. investigated how different factors influenced the effectiveness of a gross motor function rehabilitation program for children with DD only and found that the Gross Motor Function Classification System level and age ≥36 months were the most important prognostic indicators [30]. Such findings underscore the importance of considering factors such as age, current abilities, education levels, the duration of treatment, and family education levels and functions in both the design and application of rehabilitation programs for children with DD and ID [30]. Our study showed that no statistically significant differences in the treatment outcomes for the children with ID + DD and those with only DD, suggesting that the rehabilitation therapy used in this teaching hospital is appropriate for both groups. Importantly, both types of children should actively continue their rehabilitation to achieve the greatest possible levels of self-reliance and independence in their daily lives.

In conclusion, no significant differences were found in this study between the progress of gross and fine motor skill development in the DD + ID and DD-only groups after therapy. As such, it is suggested that the physical and occupational therapy used in this teaching hospital is appropriate for both types of children. Parents and therapists of both children with DD + ID and children with DD should be encouraged not to give up hope on rehabilitation and treatment. Both types of children should actively continue their rehabilitation to achieve the greatest possible levels of self-reliance and independence in their daily lives. Moreover, given the impacts of the low birth rate in Taiwan, the government should make more active efforts to promote and support early treatment interventions for such children, as every child is a valuable asset to the nation's future.

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智力障礙不會成為有發展遲緩兒童接受一年以上早期療育的障礙：一地區教學醫院的回顧性分析

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摘要

發展遲緩（DD）的兒童通常會表現出單一的或多重層面的粗動作，精細動作，語言，認知，感覺，心理，行為，聽覺和 / 或視覺發展障礙。 DD 的原因有很多種，而且有很多的 DD 是有多重的病因，許多情況下 DD 可能有多種原因。雖然智能障礙（ID）是 DD 的主因之一，但並非所有 DD 兒童都是 ID，而且 ID 兒童通常都有潛在的神經或功能障礙。所以有人會認為，即使在正常的復健下，ID 會限制改善的程度。如果這是真的，現行的復健治療，對有 ID 和 DD 的孩子和只有 DD 的孩子的進步就會有差異才對。為了回答此問題，我們設計這項回顧性研究，分析一個教學醫院兒童發展中心患有 ID 和 DD 和僅只有 DD 兒童接受至少 12 個月的物理和職能復健的療效。

結果顯示，有 DD 和 ID 的兒童和僅只有 DD 兒童的粗動作和精細動作在接受至少 12 個月的物理和職能復健的治療的進步是沒有顯著差異。因此，此項研究表明，在此教學醫院所使用的物理和職能復健適用於同時患有 DD 和 ID 的兒童以及僅患有 DD 的兒童，並且此兩類型的兒童都應積極繼續復健，以達到日常生活中能自理和獨立的最大的可能。

關鍵詞：發展遲緩，智能障礙，復健，粗動作，精細動作

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Original Article

The Relationship between Co-occurrence of Categorical Non-motor Symptoms and Subsequent Parkinson's Disease: A Population-based Retrospective Case-control Study

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Abstract

Background: Non-motor symptoms predict the risk of Parkinson's disease (PD), but the association between the number of symptom categories and the subsequent development of PD is unknown. This study assessed the effect of the co-occurrence of non-motor symptoms on PD development.

Methods: Patients with PD (ICD9-CM code 332 and receipt of anti-Parkinson treatments) treated between January 1, 2007 and December 31, 2012 and propensity score-matched controls were extracted from a Longitudinal Health Insurance Database. The propensity score was calculated according to individuals' age, sex, Charlson's comorbidity index, and geographic region, and a 1:1 ratio was used. Codes for non-motor symptoms were searched in the database 7 days before the date of the PD diagnosis. The associations of six categories of non-motor symptoms with PD risk were analyzed using logistic regression.

Results: In total, 2648 patients with PD and 2648 controls were analyzed. Gastrointestinal, sleep, psychiatry, genitourinary and other specific symptoms predicted the risk of PD with adjusted odds ratios (aORs) of 1.79, 1.96, 2.52, 1.55, and 1.98, respectively, (all $p < 0.001$). Smell/taste disorders were excluded from the analysis because only two patients exhibited these signs. The risk of PD increased from 40.6% in patients with no symptoms to 81.8% in patients with five categories of symptoms ($p < 0.001$). The aOR of PD was 1.28 (95% confidence intervals (CI) = 1.13–1.45, $p < 0.0001$) in patients with one category of non-motor symptoms, versus 3.16 (95% CI = 2.20–4.53, $p < 0.0001$) in patients with more than four categories of non-motor symptoms (p-trend = 0.030).

Conclusion: Non-motor symptoms are associated with PD, and the co-occurrence of high numbers of categories of non-motor symptoms is related to an increased risk of subsequent PD.

Key words: Parkinson's disease, non-motor, pre-motor, autonomic disorder, alpha-synuclein, disease modifying

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease that is associated with complex genetic and environmental factors. The prevalence of PD increases with age, and its prevalence is continuously increasing as population aging[1].

The diagnosis of PD is usually delayed until a relative advanced stage when individuals present significant motor symptoms. At this stage, the neurophysiological and neuropathological changes are prominent[2]. The neuropathological changes of PD are not merely confined to the nigrostriatal system. Alpha-synuclein accumulates and aggregates, forming spherical Lewy bodies, which occur throughout

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the brain as well as the cardiovascular and enteric nervous systems. These lesions overwhelmingly affect dopaminergic, noradrenergic, serotoninergic, and cholinergic nerve endings[3]. These extranigral degenerations result in miscellaneous non-motor symptoms of different domains, such as sleep disorders, autonomic dysfunction, and psychological issues[4]. In some patients, these symptoms may appear years before rigidity and serve as indicators for further diagnostic procedure and neuroprotective actions[5].

These non-motor symptoms are usually non-specific, and they could be easily neglected. As multiple symptoms of different domains form a complex, they would more likely draw a physician's attention in the primary care system. The aim of the study was to explore whether these non-motor symptoms are associated with PD and if more categories of symptoms are associated a higher risk of PD in our population.

Method

Data source

Taiwan National Health Insurance (NHI) covers >99% of the total population. The NHI Research Database was developed by the National Health Research Institute, and it covers geographic data, enrollment records, hospital claims, pharmacy-dispensing claims, outpatient clinics, and community pharmacies. Individual identities were transformed cryptographically, and the data were analyzed anonymously.

Study population

We enrolled patients diagnosed with PD from January 1, 2007 to December 31, 2012. PD was defined by the diagnostic code (ICD9-CM code 332) and the use of anti-Parkinson medications (levodopa, amantadine, pramipexole, selegiline, pergolide, bromocriptine, and ropinirole) in at least three outpatient or inpatient visits. The date of the first record was defined as the index date.

Control patients

Propensity score matching was used to select control patients who did not have PD. The propensity scores were based on patients' age, sex, Charlson's comorbidity index (CCI)[6], and geographic region. The 1:1 propensity score matching method[7] and the nearest neighbor algorithm with a perfect proportion of 0.995–1.0[8] were used to select patients who had not been diagnosed with PD as the comparator group. We assigned the index date of each patient with PD to his or her corresponding matched control. After completing the matching procedures, the cohort included 2648 patients with PD and 2648 controls.

Definition of categorical non-motor symptoms

The non-motor symptoms were based on a literature review and expert opinions[9,10]. We divided these non-motor symptoms into six categories: sleep disorders, psychiatric disorders, smell/taste disorders, gastrointestinal disorders, genitourinary disorders, and other specific disorders (most were cardiovascular). Each system type represents a separated pathophysiological system. These symptoms were then approximated to the associated ICD9-CM codes. In the researched database, coding was previously performed by physicians during outpatient visits or on admission. These extracted ICD9-CM codes of non-motor symptoms were identified in each patient's health record from January 1, 2000 (the start date of our version of the database) to 7 days before the index date of the PD diagnosis. Diagnostic codes suggestive of motor symptoms of PD (e.g. tremor, abnormal posture, shoulder pain, spasm of muscles, abnormal involuntary movements) were not set as excluding parameters. Details of the ICD9-CM codes are listed in Appendix I.

Statistical analysis

The baseline data are presented as frequencies with percentages for categorical variables and

Appendix I

ICD 9-CM chart of risk factor diagnosis.
The six categories were listed as follows:
1. Gastrointestinal: 564.00, 564.01, 564.02, 564.09, 564.32, 530.11, 530.81, 536, 537, 787.61.
2. Sleep disorders: 327.30, 327.31, 327.32, 327.36, 327.37, 327.42, 327.51, 333.94, 780.50, 780.52.
3. Smell and taste: 781.1.
4. Psychological disorders: 300.00, 300.01, 300.02, 300.10, 300.20, 300.4, 330.9, 311.
5. Genitourinary: 607.84, 788.41, 788.42, 788.43, 788.2, 788.3, 788.91.
6. Other specifics: 333.0, 355.9, 337.9, 458.0, 780.4, 785.1, 786.59.

Note: Each diagnosis was counted when the individual had more than two records of diagnosis in the outpatient department or more than one record of hospitalization.

as the mean and standard deviation for continuous variables. The *t*-test and χ^2 test were used to describe the differences between the PD and control groups for categorical variables and continuous variables, respectively. The odds ratio (OR) of each category of ICD9-CM codes (symptoms) was calculated using logistic regression. The adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated with adjustments for confounding factors of PD.

To evaluate the effect of multiple symptom categories, we divided the subjects into groups simultaneously carrying symptoms from 0, 1, 2, 3, 4, and ≥5 categories and examined the risk of PD in each group. All p-values were two-sided, and $p < 0.05$ denoted significance. Receiver operating characteristic (ROC) curves and area under the ROC curve (AUC) were used to assess the best number of symptom categories that predicted the risk of PD. All analyses were computed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

Ethics

This study was approved by Tungs' MetroHarbor Hospital Institutional Review Board (No: 109021).

Results

The baseline characteristics of the PD and control groups were comparable (Table 1). The percentage of male patients did not differ between the groups ($p = 0.68$), and age did not differ between the groups after adjustment for confounders. The geographic region and CCI were similar between the groups ($p = 0.887$ and $p = 0.081$, respectively).

The number of cases and ORs of each category of non-motor symptoms in association with PD are presented in Table 2. In the unadjusted analysis, gastrointestinal disorders (OR = 1.67, 95% CI = 1.48–1.88, $p < 0.001$), sleep disorders (OR = 1.89, 95% CI = 1.62–2.21, $p < 0.001$), psychological disorders (OR = 2.45, 95% CI = 2.09–2.86, $p < 0.001$), genitourinary disorders (OR = 1.50, 95% CI = 1.18–1.91, $p < 0.001$), and other specific disorders 1.84 (OR = 1.84, 95% CI= 1.62–2.09, $p < 0.001$) were associated with an increased risk of PD. Only two patients were coded with smell/taste disorders, and this category was not included in the adjusted analysis. After adjustment for confounders, the aforementioned categories remained significantly associated with the risk of PD.

Table 1. The baseline characteristics of Parkinson's disease (PD) and control patients

	PD N=2648	Control N=2648	*p* value χ^2 test
Sex			0.680
Female	1,276 (48.2)	1,291 (48.8)	
Male	1,372 (51.8)	1,357 (51.3)	
Age			
<60	441 (16.7)	430 (16.2)	<.001
60-70	515 (19.5)	440 (16.6)	
70-80	999 (37.7)	899 (34.0)	
80^+	693 (26.2)	879 (33.2)	
mean±SD	72.8 ± 13.9	71.2 ± 13.2	<.001
Geographic Region			
Northern	1,080 (40.8)	1,068 (40.3)	0.887
Central	673 (25.4)	686 (25.9)	
Southern	815 (30.8)	822 (31.0)	
Eastern	80 (3.0)	72 (2.7)	
CCI score			0.039
0	960 (36.3)	930 (35.1)	
1-5	1,268 (47.9)	1,228 (46.4)	
6^+	420 (15.9)	490 (18.5)	
mean±SD	3.1 ± 3.0	3.0 ± 2.9	0.081

The percentage of patients with PD increased as the number of relevant categories increased. Specifically, the rate of PD among patients with zero symptom categories was 40.6%, versus 81.8% for patients with five symptom categories (p < 0.001). Subsequently, the risk of PD was assessed according to the number of categories (Table 3). When the individual carried one category of non-motor symptoms, the aOR for having PD was 1.28 (95% CI = 1.13–1.45, p < .0001). When the individual carried more than four categories, the aOR for having PD increased to 3.16 (95% CI = 2.20–4.53, p < 0.0001). There was a cumulative effect of carrying multiple non-motor symptoms (p-trend = 0.030). The cut-off for best discrimination was two

Table 2. Case numbers and the odd ratios (ORs) of each symptom category in Parkinson's disease (PD) and control patients

Symptom Category	PD	Control	*p* value χ^2 test	Crude OR for PD vs. control (95%CI)	*p* value	Adjusted OR* for PD vs. control (95%CI)	*p* value for logistic regression model
Gastrointestinal				1.67(1.48-1.88)	<.001	1.79(1.56-2.03)	<.001
No	1,759(66.4)	2,032(76.7)	<.001				
Yes	889(33.6)	616(23.3)					
Sleep disorders				1.89(1.62-2.21)	<.001	1.96(1.68-2.30)	<.001
No	2,144(81.0)	2,355(88.9)	<.001				
Yes	504(19.0)	293(11.1)					
Smell and taste				(-)		(-)	
No	2,647(99.96)	2,647(99.96)	1				
Yes	1(0.04)	1(0.04)					
Psychological disorders				2.45(2.09-2.86)	<.001	2.52(2.15-2.96)	<.001
No	2,074(78.3)	2,379(89.8)	<.001				
Yes	574(21.7)	269(10.2)					
Genitourinary				1.50(1.18-1.91)	<.001	1.55(1.22-1.97)	<.001
No	2,473(93.4)	2,529(95.5)	<.001				
Yes	175(6.6)	119(4.5)					
Other specifics				1.84(1.62-2.09)	<.001	1.98(1.74-2.26)	<.001
No	1,833(69.2)	2,133(80.6)	<.001				
Yes	815(30.8)	515(19.5)					

*Adjusted sex, age, geographic region and CCI score.
OR: odds ratio.

