行政院及所屬各機關出國報告

（出國類別：研究）

步態分析在復健醫學之應用

服務機關：成大醫院　復健科

出 國 人 職　　稱：主治醫師

姓　　名：官大紳

出國地區：美國

出國期間：89 年 8 月 17 日至 90 年 07 月 28 日

報告日期：90 年 10 月 25 **日**

行政院及所屬各機關出國報告提要　　系統識別號:C09004895

出國報告名稱：　　頁數:　含附件：

步態分析在復健醫學之應用

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出國類別：□1 考察　□2 進修　■3 研究　□4 實習　□5 其他

出國期間：民國 89 年 8 月 17 日-民國 90 年 07 月 28 日

出國地區：美國

報告日期：　民國 90 年 10 月 25 日

分類號/目：J2/西醫

關鍵詞：gait analysis, fibromyalgia

內容摘要：　[詳次頁]

摘　要

步態分析是近十年來運用高科技電腦在復健醫學上的一個成功範例。藉由最新發展之電腦的高運算、與多重功能的特點，它能將人體步行時肉眼不易看清之各項特質，客觀而精密地加以測量出來。這使得它在復健醫學領域裡，不管是對於腦性麻痺兒、腦中風、腦外傷、以及各種神經肌肉系統之疾患所伴隨的動作與步態異常，在輔助診斷與評估治療效果方面，皆佔據了十分重要的地位。

本人此次在美國進修，首先跟隨 Dr. Sutherland，在他的實驗室裡，見識到更為先進的步態實驗設備，也與實驗室同仁們研討了步態分析出來數據判讀的要領，還學到 Fine wire EMG 的操作技術，對於將來我們在國內推展步態分析的研究，將有甚大的助益。

在研究方面，我們嘗試將步態分析與復健領域裡的疼痛醫學，做了聯結性的研究。我選定的主題是纖維肌痛症(Fibromyalgia)的病人。纖維肌痛症是一種全身到處都疼痛的病症，常常還伴隨著焦慮、沮喪、失眠、胃腸不適…等症狀。這種全身性疼痛的病人，會造成怎麼樣的步態異常，臨床上還沒有人做過這樣的研究。我跟隨的指導教授 Dr. Russell，是纖維肌痛症這一方面世界知名的大師。在我們第一階段的研究裡，是收集纖維肌痛症病人腦脊髓液裡的各種神經化學物質(neurochemicals in CSF)，與正常人腦脊髓液裡的神經化學物質相互比較，找出哪一些神經化學物質可以將纖維肌痛症與正常的人正確地區分出來，所建立的區分公式為：$Log[y/1-y]= -7.156 +0.359[SP] +0.051[NGF]–0.067[5HIAA]$，它所達到的區別準確率為 90.6%。

臨床上，纖維肌痛症的病人症狀越嚴重，其所顯現出來的異常步態也越明顯，包括步伐長度較短、站立期(stance phase)較長、擺盪期(swing phase)較短、穩定度較差…等；其間的關聯性以及在臨床上的重要性，都是我們下一步所欲探討的重點。

目次

正　文

一、 目的

(1) 瞭解目前世界上步態分析之最先進科技與研究趨勢

(2) 學習肌肉疼痛醫學(纖維肌痛症候群)的研究理論與方法

(3) 探討步態異常與肌肉疼痛的相關性

二、 過程

步態分析在近十年來，逐漸成為國內研究的熱門課題。本(復健)部因地利之便，得到本校醫學工程研究所的大力協助，因此在步態分析的研究上，起步還算很早。本人在攻讀醫學工程碩士學位時，即以腦中風患者的步態分析為研究主題，所得到的研究結果也曾在日本、美國等國際學術會議上發表。然而，電腦科技的發展日新月異，新的技術與機器不斷推陳出新；在得知獲得教育部補助出國研究的消息後，遂決定出國研習最新的步態分析技術。在醫工所蘇方慶所長、骨科部揚俊佑主任、林啟禎教授的推薦下，我前往位於美國加州 San Diego Children' s Hospital 裡，跟隨 Dr. Sutherland 從事步態分析的研究。

Dr. Sutherland 是一位骨科醫師，也是一位知名的步態分析大師。他在 Children' s hospital 所成立的步態分析實驗室，幾乎是一個獨立的部門。在獨棟的建築裡，有動現流暢的掛號處、等候區、辦公室、研究室、以及空間寬敞的步態分析實驗區。Dr. Sutherland 顯然是一位相當懂得經營的企業家，據說這整棟的