Table 3. The percentage and odd ratio (ORs) of Parkinson's disease (PD) in each group based on symptom-category numbers.

Number of Symptom categories	Number of cases, (%)	Number of PD cases in each group	Percentage of PD	P for chance of PD	Crude OR for PD vs. control (95%CI)	*p* value	Adjusted OR* f or PD vs. control (95%CI)	*p* value for logistic regression model
0	2,602 (49.1)	1,057	40.6%	<.0001				
1	1,351 (25.5)	738	54.6%		1.28(1.13-1.45)	<.0001	1.28(1.13-1.45)	<.0001
2	795 (15.0)	478	60.1%		1.62(1.39-1.89)	<.0001	1.68(1.44-1.96)	<.0001
3	386 (7.3)	255	66.1%		2.05(1.65-2.55)	<.0001	2.12(1.70-2.64)	<.0001
4	140 (2.6)	102	72.9%		2.95(2.06-4.20)	<.0001	3.16(2.20-4.53)	<.0001
5	22 (0.4)	18	81.8%					
total	5296	2648					(p-trend p=.030)	

*Adjusted sex, age, geographic region and CCI score. OR: odds ratio.

categories (AUC = 0.625, Youden index = 0.52719 [sensitivity] + 0.6571 [specificity] − 1 = 0.18429), as presented in Figure 1.

Discussion

This study revealed the cumulative effect of non-motor symptoms on the risk of PD. This was a proof-of-concept result based on a healthcare database.

Non-motor symptoms have been commonly reported in the early stage of PD. Some symptoms are present several years before PD is diagnosed and are underrated or neglected by clinicians[11]. Several cohorts have analyzed national health databases at great scale regarding the predictive associations of single factors such as constipation, depression[12], and anxiety[13] with the risk of PD. However, these non-motor symptoms are insufficiently specific (e.g., constipation) to prompt any action when present alone.

Questionnaire-based tools encompass batteries of autonomic features (SCOPA-AUT)[9] or combined sleep, psychological, and memory problems (NMS-Quest)[10,14] and are more comprehensive assessments. However, these questionnaires were developed and validated based on subjects of diagnosed PD. Some sub-items in the list, such as drooling and intense dreaming, are better for assessing disease severity, the degree of disability, and quality of life because of their high levels of detail. They were conceptualized as aids in clinical visits but not for risk prediction.

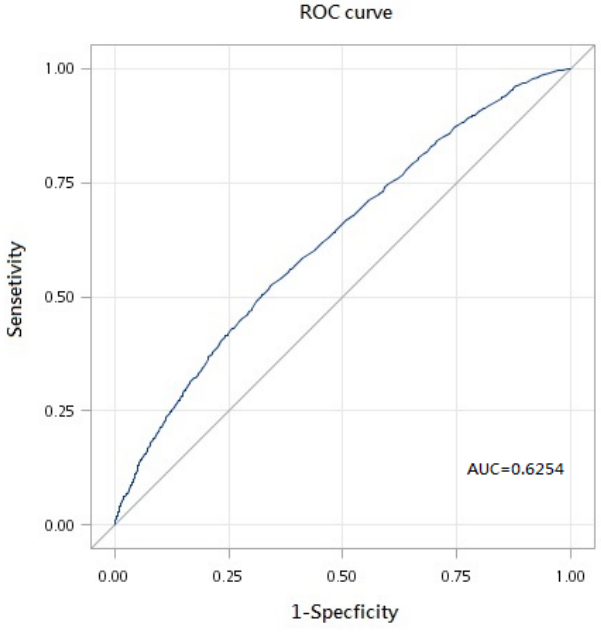

Figure 1. Receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) for predicting the risk of Parkinson's disease.

PREDICT-PD is a broadened and complicated scoring algorithm of 14 items, including geographic data, family history, head injury, substance use, hypertension, medications, mood disorders, constipation, and erectile dysfunction[15]. It was established as a screening tool for predicting the risk of PD based on a previous meta-analysis, and it was validated in a 6492-person sub-cohort of the Rotterdam Study, an independent population-based sample covering a 20-year period. PREDICT-PD slightly improved the long-term prediction of PD (hazard ratio = 1.30; 95% CI = 1.06–1.59)[16].

Based on a nationwide database, we also confirmed that patients were more likely to experience five different types of non-motor symptoms than propensity score-matched controls in the period before the diagnosis of PD, including gastrointestinal, sleep, psychological, genitourinary, and cardiovascular disorders.

In most previous studies of non-motor symptoms in patients diagnosed with PD, symptom co-occurrence was common. Most NMSQuest PD cases carried at least 10 symptoms simultaneously, of which had weaker correlations with disease duration than with disease severity[16]. In a recent study based purely on administrative claims data, the author proved that as many as 536 diagnostic and procedure codes had good prognostic value for PD[17].

We intended to establish a simple, symptoms-based, NMSQuest-like assessment of our study population. Each symptom category represents a separated pathophysiological system. The effect of the co-occurrence of multiple symptom categories prior to PD was cumulative. Our study result suggested that by systemically assessing and calculating other types of non-motor symptoms during patient visits, clinicians may have an opportunity to discover PD as an ongoing disease process.

The best AUC was 0.625 at two categories, and despite not being extremely impressive, it was comparable with those of NMSQuest and 'Sniffin' Sticks' (AUC = 0.623 and AUC = 0.567, respectively), which were tested in a small set of 62 cases)[20].

Only two patients in our cohort had diagnoses of

smell/taste disorders, probably because of underreporting or underdiagnoses in our health care system. This finding might provoke further attention toward smell and taste problems in primary care facilities.

The pathophysiology of early non-motor symptoms remains unknown. It was assumed that the earliest pathological disturbance occurs at synapses[18, 19]. Alpha-synuclein micro-aggregation, synaptic vesicle clustering, and decreased dopamine release occur in this prodromal phase. Early non-motor complaints might be presentations of the neurophysiologic dysfunction at synapses, and intervention at this stage may have a critical impact on the disease course before neuronal death. Identifying people in the general population at risk of PD based on the presence of early non-motor symptoms might enable recruitment for biomarker studies and risk-determination trials and facilitate the development of early disease modifying treatments.

This study had some potential limitations. This was a retrospective study using a national health database. People who did not request any medical help were not studied. Several known risk factors of PD were not available in database coding system. Risk underestimation bias exists during the symptom extraction and coding process. After propensity score matching, the final case number was small. Diabetes and hypertension are known risk factors of PD, but because they are items comprising CCI, they were adjusted. In addition, temporal patterns of co-occurrence and frequency of symptoms were not analyzed in the current study.

Conclusions

Non-motor symptoms are associated with PD, and the co-occurrence of high numbers of categories of non-motor symptoms is related to an increased risk of subsequent PD.

Declarations of interest: none.

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Contribution of authors

- Study conception and design: H-F W, Y-K C
- Acquisition of data: Y-K C
- Analysis and interpretation of data: H-F W, Y-K C, C-Y C, H-C F.
- Drafting of manuscript: H-F W, Y-K C
- Critical revision: H-F W, H-C F

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非運動型障礙類型之數量與帕金森氏症的關係：一個以族群為基礎的回溯性病例對照研究

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摘要

研究背景：非運動型障礙與帕金森氏症有關，但是這些非運動型障礙類型的數量和帕金森氏症的相關性仍然未知。本研究目的就是要評估不同類型的非運動型障礙同時發生時與疾病的關係。
研究方法：本研究的樣本是來自 2000 年台灣健保資料庫百萬抽樣檔，選取 2007 年 1 月 1 日到 2012 年 12 月 31 日診斷碼為 ICD9 為 332 並有服用巴金森氏症藥物的病患。利用傾向因子分數納入年齡、性別、查爾森共病症指數及投保地區，以 1 比 1 的比例選取年齡、性別、共病症及投保地區相似的對照組。病患有無非運動型障礙只計算於從巴金森氏症的診斷日之前 7 天往回溯至資料庫起始日。本研究使用邏輯式迴歸分析六類非運動型障礙與巴金森氏症的關係。
研究結果：各有 2648 名巴金森氏症及非巴金森氏病患納入分析。除了嗅味覺異常因案例數極少而排除分析之外；和非巴金森氏症病患相比，巴金森氏症病患在腸胃道類障礙、睡眠類障礙、心理類障礙、泌尿生殖類障礙及其他類非運動型障礙的勝算比，分別為 1.79、1.96、2.52、1.55 及 1.98，皆達統計顯著差異。有巴金森氏症病患的勝算比會隨著有非運動型障礙類型數目的增加而增加，從有一類的勝算比 1.28 增加到有四類為 3.16，且都達到統計顯著差異。
結論：研究結果顯示非運動型障礙和巴金森氏症的發生風險有關，伴隨非運動型障礙類型的數量可以作為預測巴金森氏症風險的參考。

關鍵詞：巴金森氏症，非運動型障礙，前運動期障礙，自律神經異常，阿爾發突觸核蛋白，改變病程因素

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Case Report

Cervicomedullary Myelitis Related to Sjögren's Syndrome and Breast Cancer Mimicking Acute Ischemic Stroke

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Abstract

Distinguishing between acute myelitis and ischemic stroke within a limited time frame for initiating thrombolytic therapy is challenging. A 70-year-old woman presented to the emergency department with acute right limb weakness, and brain magnetic resonance imaging (MRI) revealed a hyperintense lesion at the cervicomedullary junction. Sjögren's syndrome-related myelitis was diagnosed based on an elevated anti-SSA antibody level, positive Shimer's test, and radionuclide sialoscintigraphy even though anti-aquaporin-4 antibody levels were normal. Her hemiparesis improved rapidly after steroid treatment but she developed painless muscle spasms in the left side of the neck and both hands and feet that were refractory to medication. Next, she was also diagnosed with cancer of the left breast that was positive for anti-recoverin autoantibody. The spasms markedly improved after her medication was changed to oxcarbazepine and upon mastectomy for the cancer. This case report indicates that Sjögren's syndrome and a paraneoplastic syndrome can coexist and that cervicomedullary myelitis can mimic hyperacute stroke.

Key words: Acute ischemic stroke, Sjögren syndrome, autoimmune myelitis, breast cancer, paraneoplastic myelitis

Introduction

Acute hemiparesis is a crucial symptom of stroke that is based on the Cincinnati Prehospital Stroke Scale [1]. Importantly, the positive predictive value of code stroke activation in the emergency department has been reported to be close to 72% for the presence of any three signs, e.g., facial droop, arm weakness, and speech disturbance [2]. Conditions that mimic a stroke account for up to 30% of all suspected stroke cases, and the most common are seizure, complicated migraine, conversion disorder, and metabolic disorders [3]. Interestingly, spinal cord disease accounts for less than 3% of all cases of stroke mimics [4].

Infection and immune-mediated responses are common causes of acute myelitis, and paraneoplastic syndromes affecting the spinal cord are considered to be autoantibody-mediated processes as antigens in the central nervous system originate from the cancerous lesion. Furthermore, investigating the etiology of myelitis is complicated; hence, distinguishing between acute myelitis and ischemic stroke within a limited timeframe in patients who are eligible for thrombolytic therapy in the emergency department is challenging. Here, we describe a case of cervicomedullary myelitis presented to the emergency department with acute right limb weakness mimicking acute stroke.