建築與實驗的設備都是他用研究計劃所爭取之經費而來的；而整個實驗室的成員，包括骨科醫師、物理治療師、小兒科醫師、還有醫工的博士專家、電腦程式設計師…，真可謂是人才濟濟！ 印象頗深的是其中一位醫工背景出身的教授，其所主講的一場關於肌肉的演講裡，其精辟入裡的程度，連我們這些科班出身背景的 醫師，都自嘆弗如！除了這所實驗室的建築，其實整個兒童醫院的建築內部與外觀，都是專為兒童所設計的，實在是令人欽佩他們對於兒童的照顧，與對自己所從事之事務的專注。

最值得一提的是，利用此次研習的機會，見識到美國目前最新的步態分析儀器。步態分析基本上就是一連串複雜電腦運算出來的數據，它可以經由六架紅外線攝影機攝取貼在身體上各個特定解剖位置上的反光球，再將這些光點輸入電腦主機裡，經過複雜而冗長的運算過程，才能將人體各段肢體在三度空間裡的位置顯現出來。這種運算過程，如果是用我們復健部原有的步態分析儀器(Ortho Track 2.0)來做的話，一般都要三至四個小時，既耗時又辛苦！而 Dr. Sutherland 實驗室現在所擁有的儀器，是(Ortho Track 5.0)，運算速度極快！幾乎是在受測者步行的同一時間，步態分析的運動學(kinematic)影像數據也馬上呈現出來，真是達到所謂的 real time 的境界！令曾經飽受舊機器耗時苦頭的我，大為讚嘆而佩服！這種立即顯像的功能，可以讓病人或受測者在受測試的當時，馬上能夠得知自己步行的實際狀況，不必再等一兩天以上才能看到報告，臨床上實在有極大的便利！

在研習期間，剛好趕上他們實驗室舉辦的步態分析研討會，使我有機會和來自世界各地約五十幾位的學者，共同研習步態分析的數據判讀，以及豪針肌電圖(Fine EMG)的操作技術。豪針肌電圖目前在國內還沒聽過有人做過，對我來說還算是相當新鮮的技術。它是使用相當細微的電極針，經過特殊的技術穿刺皮膚植入肌肉後，就能夠一面活動肌肉，一面同時紀錄該肌肉的動態肌電圖(dynamic EMG)。這種方法得出來的動態肌電圖，不同於傳統方式在靜止狀態下所測得的肌電圖，可以讓我們瞭解肌肉在整個運動過程當中真正的運作情形，不僅對於分析步態時有很大的貢獻，在手外傷的肌肉重建復健方面也相當重要。希望回國後能儘早克服軟硬體方面的問題，早日應用這種技術來服務臨床的病患。

在研究主題的設定方面，由於之前曾做過腦中風患者的步態分析，而最近這幾年本科部在前主任洪章仁教授的指導下，在肌肉疼痛(尤其是肌筋膜疼痛症候群 Myofascial pain syndrome)方面的研究成果是有目共睹的，因此便思索著如何結合這兩者的專長來做一關聯性的研究。經過洪章仁教授的推薦，我來到了德州大學聖安東尼奧健康科學中心(University of Texas Health Science Center at San Antonio; UTHSCSA)，跟隨 Dr. I Jon Russell 從事纖維肌痛症候群(Fibromyalgia syndrome)的研究，希望能探討出肌肉疼痛患者在步態方面是否有什麼特定的異常步態。

Dr. Russell 是纖維肌痛症 (Fibromyalgia) 世界知名的大師，他本身是 Journal of Musculoskeletal Pain 的主編，同時也是 International Myopain Society 的

主席。 Fibromyalgia syndrome 是一個全身性疼痛的症候群，它常伴隨著疲勞、失眠、全身酸痛、憂鬱、焦慮、排便與膀胱障礙…等多種症狀。雖然它多半是以肌肉疼痛為主要表徵，然而多年來的研究仍舊無法在肌肉組織裡找到任何病灶性的證據。近年來學界已逐漸將研究重點擺向中樞神經方面，各種與疼痛傳導有關的神經介質 (nociceptive neurotransmitters)，包括：serotonin、substance P、5 hydroxyindole acetic acid.…，都已被證明在 fibromyalgia 患者的身上有不正常的數值發生。我的第一篇研究，是將 Dr. Russell 所收集的 300 多位 fibromyalgia 患者腦脊髓液(CSF)裡的各種神經介質，運用多變異項、複迴歸的統計方式，歸納出一個可以區分出 fibromyalgia 患者與正常人的神經介質多項式方程式。第二篇的研究主題，則是將臨床上用來分析 fibromyalgia 的十幾項臨床指標，運用因素分析(factor analysis)的方法，將這些臨床指標歸納分類為四個因素；再將這四個因素與第一篇研究所建立出來的方程式，做相關性的分析，以驗證這個方程式的區分 fibromyalgia 患者與正常人的準確度。這兩篇論文都已被第五屆肌筋膜疼痛與纖維肌痛症世界大會所接受，即將在今年九月初在美國波特蘭市(Portland)所舉辦的大會上做口頭報告式的論文發表。兩篇論文的題目分別是：Discrimination of fibromyalgia patients from normal controls using the levels of cerebrospinal chemicals. 以及 Correlations of clinical variables with cerebrospinal chemical levels among fibromyalgia patients and healthy normal controls。而纖維肌痛症與步態分析的關聯性，將是我回國後接著展開的研究重點工作。