Case Report

A 70-year-old woman with a 3-year history of hypertension presented to the emergency department with right limb weakness upon waking up in the morning. On examination, she was alert; no dysarthria, dysphagia, or facial palsy was noted; and muscle strength of her right arm and right leg was

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graded as 3/5 (Medical Research Council of Great Britain). Emergent brain computed tomography (CT) revealed an old infarct in the right basal ganglion, and an acute ischemic stroke due to a pure motor lacunar infarct was suspected. Owing to prolonged prehospital delay and relatively mild stroke severity, neither intravenous thrombolytics nor endovascular thrombectomy was considered. However, her right limb muscle strength decreased to grade 2 on day 2, and a brain magnetic resonance (MR) angiography scan revealed a hyperintense lesion at the cervicomedullary junction in T2-weighted images (T2WI). Additional cervical spine MR imaging (MRI) corroborated the presence of the same hyperintense lesion on T2WI (Fig. 1), and digital subtraction angiography of the cerebral vessels excluded the possibility of an abnormal dural arteriovenous fistula. A visual evoked potential study revealed prolonged responses in both eyes. Cerebrospinal fluid (CSF) analysis was normal for cell count, protein and glucose levels, and immunoglobulin G index. Serum and CSF virological tests were negative, and while the immunological panel was negative for anti-aquaporin-4 antibody, slightly elevated anti-SSA antibody levels were seen. She also complained of dry eyes and mouth for the last nearly one year, and Shirmer's test revealed 0 mm of moisture in 5 minutes in both eyes, indicating tear deficiency. As additional radionuclide sialoscintigraphy revealed marked-to-severely impaired uptake in the parotid and the submandibular glands bilaterally, she was diagnosed with Sjögren's syndrome-related myelitis on day 5. She required urinary catheterization on the day 3 of hospitalization for acute urinary retention.

We initiated intravenous methylprednisolone (40 mg; four times/day for 5 days) on day 5, followed by oral prednisolone, which improved muscle strength her right hand and leg. However, prednisolone was discontinued on day 18 as she developed a urinary tract infection. Next, frequent short-duration painless tonic spasms of the muscles in the left neck, shoulder, and arm were observed from day 7 onwards; specifically, while they initially occurred every several hours and lasted approximately 30 seconds, they progressively worsened, extended to all four limbs, occurred every 30–60 minutes except when sleeping, and were possibly triggered by either active or passive movement of the upper limbs. Importantly, in the following 3 weeks, these painless tonic spasms were refractory to drug treatment, including clonazepam, baclofen, pregabalin, and phenytoin. After confirming absence of HLA allele B*1502, we prescribed oxcarbazepine on day 28, at a dose of 300 mg twice daily, and increased it to 600 mg twice daily on day 32, resulting in improvement in the frequency, duration, and distribution of the painless tonic spasms.

A detailed physical examination on day 10 revealed a firm soft tissue mass on her left anterior chest wall and a chest CT showed a 2.2 × 2.0-cm ovoid solid mass with irregular margins in the upper inner quadrant of the left breast (Fig. 1E). She initially

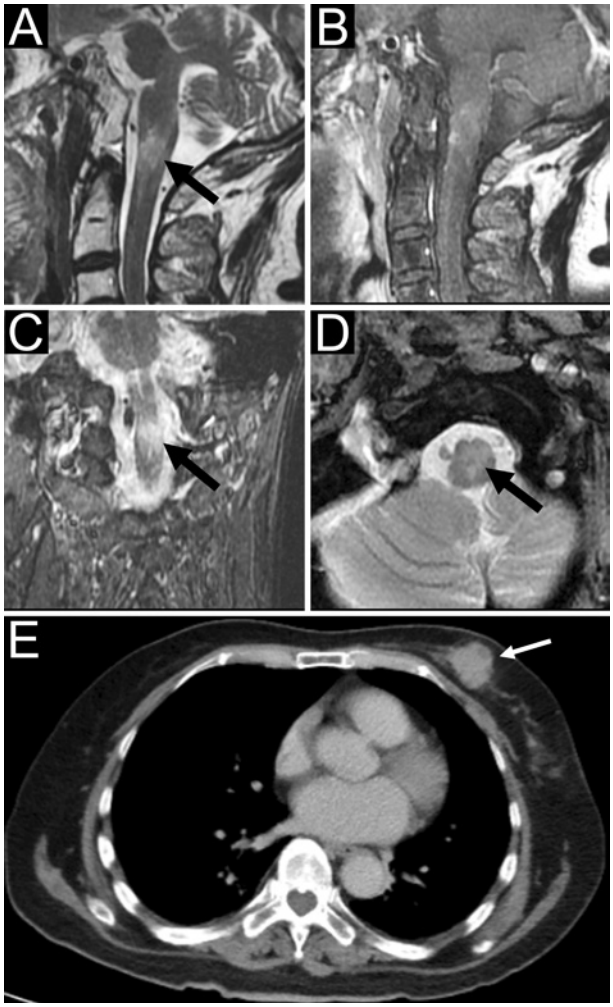

Fig. 1 Initial cervical spinal MR imaging displays a hyperintense lesion (large arrows) that is predominately located ventrally and to the left side of the spinal cord on T2-weighted images at the cervicomedullary junction in the sagittal view (A), coronal view (C), and axial view (D). Enhanced sagittal T1-weighted image shows faint enhancement of the lesion (B). (E) Chest computed tomography shows a soft tissue lesion at the left anterior chest wall (small arrow).

refused to undergo further intervention with respect to the mass but an autoantibody survey of 12 antibodies for paraneoplastic neurologic syndrome, including anti-Hu, anti-Yo, anti-Li, anti-GAD65, anti-amphyphysin, anti-recorerin, anti-CV2, anti-Tr/DNER, anti-Zic4, anti-titin, anti-SOX1, and anti-PNMA2 (Ma2/Ta), was positive for the anti-recoverin antibody. Ophthalmic evaluation, i.e., funduscopic examination and microsonographic study, could not identify any abnormal lesions. She underwent a needle biopsy of the mass in the left breast one month after admission, and as the tissue was determined to be an invasive carcinoma, she underwent a modified radical mastectomy on day 35. The tonic spasms improved markedly once her medication was changed to oxcarbazepine and after removal of the cancerous mass, and they completely subsided one month after the mastectomy. She was discharged on day 45 .

She developed hyponatremia during the follow-up period, which was managed by reducing the dosage of oxcarbazepine to 150 mg/day, but as she continued to experience occasional transient spasm-like sensations in the right arm, oxcarbazepine dosage was maintained between 150 and 300 mg/day. A follow-up cervical MRI 2 months later showed regression of the cervicomedullary myelitis (Fig. 2) and she recovered well by 10 months after initial symptom onset, except for dysuria.

Discussion

Acute hemiparesis, which is a common symptom of acute stroke, is an unusual initial presentation of myelitis. Barreras et al. analyzed 457 patients with myelopathy and noted that hyperacute (<6 hours) or acute (6–48 hours) onset of clinical symptoms was observed in 98% of patients with spinal ischemia, whereas only 17% (69/395) of the other patients exhibited acute symptoms [5]. Additionally, etiological lesions for most stroke mimics of spinal disorders with acute hemiparesis were located in the cervical spine. A study reported that only 15 patients with spinal disorder were treated with thrombolytic therapy due to symptoms mimicking an acute stroke [6]. Although no intravenous thrombolytic therapy was provided to our patient because of prolonged prehospital delay, we believe that thrombolytic therapy would have been appropriate if she had arrived at the emergency department within the therapeutic window.

Hyperintense lesions on T2W images, with various degrees of enhancement on T1W images, can be due to infection, inflammation, infarction, demyelination, or swelling from venous congestion; notably, MRI features of spinal cord infarcts and neuromyelitis optica show similar overlap. However, vascular ischemic lesions occur less frequently in the upper cervical cord area because of relatively greater collateral flow from the vertebral arteries. In our patient, the negative anti-aquaporin-4 antibody test concurred with the involved spinal lesions spanning less than three vertebral segments and excluded the possibility of neuromyelitis optica.

Our patient fulfilled five of the six consensus criteria for the diagnosis of primary Sjögren's syndrome

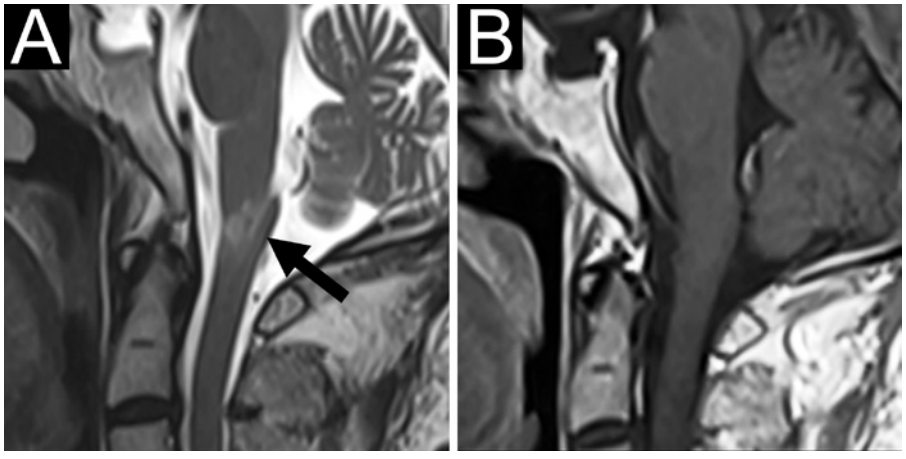

Fig. 2 Follow-up cervical spinal T2-weighted MR images at the cervicomedullary junction in the sagittal view show regression of the hyperintense lesion (arrow) (A), and without enhancement in the T1-weighted contrast image (B).

established by Vitali et al [7], and the diagnosis of Sjögren's syndrome-related myelitis was based on a slightly elevated anti-SSA antibody level, a positive Shirmer's test, and abnormal sialoscintigraphy. Even though she did not complain of vision problems, subclinical optic neuropathy could be present in patients with Sjögren syndrome who show abnormal visual evoked potentials. Analysis of a large case series by Delalande et al. revealed that spinal involvement occurred in 35% of Sjögren's syndrome patients with neurologic manifestations [8]. Further, even though myelopathy could be acute, subacute, or chronic, with progressive remission and relapse symptoms presenting as tetraparesis and paraparesis when motor symptoms were involved, only 1 of 29 patients with myelopathy presented with acute lateral cervical myelitis resulting in hemiplegia. Proposed etiopathologies include immune response confusion between infectious and common antigens in the spinal cord, immunologically mediated spinal vascular damage, development of antineuronal antibodies (e.g., aquaporin-4 antibodies), and a direct role for anti-SSA antibodies [8,9], and corticosteroids and immunosuppressants constitute recommended primary therapy.

Tonic spasms markedly improved with a standard dose of oxcarbazepine and after the mastectomy for breast cancer, but we believe that oxcarbazepine played a major role because tonic spasms tended to recur upon dose tapering. Painful or painless tonic spasms have been described in cerebral and spinal disorders, such as multiple sclerosis, neuromyelitis optica, cerebral infarction, and demyelinating and inflammatory myelopathy, and are thought to be caused by transversely spreading ephaptic activation of axons within a partially demyelinated lesion in the fiber tracts somewhere in the central nervous system [10]. Another hypothesis posits that ectopic induction of voltage-gated sodium channels at demyelinated axons contributes to ephaptic transmission [11]. Carbamazepine and its structural derivative, oxcarbazepine, are sodium channel-blocking anticonvulsants that have demonstrated superior control of tonic spasms [12]. However, the strong association between the potentially life-threatening Steven–Johnsons syndrome and carbamazepine, particularly in Asians with the HLA B*1502 allele, limits its clinical application.

The detection of a lesion in the left breast, concurrent with treatment-refractory tonic spasms, prompted us to suspect concomitant paraneoplastic myelitis as it is predominantly seen in patients with lung and breast cancers. Further, the anti-Hu antibody, which is most-commonly detected, usually presents with rapidly progressive limb weakness and urinary sphincter involvement. Even though no other paraneoplastic antibodies, except for anti-recoverin antibody, were detected, the possibility of concomitant paraneoplastic and Sjögren's syndrome-associated myelitis could not be completely excluded in our patient and repeated neoplastic antibody surveys were necessary. Presence of the anti-recoverin antibody is associated with cancer-related retinopathy, which can occur long after a diagnosis of malignancy; hence, long-term follow-up of symptoms, including visual acuity, are important.

Conclusion

Our case report implies that acute cervicomedullary myelitis can present as acute hemiparesis mimicking a stroke, and that Sjögren's syndrome myelitis might coexist with paraneoplastic myelitis related to breast cancer. Oxcarbazepine, along with the removal of the cancer lesion, was effective in controlling frequent tonic spasms of the limbs, which is an unendurable complication of myelitis.

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Declarations of interest: none.

Conflicts of interest

Authors have no conflict of interests.

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與修格蘭氏症候群和乳腺癌相關的頸延髓脊髓炎類似急性缺血性中風之表現

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摘要

在有限時間內區分腦中風與急性脊髓炎進行溶栓術具挑戰性。70 歲的婦女發生急性右側肢體無力。腦部磁振造影顯示頸延髓交界處高強度病變。免疫學檢查顯示 anti-SSA 升高而 anti-aquaporin-4 陰性。Shirmer 檢驗顯示淚液缺乏，唾液腺攝影檢查顯示雙腮腺和下頜下腺功能受損。診斷為修格蘭氏症候群脊髓炎。病人的偏癱經類固醇治療後迅速好轉。但左頸和四肢頻繁發生無痛性強直性痙攣難以控制。此外，發現左側乳腺癌併陽性的 anti-recoverin 抗體。痙攣在更改藥物為 oxcarbazepine 及乳癌手術後明顯改善。急性頸延髓炎可表現出類似中風的偏癱，修格蘭氏症候群脊髓炎可能與乳腺癌伴生脊髓炎並存。

關鍵詞：急性缺血性腦中風，修格蘭氏症候群，自體免疫性脊髓炎，乳腺癌，伴生性脊髓炎

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Case Report

Painful and Swollen Scrotum: A Rare Complication of Acute Pancreatitis

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Abstract

Acute scrotal swelling may be caused by the extension of a pancreatic collection or abscess through the inguinal canal into the groin area and is a rare complication of acute pancreatitis. Although this complication has a low incidence, we must consider this condition as it may be misdiagnosed as other more common pathologies of a swollen scrotum such as testicular hydrocele, orchiepididymitis, testicular torsion, inguinal hernia, and testicular tumor and may result in inappropriate or delayed treatment. Herein, we describe a case of right scrotal swelling caused by severe acute pancreatitis in a 52-year-old man. Computed tomography was helpful in the diagnosis. Typical imaging demonstrated peripancreatic fluid through the inguinal canal to the right scrotum and confirmed the diagnosis by aspirated scrotal fluid with elevated lipase levels.

Key words: pancreatitis, complication, scrotal swelling

Introduction

Clinically significant scrotal swelling due to a pancreatic fluid collection is a rare complication of severe acute pancreatitis and is believed to be caused by fat necrosis of the soft tissue of the scrotum due to the destructive effect of pancreatic fluid. With a high index of suspicion, a careful analysis of the patient's history and examination along with computed tomography may provide an accurate diagnosis. Local drainage may be essential to control sepsis and also provide an egress route for intra-abdominal collections. Here we describe a case of right scrotal swelling caused by severe acute pancreatitis in a 52-year-old man.

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Case report

A 52-year-old man with no chronic medical conditions presented with fever, persistent upper abdominal dull pain for 7 days after binge drinking, and right scrotal pain 4 days after the onset of abdominal pain. Before presenting to our hospital, he had already received conservative management at a local hospital for 7 days under the diagnosis of acute pancreatitis and acute epididymitis. Initial laboratory tests revealed leukocytosis and an elevated serum lipase level of 577 IU/L. Computed tomography of the abdomen, which was performed on the third day of abdominal pain, showed extensive peripancreatic inflammation and fluid accumulation in the retroperitoneal space, which was consistent with grade E acute pancreatitis according to Balthazar's grading system. However, his scrotums were bilaterally intact. Upon arrival at our emergency department, his blood pressure was 205/98 mmHg, heart rate was 107 beats per minute, and body temperature was 38.4°C. On

examination, the right scrotum was swollen, tender, with erythematous change over the skin (Figure 1). Laboratory investigations revealed a white blood cell count of 13×10^3 with 76% neutrophils and an elevated C-reactive protein level of 31.63 mg/dl. His lipase and amylase levels were within the normal limit. Bedside echography disclosed mild right hydrocele and phlegmons in the scrotal cavity (Figure 3). Repeated computed tomography of the abdomen revealed grade E acute pancreatitis with homogeneous enhancement and swollen pancreas, peripancreatic stranding with fluid collection, and diffuse fluid in the abdomen and pelvis. The retroperitoneal fluid flowed through the right inguinal canal to the right scrotum (Figure 2). We also performed percutaneous echo-guided needle-aspiration of right scrotal fluid, and a turbid yellowish fluid of approximately 15 ml was aspirated, which revealed a lipase level of 71 IU/L (normal value: <60 IU/L). The clinical impression was acute pancreatitis with pancreatitis-related scrotal swelling and pain, and the patient was admitted to the gastroenterology ward. During the hospitalization period, he was treated with antibiotics for infection control, and percutaneous transretroperitoneal drainage was performed for adequate drainage of the pancreatic fluid. Subsequently, the patient recovered well and was discharged in a satisfactory condition after 10 days of hospitalization.

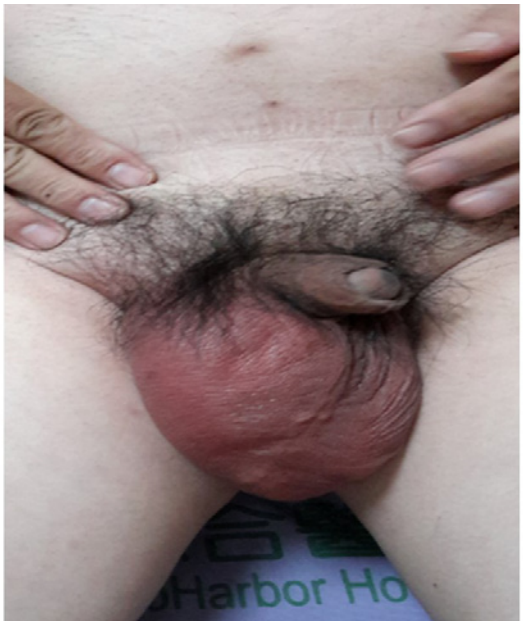

Fig. 1 Right scrotum was swollen, tender, with erythematous change over the skin.

Discussion

Pancreatitis is an extremely rare cause of scrotal pain. As pancreatitis progresses, fluid arising from the pancreas can leak into the retroperitoneal and peritoneal spaces. This fluid containing pancreatic exudates and debris may flow down the retroperitoneum into the inguinal canal and scrotum, causing local irritation and fat necrosis [1].

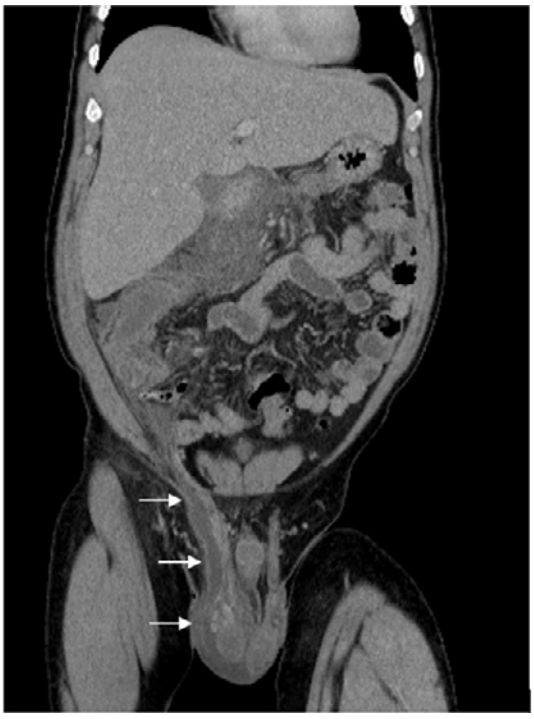

Fig. 2 Abdominal computed tomography with contrast coronal view showed diffuse fluid in the abdomen and pelvis. The retroperitoneal fluid extended through the right inguinal canal to the right scrotum (white arrow).

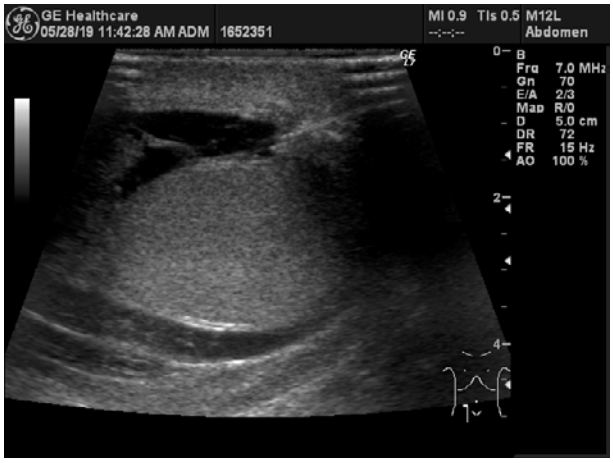

Fig. 3 Bedside echography showed mild right hydrocele and phlegmons in the scrotal cavity.

Based on a review of literature reports of cases of inguinal, scrotal, and/or penile extension of pancreatic collections, we found that most cases affected the left side of the scrotum. Excessive binge drinking is the most common cause of pancreatitis. Gallstones and pancreatic surgery such as Whipple's procedure have also been reported [2].

The clinical signs of a pancreatic fluid accumulation in the scrotum will result in scrotal swelling, pain, and ecchymosis. In such cases, the condition can also be confused with epididymitis, testicular hemorrhage, orchitis, hydrocele, testicular tumor, strangulated hernia, or testicular vasculitis. The correct diagnosis depends on detailed history-taking, physical examination, and imaging with ultrasound and computed tomography, which are the most common methods. A missed diagnosis may lead to unnecessary surgery and inappropriate or delayed treatment [2-3].

The clinical management of pancreatitis-induced scrotal swelling includes supportive care with intravenous fluid and prophylactic antibiotics, and some patients may require percutaneous drainage of retroperitoneal and scrotal collections for complete resolution [2]. Some patients may even require surgical exploration to clear the pancreatic collection and debris.

In our case, the patient completely recovered after percutaneous drainage. Unnecessary surgery was avoided because of detailed history-taking and appropriate imaging examinations, which disclosed the pancreatic fluid extending from the peripancreatic space to the scrotum.

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疼痛腫脹的陰囊：一個罕見的急性胰臟炎併發症

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摘要

急性陰囊腫脹可能是因為胰液或者胰臟膿腫經由腹股溝延伸至陰囊，這是急性胰臟炎的一個少見的併發症。儘管這種併發症發生的機率很低，但它確實引起我們的注意，因為它可能被誤診為其他更常見的疾病，例如睪丸鞘膜積液、睪丸附睪丸炎、睪丸扭轉、腹股溝疝氣或者睪丸腫瘤等等，可能會因此造成不必要的手術或者延誤治療。因此我們提出一個案例，一位 52 歲的男性因位胰臟炎併發症而產生的急性陰囊腫脹。電腦斷層檢查提供了一個很有效的診斷方式，典型的電腦斷層看到胰臟周圍有液體存在，這些異體經由腹股溝流到右側陰囊，並且最後經由抽吸陰囊內液體檢測脂肪酶的方式確診。

關鍵詞：胰臟炎，併發症，陰囊腫脹

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Case Report

Foldable IOL Crack and Surface Scratch in Microincision Cataract Surgery: A Report of 3 Cases

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Abstract

Purpose: To describe and evaluate surface abnormalities of AcrySof intraocular lenses (IOLs; SA60AT) that were implanted by Alcon Monarch III injector with D cartridge.
Methods: This study comprised 98 eyes that underwent small-incision cataract surgery where foldable acrylic IOLs (SA60AT, Alcon) were inserted in all cases. All surgeries used the same viscoelastic agent: sodium chondroitin sulfate and sodium hyaluronate combination (Viscoat). Alcon Monarch III injector with D and C cartridges was used in 56 and 42 cases, respectively.
Results: Three IOLs using D cartridge had white longitudinal lines on the anterior surface immediately after implantation. We removed one IOL during an operation because of severe while lines resembling cracks. The best-corrected visual acuity of the other two patients was 0.9 despite white lines on the surface of IOL.
Conclusion: The surface abnormalities of IOL did not disappear within one month postoperatively. Although surface abnormalities might not influence the visual acuity of the two patients, severe cracks on the only removed IOL might. The cracks are probably caused by the friction in the injector cartridge D and change in viscosity of Viscoat under abnormal temperature. However, due to the small sample size and short follow-up, further research is necessary.

Key words: microincisional cataract surgery, intraocular lens surface abnormality, IOL delivery system

Introduction

The appearance and development of small-incision cataract surgery led to an increased interest in foldable intraocular lenses (IOLs) [1, 2] because it results in earlier rehabilitation by reducing postoperative astigmatism and inflammation [3, 4]. Acrylic IOLs have several advantages over silicone IOLs, leading to their increased use [5]. Silicone IOLs caused more ocular inflammation and induced much more capsular opacification, both posterior and anterior, than hydrophobic acrylic IOLs. Besides, the acrylic IOLs have better contrast sensitivity, functional visual performance, and scotopic/mesopic vision performance and less severe ocular aberrations than silicone IOLs [6]. However, surface abnormalities and changes in the lens material, such as glistening [6], marks and scratches [7-10], stress fracture [11], and cracks [12, 13], have been described.

A smaller corneal wound can cause less surgically induced astigmatism[17]. Because more and more premium IOLs such as toric or multifocal IOL are introduced, it is usually preferable to have a smaller corneal incision during the surgery. Monarch III (Figure 1) is an IOL delivery system used for multipiece and single-piece IOLs. With the introduction of the small corneal size phacoemulsification system, we changed the corneal incision wound from 2.75 mm to 2.2 mm in this study. Additionally, we used Monarch III IOL injector with a D cartridge that can deliver the IOL through 2.2 m corneal wound. Herein, we describe cracks and scratches that appeared on the surface of

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single-piece acrylic Alcon SA60AT IOLs after implantation by Monarch III IOL injector with D cartridge.