三、 心得

此次有幸能獲得教育部補助，到美國做為期一年的研習，不僅有機會見識美國這個做為世界超強國家的醫療設施與醫學研究，還有機會能長期浸潤在他們的生活文化裡，親身感受到這種促使他們成為朝氣蓬勃之世界一流大國的氣息，內心實在有著無數的感想與省思。今僅就幾點簡述如下：

(1).政治成熟、民主守法

美國是全世界民主國家的始祖，民主的素養相當高。我在美國研習期間，剛好遇到 2000 年美國總統大選，由於票數不相上下，最後在最高法院的裁決下，由喬治‧布希獲得總統寶座，想想這種情形要是發生在台灣，不是又要聚眾抗議、紛爭不休嗎？美國人在政治上有這樣民主的素養，實在是植基於日常生活裡每個小地方的守法觀念；舉凡開車時的禮讓、遇到小學校車時要停車禮讓、超市與購票時的排隊習慣，大家就是自自然然地按照規定來做，不會有爭先恐後的情形發生。

(2).專本業、盡己職

在美國，不論是醫院裡的醫師、護士，或是大門的警衛、清潔員，總是可以看到他們衣著整齊，態度和藹親切。各行各業，不論職務大小，總是讓人感到他們對於自己的工作感到愉快而驕傲，這種愉快的感覺很容易讓別人感受得到，使得不管是員工或是客戶，在整個工作環境裡都能培養出一種愉快的氣氛。雖然也有人批評美國人只注重表面的親切，彼此個人生活方面的私交則不像我們中國

人這樣熱絡；而且想到台灣的地狹人稠，那種過度的人際交往所產生的競爭與冷漠，總是很難讓人在工作環境中感到有愉快的氣氛。雖然台灣客觀的環境很多地方不如美國，不過我們還是需要用心去鼓勵工作團隊(醫院)裡的每一個成員，以他們所扮演的角色為榮，再激發他們的敬業心，才能夠提昇整個工作團隊的氣氛。

(3).深入而執著的鑽研

在美國研習的這一年，看到不論是 Dr. Sutherlannd 或是 Dr. Russell，他們各自在其研究領域裡，投入的幾乎都是一輩子的心血與精力。 Dr. Sutherland 窮畢生之力，設立了世界知名的步態分析實驗室，組成了陣容堅強的研究團隊，每年都吸引各國學者前來研習。而 Dr. Russell 一生在 fibromyalgia 的鑽研，不僅在世界上佔有一定的知名度，現在還是 International MyoPain Society 的主席。他曾很大方地打開他的書櫃，秀出整櫃的文獻都是他這幾十年來的著作，真是令我嘆為觀止，深深地感受到：什麼時候我們才能寫出一書櫃自己的文章呢？經過這樣親身的相處，深切體會到一個被人家尊崇而看重的學者，他對於學問的追求是這麼樣的認真與執著，對於身為年輕一輩的我們，實在具有很大的啟發與鼓舞作用。

(4).對下一代的尊重

美國人對小孩子的重視是眾所週知的。此次研習全家同行，剛好也深刻地體會到人家所說的〝美國是小孩子的天堂〞這一句話的意義。不管是商場上的玩具，或是電視裡的兒童節目，都佔有極大的比重。好的書店甚至闢有兒童專屬的

圖書區，備有玩具與童書，可以讓小寶寶在那裡消磨一陣子。在生活上，美國人也非常尊重小孩子的權益，他們會徵詢小孩子的意見，而不像我們傳統的中國人是以父母的意見為意見。如果我們讓小孩子從小就有空間為自己來做選擇，並培養他們從小就為自己的選擇而負責，這不就是一種很好而且很成熟的教育嗎？這不就是民主教育的最根本所在嗎？