Patients and Methods

This study comprised 98 eyes with senile cataracts that underwent phacoemulsification and implantation of a foldable acrylic IOL (SA60AT, Alcon). Informed consent was taken, and patients received standard phacoemulsification by a single surgeon on a single machine. 42 IOLs were implanted by Monarch III injector with cartridge C and 56 IOLs were implanted with cartridge D. Viscoelastic agent (Viscoat) containing 40 mg sodium chondroitin sulfate, 30 mg sodium hyaluronate, 0.45 mg sodium dihydrogen phosphate dihydrate, 2.0 mg disodium hydrogen phosphate, and 4.3 mg sodium chloride with a viscosity of 40,000 ± 20,000 cps was used in all cases. After cataract extraction by phacoemulsification, we implanted IOLs with Monarch III injector through 2.75-mm and 2.2-mm corneal wounds with cartridges C and D, respectively, without further extension of the wound.

Before IOL implantation, the capsular bag was filled with Viscoat solution. A small amount of Viscoat was applied to the inner side of the cartridge while using the Monarch III injector. Then, the IOLs were grasped by the haptic with MacPherson forceps and placed into the cartridge. Afterward, the cartridge was loaded into the injector handpiece (Monarch III). The hydrophobic acrylic IOLs (Alcon SA60AT) were injected into the capsular bag slowly and carefully. Postoperatively, patients received Pred-forte and gentamycin eye drops four times a day, which were tapered over 4 weeks. Photographs of abnormalities were taken with a dilated pupil one day and one month postoperatively when surface abnormalities were detected.

Fig. 1 Monarch III IOL Delivery System (Alcon). Cartridge C or D is loaded at the anterior area during the intraocular lens implantation.

Results

All surgeries were uneventful, and all IOLs unfolded without complications. The same experienced surgeon has performed all the surgery. After an uneventful series of 16 IOLs implantation with cartridge D and Monarch III injector, we encountered three cases of IOL posterior surface longitudinal scratches immediately after implantation with cartridge D, and the three IOLs had a central crack on the same day (Figure 2a). The white lines could not be removed by irrigation or by rubbing with MacPherson forceps.

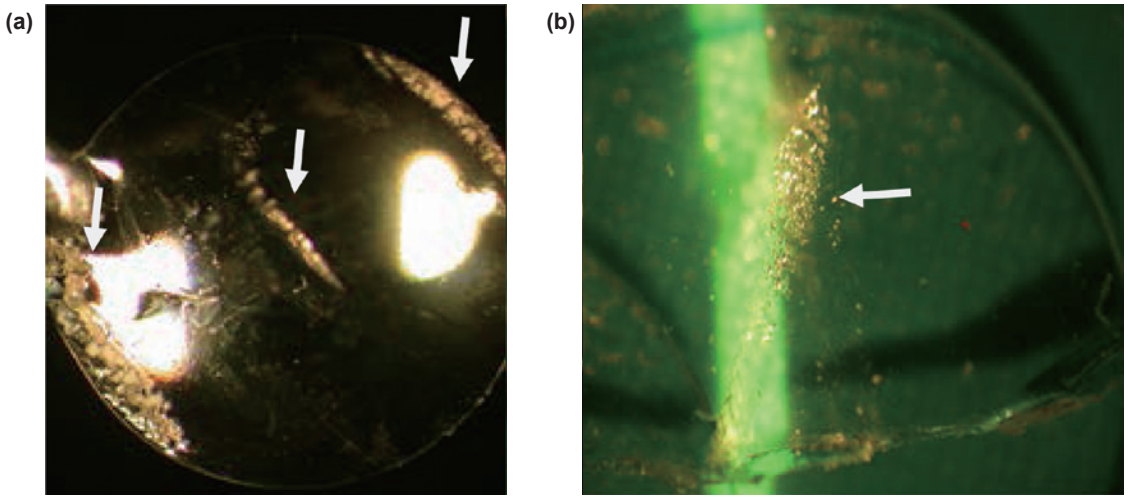


Fig. 2 (a) Three obvious deep crack lines (arrows) in the central and peripheral anterior surface of the intraocular lens (IOL) were noted after the implantation by an injector with a D cartridge. (b) We removed the IOL after cutting it into two pieces during the operation.

Case 1

A 74-year-old female had left cataract extraction followed by IOL insertion. The pre-operative corrected distance visual acuity (CDVA) was 0.05. On day one after the operation, the intraocular pressure was 18 mmHg. Her corneal wound was self-sealed, and the cornea was clear without edema. One week after surgery, the refractive status was +0.75D/−0.5D Ax 170 in the left eye. At the same time, the best-corrected visual acuity (BCVA) was 0.9 in the affected eye (Figure 3a).

Case 2

A 51-year-old female had right eye phacoemulsification followed by IOL insertion. The pre-operative CDVA was 0.3. One day after the surgery; her right eye intraocular pressure was 23 mm Hg. The corneal wound was self-sealed with mild edema. One week after the surgery, the refractive status was −0.5D/−0.75D Ax 70 in the right eye. The BCVA was 0.9 in the affected eye (Figure 3b).

Case 3

A 67-year-old male had left cataract extraction followed by acrylic IOL implantation. The pre-operative CDVA was 0.1. During the IOL implantation, the IOL surface scratch was obvious. We enlarged the corneal wound to 3.5 mm and removed the IOL immediately because of significant central cracks (Figure 2b). The corneal wound was closed with one nylon suture (10-0 nylon). One day after the operation, the intraocular pressure was 22 mmHg. The corneal wound was sealed, and the central cornea was moderately edematous. One week after the surgery, the corneal edema subsided. The refractive status was −0.75D/−1.25D Ax 140 in the left eye. The BCVA was 0.8 in the affected eye.

After these three cases, the other 37 IOL implantations by cartridge D were done smoothly. There were no similar findings with IOL implantation with cartridge C.

Discussion

Several possible causes might lead to the IOL cracks/scratches noticed in our cases. First, it has been suggested that hydrophobic acrylic IOLs are more fragile than silicone IOLs, which may result in IOL cracks after folding with forceps [7, 14], although the alterations caused by folding did not affect visual acuity in this study. However, there were no IOL cracks found in the IOLs implanted by cartridge D with the 2.75-mm corneal wound.

Second, poor IOL-cartridge design may result in the cartridge and/or IOL deformation during implantation. Singh described cartridge cracks during foldable IOL insertion and recommend the use of chondroitin-based viscoelastic agents because almost all cracks (98.1%) occurred in cases where Healon was used to load the IOL [15]. Faschinger et al. described surface abnormalities on high water content (26%), biconvex IOL with plate-haptic design. The IOLs were folded in a cartridge under hydroxypropyl methylcellulose and implanted by an injector [10]. However, the abnormalities on the posterior surface disappeared or were almost gone within 1 month postoperatively.

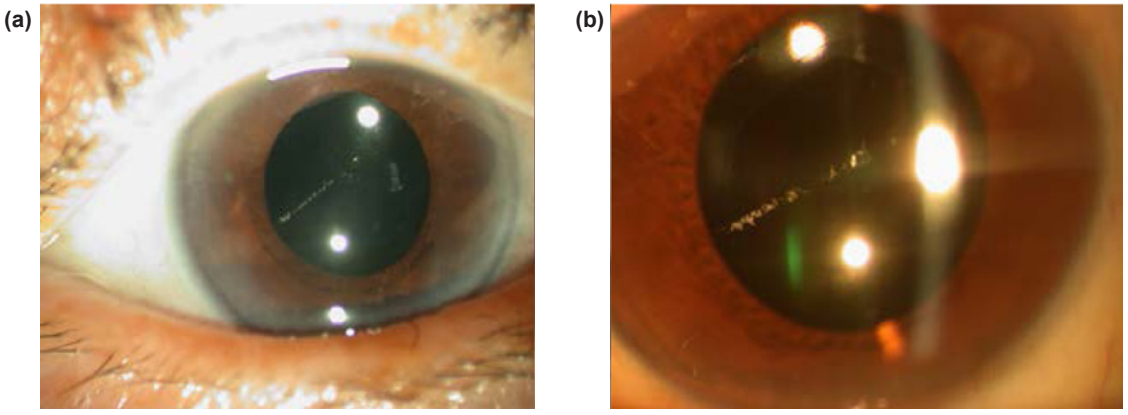


Fig. 3 (a) Case 1. A 74-year-old female. The pre-operative visual acuity (VA) was 0.05. The scratch was noted immediately after the operation. The picture was taken one week postoperatively. (b) Case 2. A 51-year-old female. A one scratch line was also noted on the central anterior surface of the intraocular lens. There was no significant change in VA. The best-corrected visual acuity of both patients was 0.9.

These abnormalities are likely the result of the IOLs hydrophilicity, high water content, and friction in the injector barrel. However, although the IOLs they described were hydrophilic, the properties were significantly different from our hydrophobic IOLs.

Third, the cracks may result from the increased friction in the injector cartridge due to the inappropriate selection of cartridge size for the IOL dimensions. The cartridge we used was type C or D and the IOLs implanted were SA60AT (lens diameter of 13 mm with 6.0 mm optic diameter). The Monarch III D cartridge has a 33% reduction in nozzle tip (versus C cartridge) for ease of small-incision implantation. IOL cracks/scratches in our cases were noticed with the D cartridge only. Because of the smaller corneal size and smaller inside dimensions of cartridge D, the IOL-cartridge friction-related cracks/scratches are one of the possible causes [16].

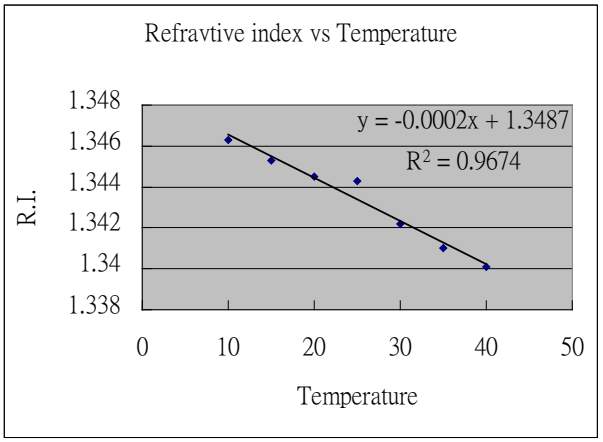
Fourth, the resistance in the cartridge may also be a factor. Besides cartridge inner size, the viscosity and lubricant function of Viscoat should be concerned.

VISCOAT® Viscoelastic Solution is a sterile, nonpyrogenic, viscoelastic solution of a highly purified, noninflammatory, medium-molecular weight fraction of sodium chondroitin sulfate and sodium hyaluronate. The viscosity and lubricant function of Viscoat reduce the friction between IOLs and injector cartridges. An alteration of Viscoat viscosity may result in increased friction in the injector barrel during IOL implantation. As the viscosity of the material decreases with increasing temperature, the viscosity–temperature relation could be described as $v = A \exp(Ev/k T)$, where v is the kinematic viscosity, k is Boltzmann's constant, T is the temperature, and A and Ev are constants. Although the official recommended storage temperature is between 2°C–8°C (36°F–46°F), the inappropriate temperature was possibly encountered during the transportation or storage of the viscoelastic materials.

We checked the refractive index of Viscoat between seven different temperatures from 10°C–40°C (Table 1). As temperature increases, the refractive index lowers. As a result, at a lower temperature, the viscosity becomes higher. With the higher viscosity of Viscoat, the friction between IOL and cartridge can be reduced. That should be one of the major reasons that the storage temperature of Viscoat is between 2°C–8°C (36°F–46°F).

Table 1. Viscosity has a good relation to the refractive index. We use refractive index change to represent viscosity change. The test shows good correlation between refractive index (n) and temperature.

The refractive index of Viscoat at seven different temperatures						
10	15	20	25	30	35	40
1.3463	1.3453	1.3445	1.3443	1.3422	1.3410	1.3401



We, therefore, hypothesized that viscosity change between the IOLs and cartridges also induces cracks and scratches. The storage temperature of our Viscoat was higher than the recommended ones. During the operation day, we took out Viscoat from a refrigerator in the morning and sometimes used it in the late afternoon. It might have reduced the viscosity of Viscoat and increased the friction between IOL and cartridges. Alternatively, the viscoelastic nature might have been changed totally due to improper storage temperature.

So, we request strict temperature control while storing viscoelastic solutions after the event. Besides, we have filled more Viscoat in cartridge D than in cartridge C. There are no more abnormal findings on the surface of IOLs during operations. However, due to the small sample size and short follow-up time, further research is necessary.