四、建議

(1) **本人此次能有機會獲得補助出國進修研習，不僅在學術研究與教學交流方面，獲得很大的學習與啟發；在生活的態度與見識方面，也得到很多的增長與擴展。希望政府與教育相關單位，能繼續支持補助出國進修與研習的計劃，以利國內學術研究的大幅提昇。**

(2) **我國的研究環境與研究經費本來就比美國要差。此次出國，親身見識到國外豐沛的研究經費與完善的研究設備，誠摯地希望國內在這一方面能盡量有所改善。國內政經情勢在這一段時間裡有很大的變化，健保局的經費核負也大大地限制了教學醫院在研究經費上面的編列，因此想要在學術研究上與世界各國並駕齊驅，政府與教育研究相關單位非得群策群力來克服這些難題。**

(3) **雖然美國樣樣都好，但還是比不上自己的家鄉—台灣好！期許自己能在回國後，盡量找機會將自己在美國所看到的，不管是做學問的態度與做研究**

的方法，或是生活上守法的習慣與教育子女的態度，擴散出去進而影響他人，使國內的民眾也能逐漸地培養出這些外國人所具備的優點，進而提昇我們整個國家的競爭力，與整個社會的生活品質。

(4) **建立學術是有價的觀念。美國的研究經費豐沛，雖然一大部分來自於政府的補助，但是也有一大部分來自於私人的捐助與學術單位自己的籌款。因此，我在美國參加的幾個研習會**(workshop)**，其費用皆相當昂貴。一方面他們有必須研修繼續教育學分的設計，一方面他們也不斷地推陳出新，來使上課的內容更具有吸引性。國內很多的醫學會議或研習會還是停留在免費或低學費的階段，對於醫學研究的推展還是有很大的阻力！希望有關的學術單位能共同來推展〝學術是有價的〞這個觀念。**

附錄(一)

論文發表：Discrimination of fibromyalgia patients from normal controls using the levels of cerebrospinal chemicals

Discrimination of Fibromyalgia Patients from Normal Controls Using the Levels of Cerebrospinal Neurochemicals

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Date of Submission: Oct 25, 2001

Short Title: CSF Neurochemicals for Discrimination of FMS and HNC

Keywords: Fibromyalgia, serotonin, substance P, nerve growth factor, logistic regression analysis.

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ABSTRACT

Objectives: To develop a formula, using only neuro-chemicals in the cerebrospinal fluid [CSF], which will discriminate fibromyalgia [FMS] patients from healthy normal controls [HNC].

Methods: An extensive bank of CSF samples collected from clinically characterized, medication-free, primary FMS [ACR 1990 criteria] and HNC was utilized. From that bank, demographically similar cohorts of FMS and HNC were selected. Measured in CSF were substance P [SP], nerve growth factor [NGF], and 5-hydroxy indole acetic acid [5HIAA], and others. Logistic regression analysis and discriminant analysis methods were used to identify variables that could contribute to distinguish FMS from HNC.

Results: The study sample included 28 FMS and 25 HNC. The FMS were 45.0 ± 8.8 years, 78.6% female, 53.6% Caucasian. Logistic regression analysis and discriminant analysis methods both revealed that the CSF neurochemicals with significant regression and discriminant coefficients were: SP, NGF and 5HIAA. The best formula developed by logistic regression was found to be:

$$\log \frac{y}{1-y} = \mathbf{-7.156 + 0.359[SP] + 0.051[NGF] - 0.067[5HIAA].}$$

This formula distinguished FMS from HNC with an accuracy of 90.6%, which was better than the accuracy by discriminant analysis [83.0%]. Logistic probability

scores correlated with the tender point index [TPI] .77 whereas discriminant function scores correlated with TPI .64.

Conclusion: Using only the concentrations of three CSF neurochemicals, a formula was developed which was able to distinguish FMS from HNC. Its "diagnostic" accuracy was comparable to that of the clinical criteria [ACR 1990] used to diagnose the FMS group. This finding provides a new tool for the study of patients with FMS. In addition, it adds to the confidence that FMS is a clinical disorder in which there are objective neurochemical abnormalities.