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在小傷口白內障手術中折疊式人工水晶體表面的裂紋和刮痕：3 個病例的報告

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摘要

目的：報告和描述白內障手術中使用 Alcon Monarch III 注射器與 D 型植入器所引起的人工水晶體（SA60AT）表面裂紋和刮痕。

方法：本研究包含了 98 例小切口白內障手術的眼睛，並在所有眼睛均植入了折疊式人工水晶體（SA60AT，Alcon）。所有手術均使用相同的粘彈性劑：硫酸軟骨素鈉 - 透明質酸鈉（Viscoat）。56 例使用 D 型植入器和 Alcon Monarch III 注射器，另外 42 例則是使用 C 型植入器。

結果：三個使用 D 型植入器的人工水晶體在晶體表面縱軸方向上都有白色刮痕線。我們在手術過程中移除了一例的人工水晶體，因為此刮痕很像裂縫而且情況較嚴重。另外兩例眼睛儘管人工水晶體表面有白線，但患者術後的最佳矯正視力可達 0.9。

結論：術後一個月人工水晶體表面刮痕並未消失。儘管它可能沒有影響患者的視敏度，但是我們遇到較嚴重裂紋的那位病患可能會影響視力。裂痕有可能是 D 型植入器內層的摩擦和在異常溫度下 Viscoat 粘度降低的結果。但是，由於樣本量小且只有較短的追蹤時間，有必要再進一步的研究。

關鍵詞：小切口白內障手術，人工水晶體表面異常，水晶體植入系統

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Case Report

A Rare Case of SMA Syndrome with Jaundice

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Abstract

We present an unusual case of superior mesenteric artery (SMA) syndrome with jaundice due to compression of the common bile duct by a gastric obstruction and a dilated duodenum. Physicians frequently confuse symptoms of SMA syndrome with acute gastroenteritis making the diagnosis of SMA syndrome a challenge in the emergency room. In this case, we found a correlation between hyperbilirubinemia and SMA syndrome. Physicians should consider SMA syndrome as a differential diagnosis in patients with upper abdominal pain, vomiting, ileus, and jaundice.

Key words: superior mesenteric artery syndrome, jaundice, gastritis symptoms

Introduction

Superior mesenteric artery (SMA) syndrome is a proximal intestinal obstruction caused by compression of the third portion of the duodenum due to narrowing of the space between the SMA and aorta. It is primarily due to the loss of the intervening mesenteric fat pad[1].

Case presentation

A 16-year-old boy presented with intermittent epigastric pain of XX days of evolution, frequent vomiting without bile, and decreased appetite. He had no history of alcohol use or previous abdominal surgery. He was evaluated in our emergency department, and some medications for gastritis were prescribed, but his symptoms did not improve. He was brought to our emergency department again. On physical examination, he had a height of 171 cm, a weight of 47 kg, and a body mass index (BMI) of 16 kg/m^2. He also had conjunctival icterus, abdominal distention, jaundice, and upper abdominal tenderness on palpation with no peritonitis.

A kidney, ureter, and bladder x-ray (Figure 1) showed gastric distension and decreased intestinal gas. Laboratory results showed leukocytosis, 11,800/μL; elevated total bilirubin, 2.8 mg/dL; direct

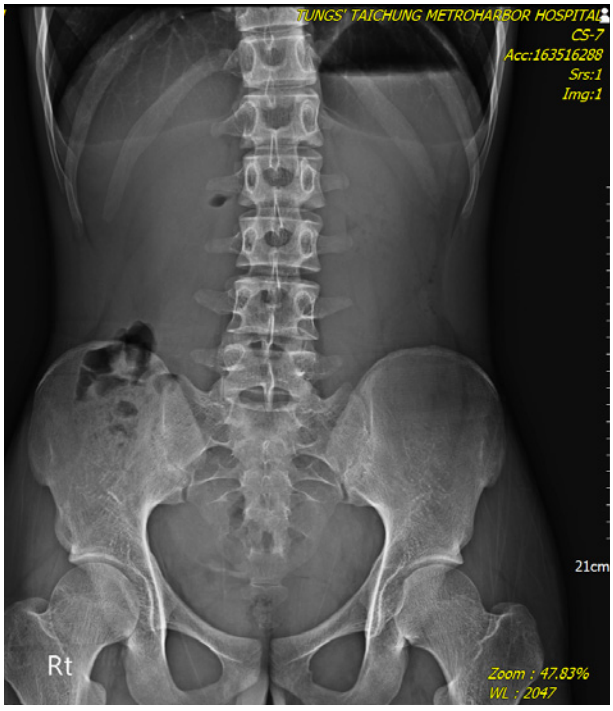

Fig. 1 The kidney, ureter, and bladder X-ray showing gastric distension and decreased intestinal gas.

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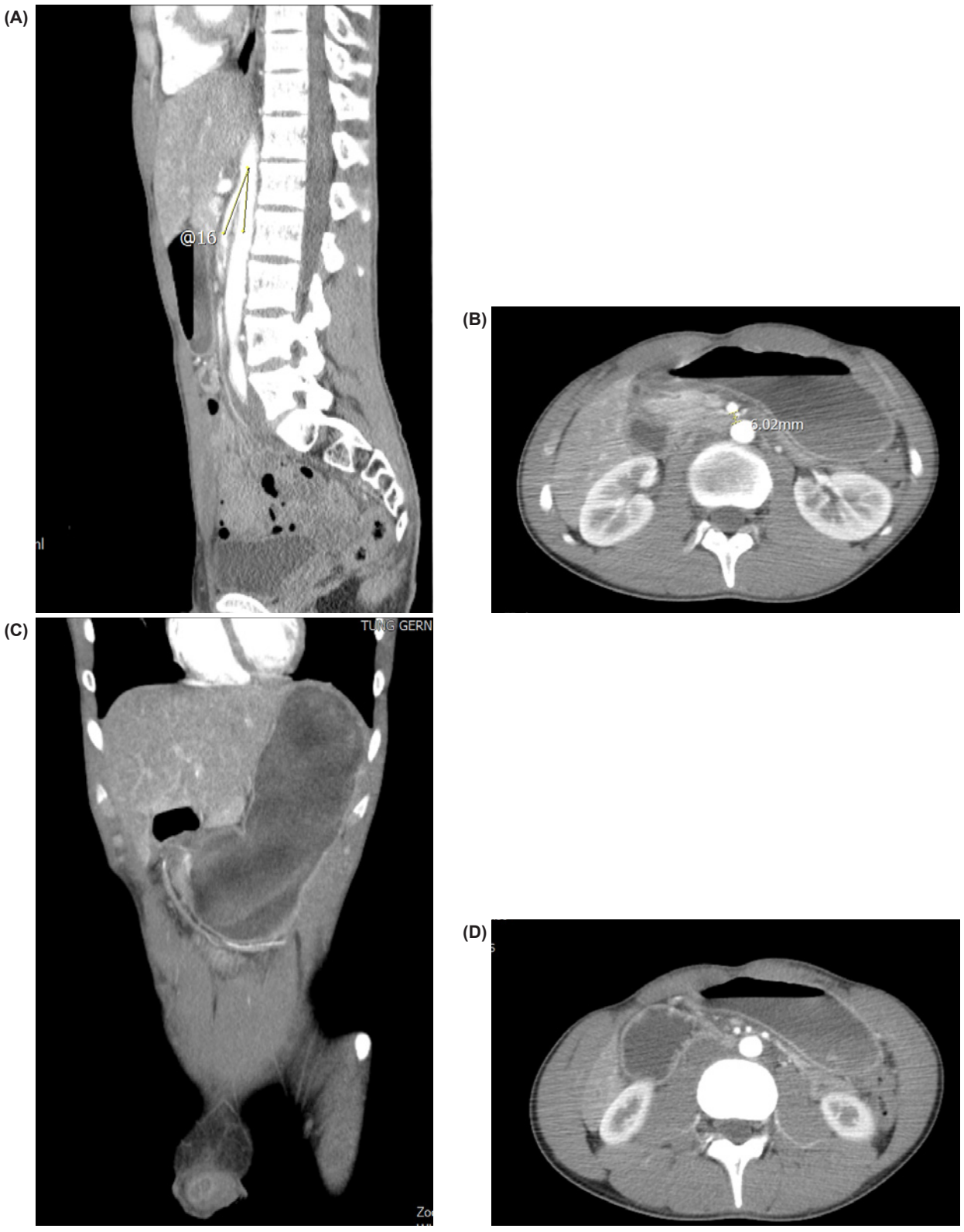

Fig. 2 CT image with diagnostic criteria of SMA; (A) Aortomesenteric artery angle, 16° (B) Aortomesenteric distance: 6.02 mm; (1) the normal aortomesenteric angle and aortomesenteric distance are 28-65° and 10-34 mm, respectively. (2) Both parameters are reduced in SMA syndrome with values of 6° to 22° and 2 to 8 mm[1,2]; (C, D) scan of the stomach and the first and second portion of the duodenum with distention.

bilirubin, 0.7 mg/dL; and alkaline phosphatase, 549 IU/L. An abdominal ultrasound showed a suspicious gastric outlet obstruction with perihepatic ascites. Abdominal computed tomography (CT) (Figure 2) revealed compression of the third portion of the duodenum by the SMA and the aorta, resulting in dilation of the proximal duodenum and stomach; a finding consistent with SMA syndrome. He was admitted for further evaluation and management with suspicion of SMA syndrome.

After a few days of IV hydration, no food and fluid intake, and nasogastric free drainage during hospitalization, the patient stopped vomiting. An upper gastrointestinal series of the small intestine on hospital day 12 showed extrinsic compression of the third portion of the duodenum compatible with SMA syndrome. Robotic duodenojejunostomy was performed on hospital day 12. After surgery, his total bilirubin returned to normal, 0.4 mg/dL. He was discharged on hospital day 16 in stable condition.

Discussion

Vomiting and abdominal distension are frequent clinical symptoms of SMA syndrome[1]. Those symptoms can also be seen in acute gastroenteritis, paralytic ileus, pancreatitis, cholecystitis, and gastrointestinal tract tumor obstruction. Thus, it is a challenge to diagnose SMA syndrome in the emergency room. In this case, there were many clues related to SMA syndrome: the low BMI of the patient, abdominal fullness after food intake, and gastric and upper duodenal obstructive ileus.

Several factors can decrease the angle between the aorta and the SMA. The most common cause is significant weight loss leading to loss of the mesenteric fat pad due to medical disorders, psychological disorders, or surgery. Congenital or acquired anatomic abnormalities can also contribute[1,2].

Elevated serum total bilirubin and alkaline phosphatase levels were noted in this case, demonstrating direct hyperbilirubinemia. However, the CT scan and sonography examination showed no obvious biliary tract dilation. One of the possible reasons for the elevated total bilirubin level is severe vomiting and dehydration. Another that is also compatible is partial obstructive jaundice. Maybe we can study the association between SMA syndrome and high ALK-P or obstructive jaundice.

We had searched the literature for SMA syndrome accompanied by jaundice in the last ten years. This case report is rare. However, jaundice with upper gastrointestinal symptoms may be a specific finding in the diagnosis of SMA syndrome. The mechanism by which SMA syndrome causes liver biochemical abnormalities is unclear; however, recognizing this association is clinically relevant. Extrinsic biliary compression with massive gastric and duodenal distention may have been the cause of the elevated bilirubin. In one case report, chronic gastric outlet obstruction was responsible for obstructive jaundice because of chronic gastric outlet obstruction, direct compression of the common bile duct by the distended stomach and duodenum, or increased intraduodenal pressure demonstrated by the rapid recovery of bilirubin and liver function tests after nasogastric tube decompression[1]. In patients with abdominal pain and abnormal liver tests, the differential diagnosis is broad. SMA syndrome should be suspected in patients with signs and symptoms of proximal small bowel obstruction[3]. Thus, this case may help emergency room doctors be aware of the disease in patients with gastritis symptoms, ileus, and jaundice. In these cases, an abdominal CT scan or panendoscopy can be arranged to confirm the diagnosis.

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上腸繫膜動脈症候群合併黃疸的少見案例

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摘要

一個 16 歲男性病人由於上腹脹痛、嘔吐與黃疸來本院急診求診。經檢查，我們發現本病人是因為上腸繫膜動脈症候群（superior mesenteric artery syndrome, SMA syndrome）所致。 臨床上黃疸與 SMA 症候群之相關病例報告罕見，我們推估是因為上腸胃道脹壓迫到膽道所致。本病例提醒我們在遇到嘔吐、上腹痛、黃疸病人，宜將 SMA 症候群列入鑑別診斷。

關鍵詞：上腸繫膜動脈症候群，黃疸，胃炎症狀

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Image

Colovesical Fistula

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Abstract

We report the case of a 69-year-old man presenting to the emergency department with a two-week history of fecaluria and pneumaturia when voiding. An abdominal CT confirmed a colovesical fistula between the sigmoid colon and bladder dome. The patient's symptoms improved after surgery, and no evidence of recurrence was found after 6 months of follow-up. Colovesical fistula is an uncommon complication of diverticulitis. Most colovesical fistulas are caused due to chronic perforated diverticulitis and have a favorable prognosis. The goals of the evaluation were to confirm the diagnosis and elucidate the underlying etiology.

Key words: Colovesical fistula, diverticulitis, pneumaturia, fecaluria

Introduction

A colovesical fistula, an abnormal connection between the bladder and colon, is a complication of diverticular disease. The fistula allows bowel material to pass from the colon into the bladder, contributing to symptoms, such as fecaluria, pneumaturia, or Gouverneur syndrome, which cause suprapubic pain, frequency, dysuria, and vesical tenesmus.