INTRODUCTION

Fibromyalgia syndrome [FMS], now a well-recognized condition, is the third most common clinical disorder confronted with rheumatologists in their clinics (1). The prevalence of fibromyalgia in the general population was estimated to be 2% (2). Eighty to ninety percent of patients were female, and the peak age was 30-50 years (2,3). Based on a history of chronic widespread musculoskeletal pain for more than 3 months and the presence of at least 11 of 18 tender points at discrete anatomic locations, the 1990 American College of Rheumatology [ACR] published criteria (3) for the classification of FMS with high sensitivity [88.4%] and specificity [81.1%]. While soft tissue pain is the primary symptom of FMS, there are some other important features, but not required by the ACR criteria, including sleep disturbance, fatigue, headache, irritable bowel syndrome, interstitial cystitis, paresthesias, cognitive deficits, depression and anxiety.

Up to date, the definitive etiology of FMS has not been completely understood. Although the skeletal muscles where FMS patients complained of pain were at first considered to be the primary problem, delicate histological and ultra-structural study has failed to identify any abnormality in skeletal muscles (4). On the other hand, the characteristic feature of the diffuse pain in FMS is proposed to have a central,

systemic and neurochemical pathogenesis. The proposition comes from several clinical observations, such as: the tender structures are not only limited to the muscle, but also include tendons, ligaments, bursae and etc; even the so-called "control points" ["non-tender sites"] are highly correlated with the anatomically defined "tender points" on the severity of tenderness; FMS patients have consistently disclosed a lower than normal pain threshold by dolorimetry. The lower than normal pain threshold, as “allodynia” defines, is a clinical situation in which pain results from a stimulus which should not normally be painful (5). Thus, FMS can be defined mechanistically as “chronic widespread allodynia” (6). Since allodynia has been demonstrated to be induced by abnormalities in the absolute concentrations of, or relative availability of nociceptive chemical neurotransmitters in animal study (7), it is rational to redirect the focus of FMS from the local tender points to the central nerve system in FMS patients by examining its neurochemicals for better validation of the pathogenesis of FMS.

One of the first neurochemicals to be implicated in FMS was serotonin [5HT]. Through its effect on the release of substance P [SP] from primarily afferent neurons, 5HT is known to be a down-regulator of pain perception. It also influences the magnitude of substance P's effect on the ascending dorsal horn neurons of the spinal cord (8-11). Moldofsky and colleagues were the first to suggest that 5HT might be

involved in the pathogenesis of FMS (12,13). They found a correlation between plasma tryptophan [TRP, the essential amino acid precursor of 5HT] and the severity of the clinical symptoms. Russell (14) had summarized the cumulative evidence that the serum concentrations of both TRP (15,16) and 5HT (17,18) were significantly lower than normal in FMS patients. However, it is very difficult to directly demonstrate 5HT deficiency in the brain, even in the cerebrospinal fluid [CSF], of FMS patients with current technology due to its limited sensitivity (19). On the other side, it has been possible to measure CSF levels of TRP, 5-hydroxytryptophan, and 5-hydroxy-indole acetic acid [5HIAA] (20-22). These three molecules are in the metabolic sequence by which TRP is first converted to 5-hydroxytryptophan, then to 5HT, and then to its final excretion product 5HIAA. All are low, or borderline low in the CSF of people with FMS. With the additional findings that CSF levels of both 3-methoxy-4-hydroxyphenethylene glycol [MHPG, a metabolic product derived from norepinephrine] and homovanillic acid [HVA, the terminal product of dopamine metabolism] being significantly lower than normal in FMS (20), it is indicated that there may be a major disturbance [a down regulation of several biogenic amines mediators] of brain neurotransmitter metabolism in FMS. More detailed and comprehensive researches for abnormal neurochemicals in CSF of FMS patients are warranted.

There are also many other neuropeptides being studied to reveal their relationship with "widespread allodynia" in FMS patients. In 1988, Vaeroy and colleagues (23) were the first to recognize that substance P [SP] was significantly elevated in the CSF of FMS patients compared with control subjects. Increased concentration of nerve growth factor [NGF] in the CSF of primary FMS patients was also noted in a recent study (24). Other related neuropeptides under investigation include calcitonin gene-related peptide [CGRP] (25), met-enkephalin-arg-phe (26), dynorphin A (27), …etc. While investigators are continuing to search other neurochemicals that are related to the pathogenesis of FMS, the question that which of these neurochemicals are important in discriminating FMS patients from healthy normal controls [HNCs] still remains unanswered. Yunus et al (28) first used multivariate analysis to demonstrate that a combination of several biochemical parameters could better classify FMS patients and HNCs than an individual test alone. However, they only focused on plasma amino acids, plasma and urinary catecholamines, but rather CSF neurochemicals. Since it has been proposed that the pathogenesis of FMS is related to the interaction of multiple neuroendocrine-immune factors, we believe the multivariable interaction relationship also exists among the various CSF neurochemicals. Therefore, the objective of this study is, using only CSF neurochemicals, to develop a multivariable formula to reveal which of these

neurochemicals will better discriminate FMS patients from healthy normal controls [HNC]. The correlation between the formula and the tender point index [TPI] was also measured.