Case report

A 69-year-old man with a history of hypertension presented to the emergency department with a two-week history of fecaluria and pneumaturia when voiding. On physical examination, the patient was afebrile with lower abdominal tenderness. Laboratory tests showed a white blood cell count of 12,300/uL, C-reactive protein 19 mg/dL, and normal liver and renal function; pyuria was noted on urinalysis. Plain films of the abdomen showed free air in the apex of the bladder (Fig 1A). A CT scan detected a colovesical fistula between the sigmoid colon and left anterior urinary bladder dome (Fig 1B) with multiple colonic outpouching diverticula in the sigmoid and ascending colon. The colovesical fistula was identified, and the suspected cause was chronic perforated diverticulitis. Segmental resection of the sigmoid colon with partial resection of the urinary bladder was performed. The patient's symptoms improved after surgery, and no evidence of a recurrent fistula was found after 6 months of follow-up.

Discussion

Colovesical fistulas are communications between the lumen of the colon and bladder, either directly or via an intervening abscess cavity. The male-to-female ratio of colovesical fistulas is approximately 3:1. The mean age of presentation is between 55 and 75 years. An abdominal pelvic CT with oral or rectal contrast is the imaging test of choice for diagnosis. The development of colovesicular fistulas differs depending on the specific etiology [1]. The most common cause is benign diverticular disease with a favorable prognosis.

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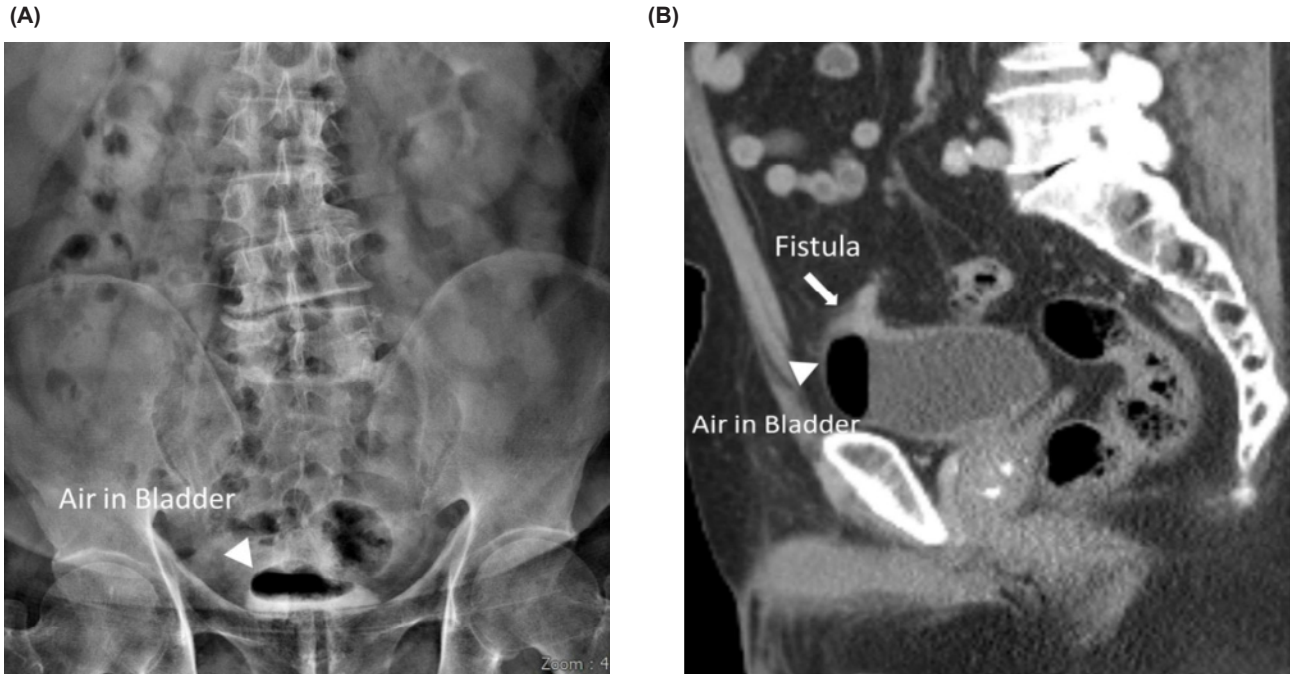

Fig. 1 (A) Free air in the urinary bladder apex. (B) The colovesical fistula was identified between the sigmoid colon and anterior dome of the urinary bladder; it was caused due to chronic perforated diverticulitis.

Malignancy that directly invades the urinary bladder is the second most common cause in 10% of cases. Crohn's colitis of the sigmoid colon may lead to colovesicular or colovaginal fistulas. Conservative treatment can be tried if the fistula is small and not due to malignancy. Symptomatic urological or abdominal sepsis from the fistula must be treated before repairing the fistula. Surgical management of a colovesical fistula is guided by its etiology [2]. Most colovesical fistulae are benign. Patients diagnosed with a colovesical fistula should undergo colonoscopy to rule out underlying malignancy (colon or bladder cancer). If there is ambiguity about whether a fistula is benign or malignant, it is best to treat it as malignant [3]. Surgical resection of an abnormal bowel segment is necessary to cure the fistula. For most patients who undergo surgical repair of a fistula due to benign causes, the outcome is excellent. However, if the cause is related to radiation or malignancy, the outcome is guarded.

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大腸膀胱廔管

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摘要

69 歲老翁來急診室為主訴頻尿、尿中帶有泡泡和尿中帶有糞便的狀況，尿液送驗出泌尿道感染，腹部 X 光檢查發現膀胱內有空氣，透過電腦斷層檢查發現腸子和膀胱已出現廔管，造成大腸糞便滲到膀胱，導致憩室發炎，引發大腸靠近膀胱的組織反覆慢性感染。經過手術及感染控制後恢復正常也無再復發情形。臨床慢性憩室發炎造成大腸膀胱廔管十分少見，主因最常見還是慢性憩室炎，除了飲食習慣和長期便秘外，還有因腫瘤侵犯、腸道自體免疫疾病及曾接受過放射治療之病患。要確定診斷通常需做進一步之影像學檢查來評估發炎的程度及範圍，以選擇最適合的治療計畫。

關鍵詞：大腸膀胱廔管，憩室炎，氣尿，糞尿

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Pathology

Sclerosing Pneumocytoma of Lung Mimic Metastatic Carcinoma

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Abstract

A 60-year-old married woman presented with a history of general weakness, limb weakness, and vaginal bleeding for 1 month. After admission to our emergency department, she underwent dilation and curettage of endometrial tissue, and the pathology report was endometrioid carcinoma, grade 3. Computer tomography of the chest revealed one round nodule measuring 1.6 cm in size in the left lower lung lobe, and it was suspicious for metastatic endometrioid carcinoma. The patient underwent staging surgery for the uterine tumor. The pathological stage of endometrioid carcinoma was IB (T1b, N0, Mx). Three weeks later, the patient underwent computer tomography-guided biopsy of the lung tumor, and the pathological diagnosis was sclerosing pneumocytoma. She was followed up in our outpatient department after surgery for endometrioid carcinoma and biopsy of lung tumor. No enlargement of the sclerosing pneumocytoma lesion and no recurrent lesion of endometrioid carcinoma were noted after 5 years of follow-up. Sclerosing pneumocytoma typically presents as a unilateral pulmonary nodule, and this tumor typically behaves in a benign manner. In endometrioid carcinoma, the simultaneous appearance of sclerosing pneumocytoma may mimic a metastatic lung lesion.

Key words: lung metastasis, endometrial carcinoma, lung tumor

Pathology Page

A 60-year-old married woman presented with a history of general weakness, limb weakness, and vaginal bleeding for 1 month. After admission to our emergency department, she underwent dilation and curettage of endometrial tissue, and the pathology report was endometrioid carcinoma, grade 3. Computed tomography of the chest revealed one round nodule over the left lower lobe measuring 1.6 cm in size (Figure 1, upper panel), and it was suspicious of metastatic endometrioid carcinoma. The laboratory data revealed an elevated CA125 level of 39.7 μg/ml. The CEA level was within the normal range. The patient underwent staging surgery to remove the uterus, bilateral ovaries, and tubes, and the bilateral pelvic lymph nodes and para-aortic lymph node were surgically dissected. The surgical specimen of the uterus revealed endometrioid carcinoma, grade 3 (Figure 1, lower panel), with tumor cells invading more than half of the myometrium. The bilateral ovaries and lymph nodes were all free of tumor metastasis. The AJCC stage was stage IB (T1b, N0, Mx).

Three weeks later, the patient underwent computer tomography-guided biopsy of the lung tumor. The lung biopsy specimen consisted of four small strips of lung tissue measuring up to 1 × 0.1 cm in size. Microscopically, the tumor cells were arranged in mixed papillary (Figure 2A), hemorrhagic (Figure 2B), and sclerotic (Figure 2C) patterns featuring the proliferation of two population of epithelial tumor cells composed of surface epithelial cells and stromal round cells. The surface cells were cuboidal, and they resembled reactive type II pneumocytes. The round

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cells were small with well-defined borders, fine chromatin, and inconspicuous nucleoli. No mitosis or tumor necrosis was found.

Immunohistochemical staining revealed positivity for cytokeratin (CK, Figure 2D) in surface cells but negativity in round cells. Staining for epithelial membrane antigen (EMA, Figure 2E) and thyroid transcription factor 1 (TTF-1, Figure 2F) was positive in both surface and round cells. The surface and round cells were also focally positive for estrogen and progesterone receptor staining (data not shown). The lung tumor was diagnosed as sclerosing pneumocytoma.

Sclerosing pneumocytoma and metastatic endometrioid carcinoma are differentiated by the absence of cellular atypia or mitosis in sclerosing pneumocytoma. Metastatic endometrioid carcinoma displays cellular pleomorphism, an increased nuclear/cytoplasmic ratio, and the presence of mitoses. Immunohistochemistry is also helpful in the differential diagnosis of sclerosing pneumocytoma and metastatic endometrioid carcinoma. Metastatic endometrioid carcinoma is negative for TTF-1. Conversely, sclerosing pneumocytoma is diffusely positive for TTF-1 (Figure 2F).

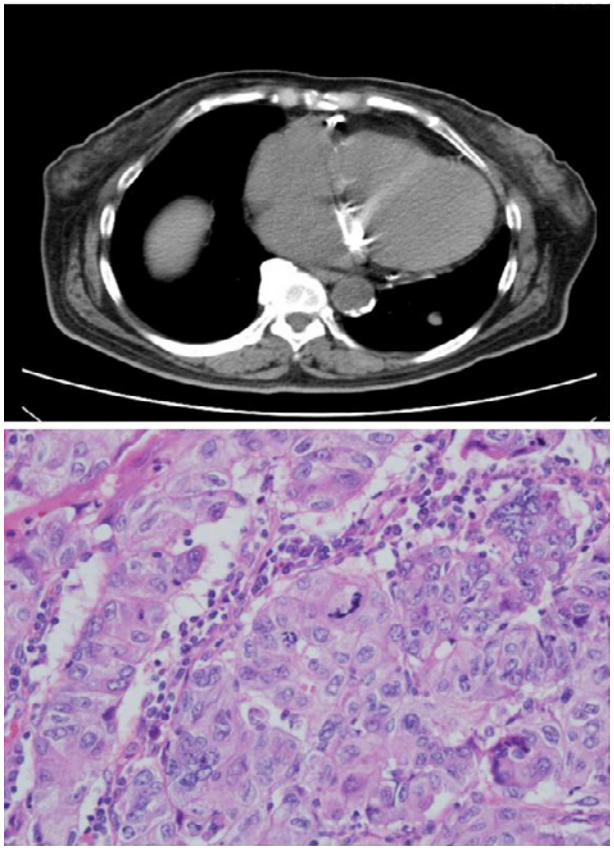

Fig. 1 Computer tomography of the chest revealed a 1.6-cm tumor nodule in left lower lung lobe (upper panel), and histopathology disclosed endometrioid carcinoma with tumor cells at high magnification (lower panel, ×400).

Primary carcinomas of the lungs including adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma all have distinct morphological patterns with cellular pleomorphism, an increased nuclear/cytoplasmic ratio, and the presence of occasional mitoses. These morphological findings of primary lung carcinoma are extremely different from those of sclerosing pneumocytoma of the lungs. The tumor cells of sclerosing pneumocytoma are arranged in papillary (Figure 2A), hemorrhagic (Figure 2B), and sclerotic (Figure 2C) patterns, featuring the proliferation of two population of epithelial tumor cells composed of surface epithelial cells and stromal round cells. The distinct immunohistochemical patterns of CK, EMA, and TTF-1 are also helpful in the differential diagnosis of primary carcinoma and sclerosing pneumocytoma. Regarding sclerosing pneumocytoma, CK staining (Figure 2D) was positive in surface cells but negative in round cells. EMA (Figure 2E) and TTF-1 staining (Figure 2F) was positive in both surface and round cells. These unique findings of sclerosing pneumocytoma are not found in primary carcinoma of the lungs.

The patient was followed up in our outpatient department for 5 years, and no progression of lung sclerosing pneumocytoma was noted. No recurrent or metastasis of endometrioid carcinoma was identified after 5 years of follow-up.

Sclerosing pneumocytoma is a tumor of pneumocytic origin with a combination of histological findings, including solid, papillary, sclerotic, and hemorrhagic regions [1, 2]. The tumor cells consist of dual populations of surface cells resembling type II pneumocytes and round cells. Sclerosing pneumocytoma has a striking female predominance, with 80% of cases occurring in women [3, 4]. Patients are typically asymptomatic, with the lesion identified incidentally. Sclerosing pneumocytoma clinically behaves in a benign manner, although lymph node metastasis has been reported previously in select cases [5, 6]. This does not appear to adversely affect prognosis. When sclerosing pneumocytoma simultaneously occurs with other cancers (such as endometrioid carcinoma), it may mimic a metastatic lesion of the lungs.

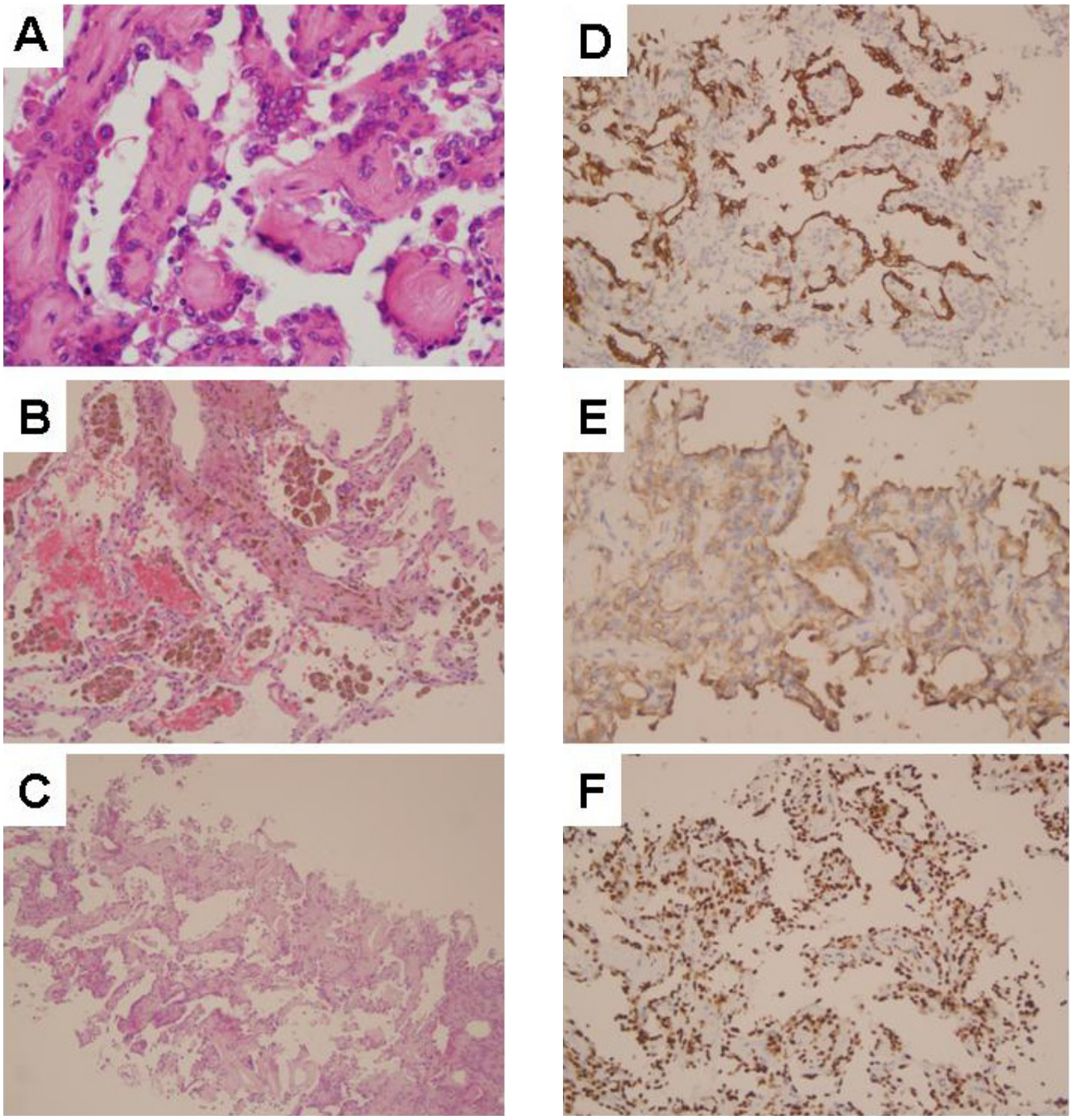

Fig. 2 Histopathology revealed lung tumor cells with papillary (panel A), hemorrhagic (panel B), and sclerotic (panel C) patterns, and immunohistochemistry for cytokeratin (panel D), epithelial membrane antigen (panel E), and thyroid transcription factor 1 (panel F) revealed positive cytoplasmic staining in tumor cells (×200; hematoxylin–eosin staining, ×400).

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硬化性肺泡細胞瘤 - 呈現似癌轉移：病例病理報告

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摘要

一位 60 歲女性因全身及四肢無力、陰道出血一個月到急診求診，入院後病患接受子宮擴刮術採檢子宮內膜，病理診斷為子宮內膜癌。胸部電腦斷層檢查顯示左下肺有一個 1.6 公分大小的腫瘤，疑似子宮內膜癌轉移肺部，病患接受子宮切除分期手術，病理分期是 IB。三週後病患接受肺部電腦斷層引導切片肺腫瘤，病理診斷為硬化性肺泡細胞瘤。病患於術後在門診追蹤五年，肺部腫瘤未明顯增大，子宮內膜癌也沒有復發。硬化性肺泡細胞瘤大多呈現單一肺部腫瘤，是良性的腫瘤，若同時有子宮內膜癌及硬化性肺泡細胞瘤，硬化性肺泡細胞瘤可能會被誤認是肺轉移病灶。

關鍵詞：肺轉移，子宮內膜癌，肺腫瘤

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3. 投稿同時請附上著作權讓與同意書。所有作者必須實際參與並同意該論述。本院於接受稿件且印刷完成後，將致贈稿酬並贈送 20 份抽印本給通訊作者，如需額外抽印本請於校稿時言明，並酌收成本費用。第一作者若需抽印本可提出申請，依份數酌收成本費用。
4. 本刊對於原稿經徵得作者之同意得伸縮或修改之。如不合本刊宗旨者，得退還之。
5. 凡刊載於本雜誌之著作，若涉及「研究用人體檢體採集」及「人體試驗」等情事，應遵守該注意事項。除不須 IRB 審查之細胞、細菌、動物實驗外，回溯性研究、資料庫分析、問卷量性研究等皆須於文章中註明 IRB 編號〔需含機構名稱〕；病例報告及影像判讀等文章需取得病人知情同意並於內文註明，以落實保障受檢人權益。
6. 論文中如涉及使用脊椎動物進行科學應用計畫者，應檢附該計畫業經所屬機構動物實驗管理小組審議認可之文件，以落實實驗動物之人道管理。

貳、寫作原則

1. 原著論文（Original Articles）按下列順序撰寫：摘要、前言、材料與方法、結果、討論與結論、誌謝、參考文獻、附表、圖片說明、圖片（含照片）。每篇字數 3000 字以內，摘要 300 字以內，參考文獻 40 篇以內。
2. 病例報告（Case Reports）按下列順序撰寫：摘要、前言、病例、討論、參考文獻、附表、圖片說明、附圖、照片。凡病患顏面部位之相片必須遮去眼睛部位，表示尊重隱私。診療資料或臨床經過之圖表，原則上均限六個月以內。每篇字數 1500 字以內，摘要 150 字以內，參考文獻 10 篇以內。
3. 綜論（Review Articles）不必按原著論文格式撰寫，但每篇字數 3500 字以內，摘要 300 字以內，參考文獻 60 篇以內。
4. 短論（Brief Communications），臨床上、技術上的精簡論著，每篇字數 750 字以內，摘要 150 字以內，參考文獻 7 篇以內。
5. 影像判讀（Images）、臨床病理討論（Pathology Page）圖例說明每篇字數 500 字以內，摘要 150 字以內，參考文獻 3 篇以內。
6. 編者的話（Editorials），每篇字數 2000 字以內，摘要 150 字以內，參考文獻 7 篇以內。
7. 其他細節，請參閱國際指導委員會（International Steering Committee）發表之生物醫學雜誌稿件統一規格（Uniform Requirements for Manuscripts Submitted to Biomedical

Journals，見 The New England Journal of Medicine 336:309-315,1997）。

8. 將可接受投稿之稿件種類之摘要字數、字數、參考文獻及圖表相關上限規定，整理於下表：

稿件種類	字數限制		參考文獻	圖 / 表
	摘　　要	內文字數		
原著論文 (Original Article)	≦ 300	≦ 3000	≦ 40	≦ 5
病例報告 (Case Report)	≦ 150	≦ 1500	≦ 10	≦ 3
綜論 (Review Article)	≦ 300	≦ 3500	≦ 60	≦ 6
短論 (Brief Communication)	≦ 150	≦ 750	≦ 7	≦ 1
影像判讀 (Images)、 臨床病理討論 (Pathology Page)	≦ 150	≦ 500	≦ 3	≦ 2
編者的話 (Editorial)	≦ 150	≦ 2000	≦ 7	≦ 1

參、投稿須知

1. 稿件須符合「生物醫學雜誌投稿之統一規定」[1]，請以電腦隔行 double space 書寫，並編行號及頁碼，中文字型以標楷體，英文字型以 Time New Roman 12 號字大小，稿紙之左右緣爲 2.54 公分，上下緣爲 3.17 公分。
2. 第一頁爲標題頁，須列出中文及英文之論文題目、中英文作者姓名、所屬機構及單位之中英文稱號（分屬不同單位，請以阿拉伯數字標出作者與單位）、聯絡人姓名、電話及中英文通訊錄。
3. 第二、三頁爲中文及英文之摘要及關鍵詞（請提供 3 至 5 個關鍵詞或簡短片語），中英文摘要須完全相同，摘要分段撰寫，依序爲背景及目的（Background and purpose）、方法（Methods）、結果（Results）及討論（Discussion）。
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. 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且不可以照片形式。圖片或照片電子檔（.jpg）必須清晰、分明。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、病例報告、綜論、短論、影像判讀、臨床病理討論、編著的話按下列格式撰寫：

A. 雜誌及期刊

中文例〔作者姓名：題目。雜誌簡稱 年號；卷數：起訖頁數〕

薛玉梅、陳建仁：皮膚砷癌之流行性病學特徵與危險因子。中華衛誌 1996; 15: 1-26。

英文例〔英文原稿中引用的參考文獻，其雜誌或期刊之簡稱應參照 Index Medicus 型式〕

1. Feely J, Wilkinson GR, Wood AJ. Reduction of liver blood flow and propranonol metabolism by cimetidine. N Engl J Med 1981;304:691-6.

2. Kaplan NM. Coronary heart disease risk factors and antihypertensive drug selection. J cardiovasc Pharmacol 1982; 4(suppl 2): 186-365.（引用雜誌附冊時）
3. Tada A, Hisada K, Suzuki T, Kadoya S. Volume measurement of intracranial hematoma by computedtomography. Neurol surg (Tokyo) 1981; 9: 251-6.〔In Japanese: English abstract〕（引用文獻之作者之本文爲非英文，但有英文摘要）。
4. 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.（作者超過 6 位時，只須列出前 6 位，其它以「等」(et al) 代替）

＊期刊若有「數位物件識別碼 (digital object identifier, DOI)」，則於文獻末。

＊＊內文文獻標示以中括號、數字、上標呈現。

B. 單行本：

中文例 [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]。

楊志良：生物統計學新論，一版。台北；巨流圖書公司，1984：33-8.

英文例 [英文單行本的書名，除介系詞及連接詞外，第一字母需大寫]

(1) 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：

中文例 [有關文章作者姓名：題目 。編輯者姓名：書名 。版數（卷數）。發行地：出版公司，年代；引用部份頁數]。

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

英文例 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.

D. 參考文獻引用時，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].

E. 參考文獻引用網路資料請列出文獻名稱及出處以及引用時間

(Accessed Month day, 2016, at http://www.house.gov/xxxx/min/inves_xxx/index_accord.htm.)

伍、著作權

若著作人投稿於本刊經收錄後，同意授權本刊得再授權國家圖書館或其他資料庫業者，進行重製、透過網路提供服務、授權用户下載、列印、瀏覽等行爲。並得爲符合各資料庫之需求，酌作格式之修改。若爲摘譯、譯稿或改寫稿，需附原作者之正本同意書，並附原文影本一份；來稿如涉及版權，概由作者自負文責。

童綜合醫學雜誌

編著的話

綜　論

原　著

病例報告

臨床病理討論

影像判讀

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