MATERIALS AND METHODS

Participants. Over the past several years there have been over 330 individuals recruited into our FMS study database through a standard protocol. Among them are over 156 patients with the diagnosis of primary FMS, which met the American College of Rheumatology [ACR] 1990 classification criteria for FMS (3). They have provided their demographic characteristics, medical history, details about the features of their FMS symptoms, etc. The healthy normal control [HNC] group comprised 57 healthy individuals who did not have symptomatic musculoskeletal pain and who did not meet the classification criteria for FMS. The ethnicity of the enrolled subjects will reflect the ethnicity of the community with efforts to match demographically to the FMS patient group. Informed consent to perform assays on the samples was obtained at the time of sample collection. The sample collection process was approved by the Institutional Review Board of the University of Texas Health Science Center.

Data collection. All medications known to reduce the severity of FMS symptoms were discontinued for at least 14 days [>5 half lives for most drugs] prior to the sample collection. The lumbar puncture for CSF samples was collected on FMS patients and HNCs under sterile conditions with the subject in the seated

position. The procedures for neurochemicals assay were performed only after all of the standardization techniques have been completed. The neurochemicals measured in the CSF samples included: SP, NGF, MHPG, HVA, 5 HIAA, CGRP, neuropeptide Y, quinolinic acid, nitrate, nitrite, dynophin A, and antipolymer antibody. Tender point index [TPI] was used to represent the clinical pain measurement, which was calculated from the severity of discomfort induced by 4 kg finger palpation pressure at each of the 18 defined tender points (29).

Statistical analysis. Statistical analysis was performed using SPSS for Windows, release 10.0.1.(30). Difference of the neurochemical concentration between FMS and HNC was assessed by Student *t*-test. Significance was set at P=0.05. To identify which variables could contribute to distinguish FMS from HNC, two statistical models for predicting group membership, logistic regression analysis and discriminant analysis, were employed to develop a distinguishing formula. The correlation between the clinical variable, TPI, and the obtained formula scores was also computed by Pearson Product-Moment method.

RESULTS

Although our database had CSF samples from 156 well characterized primary FMS patients and 57 HNCs, not every neurochemical such as CGRP, neuropeptide Y, dynophin A, ...etc. was yet measured presently in every CSF samples. Neurochemicals of interest for our study were SP, NGF, MHPG, HVA, and 5HIAA. To perform logistic regression and discriminant analysis, all the subjects must have available data in each of these variables. Because of these requirements, the initial pool of subjects was reduced to 28 FMS patients and 25 HNCs, who had data in all the analyzed variables. The mean age of FMS patients was 45.0 ± 8.8 years, 78.6 % of them were female, and 53.6 % were Caucasian. Data on demographic and clinical features were listed in Table 1.

In logistic regression analysis, we used the backward technique to determine which neurochemicals could be the better contributing components in a multivariable formula for discriminating FMS patients from HNCs. Among these 5 neurochemicals, MHPG was removed from the equation in step 2, and

HVA in step 3 [Table 2]. The criterion for removal of predictor variables from the equation was default: POUT = 0.10. This means that significance of change when a predictor is removed from the equation must be P < 0.10 in order to keep this predictor in the equation. The results showed that SP, NGF, and 5HIAA were important components with significant coefficient for discrimination between FMS and HNC. The discriminating formula was found to be:

$$\log \frac{y}{1-y} = \mathbf{-7.156 + 0.359[SP] + 0.051[NGF] - 0.067[5HIAA].}$$

In this formula, it was apparent that SP was the most important components. The accuracy of this discriminant formula in distinguishing FMS from HNC was estimated to be 90.6%.

Discriminant analysis was also used to further validate the discrimination of these CSF neurochemicals. The result again revealed that SP, NGF, and 5HIAA were significant components, which was the same result as tested by logistic regression analysis. However, the accuracy of distinguishing FMS from HNC in the discriminant analysis was 83.0%, not as high as that of logistic

regression analysis.

Τηε χορρελατιον βετωεεν λογιστιχ προβαβιλιτψ σχορεσ α νδ ΤΠΙ ωασ 0.77, ωηιλε τηατ βετωεεν δισχριμιναντ φυνχτιον σχ ορεσ ανδ ΤΠΙ ωασ 0.64.

DISCUSSION

Among 22 amino acids, Yunus et al (28) developed a multivariable formula showing that a combination of 7 variables [plasma histidine, methionine, tryptophan, norepinephrine, isoleucine, leucine, and urinary dopamine] could better classify FMS patients and HNCs than a single variable alone. The discriminant function they used provided the optimum sensitivity of 86% and specificity of 77%, with an accuracy of 81% (28). In contrast to plasma amino acid, our study focused on neurochemicals only in CSF. For further validation of the discrimination of these CSF neurochemicals, two statistical models including logistic regression analysis and discriminant analysis were used to predict group membership between FMS and HNC. Although both statistical models identified the same CSF neurochemicals, which consisted of SP, NGF, and 5 HIAA, to be contributing components in a multivariable formula for discriminating FMS patients from HNCs, the logistic regression analysis yielded a formula that provided better classification accuracy [90.6 %] than did the discriminant analysis [83.0%]. The correlation between logistic probability scores and TPI was comparable to that between discriminant function scores and TPI [0.77 vs. 0.64].

SP is an 11 amino acid neuropeptides which plays several important roles in the process of nociception (7). The levels of SP can be manipulated to induce allodynia in animal models (31). It is believed that SP may facilitate nociception by "alerting" or "arming" spinal cord neurons to incoming nociceptive signals from the peripheral. Released from activated, myelinated A-delta and C-fiber afferent neurons, SP randomly diffuses into laminae I and V [A-delta] and laminae II [C-fiber]

of the spinal cord dorsal horn where it makes contact with its effector neurokinin-1 receptor. SP can also diffuse out into the extracellular space and from there to the CSF, where it can be measured as CSF SP (32). While SP in the serum (33) (Russell et al, unpublished, 1994) and in the urine (Russell and Clauw, unpublished 1994) of FMS patients were found to be within normal range, the level of SP in the CSF of FMS patients was demonstrated to be two- to three-fold higher than normal controls (23,26,34), which is the most dramatic and consistent chemical abnormality found to date in FMS patients. Although there is evidence that SP can be slightly elevated in other painful conditions such as osteoarthritis (35), FMS is the only clinical disorder known to exhibit such profoundly elevated levels of CSF SP. Patients with a variety of neuropathic conditions were found to exhibit lower than normal CSF SP levels (36,37). The elevated CSF SP levels clearly distinguish patients selected by the ACR 1990 criteria (3) from healthy normal individuals. Age and gender had no influence on the measured CSF SP levels but minor differences related to ethnicity were noted (34). A recent study (38) using single-photon-emission computed tomography [SPECT] revealed that higher CSF SP in FMS patients correlated highly with a decrease in brain regional cerebral blood flow [rCBF] within the caudate nucleus and thalamus of the same FMS patients. The reason for this relationship is not yet clear.

Nerve growth factor [NGF] is a neurotrophin which is essential for the growth of peripheral nerves and perhaps spinal cord neurons during mammalian nervous system development (39-41). It apparently has no direct role in development of brain neurons. While developing neurons are dependent on NGF for survival during the neonatal period, especially sympathetic ganglia (42), adult neurons can survive without NGF (43,44). However, adult neurons remain responsive and plastic to NGF (43). Animal study showed that a single systemic injection of NGF could result in mechanical and thermal hyperalgesia (45). Thermal hyperalgesia was also evoked in mice 24 h after intrathecal administration of NGF (46). One possible mechanism by which NGF may affect pain transmission is the stimulation of neuropeptide production, including SP and CGRP, in primary afferent neurons (40,47). Beside its ability to promote SP synthesis, NGF has also been reported to modulate inflammatory and immune responses (48,49).

Studies related to NGF in humans are still limited (50-52). CSF levels of NGF from newborns and children of up to 6 months have been found to be the highest level [mean 23 pg/ml] and then decreasing with age to almost undetectable levels in adult (50). It seems to rise in adults when there is neuronal stress or injury. For instance, elevated CSF levels of NGF were found in patients with brain injury (51) and in patients with multiple sclerosis (50). There is also evidence that viral and

bacterial meningitis exhibit higher than normal CSF NGF levels (50). In multiple sclerosis, NGF levels in CSF seem to be chronically elevated but then rise to childhood levels with exacerbations of disease and fall back to the chronically elevated levels with remissions (50). By contrast, peripheral neuropathic disorders such as leprosy, diabetes mellitus, and nerve trauma exhibit lower than normal in the compromised neurons and the skin (52). Giovingo et al (24) recently used a modified 2 site enzyme immunoassay to measure the NGF levels in CSF of FMS patients compared to healthy controls. They concluded that CSF NGF levels in the FMS patients were significantly higher than that of controls (41.8 ± 12.7 pg/ml vs. 9.1 ± 4.1 pg/ml), which could theoretically have important implications concerning the role of neuropeptides in the pathogenesis of the allodynia of FMS.

There is convincing evidence to implicate 5HT deficiency as an etiologic factor of FMS (6,15,16,20). 5HT is a potent regulator of several CNS functions, which includes release of substance P, hypothalamic hormone secretion, deep sleep, and pain perception. Even small alterations in 5HT's availability might be expected to have rather profound effects. A total body reduction of 5HT metabolism among FMS patients is suggested by the finding of significantly lower than normal of 24 hours total urinary excretion of 5HIAA, the final metabolic product of 5HT (53). The CSF pool size of 5HIAA, as well as the CSF pool sizes of the other two 5HT metabolic

molecules [TRP and 5-hydroxy-tryptophan] in FMS patients, were all found to be significantly lower than that in HNC CSF (20,22). These findings are only indirect evidences suggesting that something is amiss with 5HT body-wide availability in FMS patients. Unfortunately, the pool size of 5HIAA does not necessarily correspond to the turnover rate of 5HT, which would be the value of greatest interest. An alternative approach might be to measure the conversion of isotope-labeled TRP to labeled 5HIAA over a defined period of time in FMS and HNC.

In summary, a multivariable formula being capable of discriminating FMS from HNC was developed using only the concentrations of three neurochemicals [SP, NGF,5HIAA] in CSF. Its "diagnostic" accuracy was comparable to that of the clinical criteria [ACR 1990] used to diagnose the FMS group. This finding provides a new tool for the study of patients with FMS. In addition, it adds to the confidence that FMS is a clinical disorder in which there are objective neurochemical abnormalities. However, We can't predict the utility of the formula at this point but it may prove useful in predicting other biochemical directions that should be further explored in the central nervous system for the pathogenesis of FMS.

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TABLES

Table 1. Demographic and clinical characteristics of study subjects

Variable	FMS (N=28)	HNC (N=25)
Age, years, ± SD	45.0 ± 8.8	37.1 ± 11.6
Sex (M:F)	6:22	13:12
Ethnic (C:H)	15:13	13:8*
TPI	26.5	13.9
SP	33.5	22.0
NGF	41.8	9.1
MHPG	33.6	38.3
HVA	46.8	41.5
5 HIAA	29.3	29.1

* the other 4 is Black, one is missing.

**P<0.05

FM: fibromyalgia, HNC: healthy normal control, C: Caucasian, H: Hispanic, TPI: tender point index, SP: substance P, NGF: nerve growth factor, MHPG: 3-methoxy-4-hydroxyphenethylene glycol, HVA: homovanillic acid,

5 HIAA: 5-hydroxy indole acetic acid.

Table 2. Logistic regression analysis of CSF neurochemicals for discrimination of fibromyalgia from healthy normal control

		B	S.E.	Wald	df	Sig.	Sig. of the change*
Step 1[a]	**SP**	.378	.133	8.055	1	.005	.000
	NGF	.052	.028	3.538	1	.060	.003
	MHPG	-.021	.038	.304	1	.581	.575
	HVA	.033	.045	.550	1	.458	.447
	5HIAA	-.095	.060	2.501	1	.114	.096
	Constant	-7.609	3.081	6.101	1	.014	
Step 2[b]	**SP**	.360	.128	7.913	1	.005	.000
	NGF	.058	.026	4.973	1	.026	.002
	HVA	.045	.041	1.206	1	.272	.249
	5HIAA	-.105	.057	3.408	1	.065	.042
	Constant	-8.173	2.983	7.505	1	.006	
Step 3[c]	**SP**	.359	.127	7.952	1	.005	.000
	NGF	.051	.024	4.351	1	.037	.004
	5HIAA	-.067	.043	2.417	1	.120	.094
	Constant	-7.156	2.701	7.020	1	.008	

SP: substance P, NGF: nerve growth factor, MHPG: 3-methoxy-4-hydroxyphenethylene glycol, HVA: homovanillic acid, 5HIAA: 5-hydroxy indole acetic acid.

a. Variables entered on step 1: SP, NGF, MHPG, HVA, 5HIAA.

b. Variable removed on step 2: MHPG.

c. Variables removed on step3: MHPG, HVA.

*. POUT=0.10