行政院國家科學委員會補助專題研究計畫進度報告

熱性痙攣續發為癲癇學童的臨床、神經認知及海馬回磁振掃瞄定量分析之研究(1/3)

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計畫主持人：黃朝慶
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Clinical, Neurocognitive Characteristics and Hippocampus MRI Volumetric Study in School-age Epileptic Children with a History of Febrile Convulsions
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中文摘要

目的 熱性痙攣是小兒痙攣最常見的原因，發生率為2-5％，復發率為30-40％，其中約2-7％會繼發癲癇。許多研究認為在學業表現、智力、行為上，熱性痙攣兒童與一般兒童無異。然而目前對熱性痙攣繼發癲癇的智力研究很少。本研究目的在瞭解熱性痙攣繼發癲癇之學齡兒童的智力特性。

對象及方法 收集三組6-12歲學齡兒童：(1) 熱性痙攣繼發癲癇組，1997-2000年間在成大醫院、嘉義基督教醫院小兒神經內科門診個案，目前的診斷為癲癇，並在癲癇發生前曾有熱性痙攣；(2) 熱性痙攣組，根據熱性痙攣繼發癲癇組選擇年齡相近者配對；(3) 手足對照組，選擇熱性痙攣繼發癲癇組無抽搐且年齡相近的兄弟姊妹。每組各30人。研究工具為魏氏兒童智力測驗與腦部磁振造影檢查。

結果 接受測驗實際年齡(平均值±標準差)分別如下：熱性痙攣繼發癲癇組(97.9±18.7個月)、熱性痙攣組(98.7±18.1個月)、手足對照組(108.1±16.9個月)。熱性痙攣繼發癲癇組、熱性痙攣組、手足對照組中智障比例分別為36.7%、6.7%及3.3%，熱性痙攣繼發癲癇組的智障比例顯著較高。與熱性痙攣組相較，除記憶廣度分測驗外，熱性痙攣繼發癲癇組的各項智慧分數均顯著較低。以統計方法調整年齡變項，與手足對照組比較，熱性痙攣繼發癲癇組智力分數均較差。排除11個智障兒童，分析智力正常兒童的智力表現，熱性痙攣繼發癲癇組在符號替代分測驗表現較其他兩組差；且在算術分測驗表現較手足對照組差。分析智力剖面圖發現：熱性痙攣繼發癲癇組在符號替代分測驗表現相對於其他分測驗明顯較差。在熱性痙攣繼發癲癇之兒童中，有21位接受腦部MRI檢查，其中約半數有異常結果，但腦部MRI異常與正常兒童之智力表現無顯著差異。

結論 本研究結果發現熱性痙攣繼發癲癇的學童在所有智力表現均差，特別是符號替代分測驗明顯更差。續發的癲癇對熱性痙攣兒童的智能發展有明顯不良的影響。

關鍵字：熱性痙攣，熱性痙攣繼發癲癇，智力，魏氏兒童智力測驗。
Abstract

**Objective:** Febrile convulsion (FC) is the most common seizure disorder in children, and the incidence is 2-5%. The recurrent rate of FC is 30-40%, and subsequent epilepsy is 2-7%. Many studies have showed that children with FC performed as well as with other children in terms of their academic progress, intellect, and behavior. Few have focused on the intelligence outcome of epileptic children with a history of FC. This study was to delineate the intelligence characteristics of school-aged epileptic children with a history of FC.

**Methods:** The epileptic children with a history of FC who visited our Pediatric Neurological Clinic from 1997-2000 were enrolled. There are three groups of children aged 6 to 12 as follows: epileptic children with a history of FC (FC-epilepsy group), age-matched FC group (FC group), and sibling control of epileptic children with a history of FC (sibling group). There were thirty children in each group. The study instruments were WISC-III and MRI.

**Results:** The age (mean age ±SD, months) of the three groups at assessment were: FC-epilepsy group (97.9±18.7), FC group (98.7±18.1), and sibling group (108.1±16.9). The rate of mental retardation (MR) (FIQ below 70) in the FC-epilepsy group (36.7%) was higher than that in the FC group (6.7%), and sibling group (3.3%). All the test scores of the WISC-III, except Digit Span subtest, in the FC-epilepsy group were significantly lower than those in FC group. As compared with sibling group, the intellectual scores of the epileptic children with FC were even worse. The FC-epilepsy group with normal IQ (FIQ>69) had lower score on coding subtest as compared with the other two groups, and also had lower score on arithmetic subtest as compared with sibling group. The profiles of intelligence revealed that a significantly relative poor performance was observed for the coding subtest in FC-epilepsy group. Ten of the 21 patients who had MRI examination in the FC-epilepsy group had abnormal findings: six had hippocampal abnormalities, two white mater lesions, one left cerebral hemispheric atrophy, and one frontal lobe tumor. There was no significant difference in FIQ between abnormal and normal MRI results in FC-epilepsy group.

**Conclusions:** We found that FC-epilepsy group had poorer intellectual performance on all aspects, especially coding subtest. The occurrence of epilepsy significantly has an adverse effect on the intellectual outcome in the children with FC.

**Key words:** febrile convulsions, epilepsy with febrile convulsions, intelligence, WISC-III.
緣起與目的

兒童熱痙攣(febtile convulsion)是兒童最常見的神經性疾病，也是小兒痙攣常見的原因。熱痙攣的定義為：發生在 6 個月到 5 歲間，抽締與發燒本身有關，診斷時必須排除任何腦內感染或確定病患證據所造成的痙攣現象。根據發作型態分型，單純型熱痙攣發作時間不超過 15 分鐘(大部分為 1-3 分鐘)，屬於全身性的發作；複雜型熱痙攣發作時間大於 15 分鐘，為局部發作，24 小時內發作兩次或兩次以上[1]。熱痙攣的發生率一般為 2-5 %，5 歲前的復發率為 30-40 % [1]，我們過去在台灣南部人口研究發現熱痙攣的發生率為 2.4 %，熱痙攣兒童中發展遲緩的比例為 3.7 % [2]。關於兒童熱痙攣智力研究，過去醫院內的臨床樣本研究結果，智障比率範圍為 6-18 % [3]；但前瞻性的社區樣本研究認為熱痙攣的長期智力結果是良好樂觀的，與一般兒童並無顯著差異[4,5]，單純型熱痙攣兒童的神經心理測驗結果與健康對照組無差異[6]。我們過去研究發現早期熱痙攣對學齡兒童的行為、學業表現及注意力之影響不明顯，甚至在分心控制、注意力反應時間上有較佳的表現[7]，工作記憶(working memory)方面的表現也較佳，不過其雖較不易犯執著性錯誤(perseverative error)，衝動性錯誤確有略多之傾向[8]。一般而言，熱痙攣對心智功能的影響並不

但在熱痙攣兒童中約 2-7 %的比例會持續發癲癇[1]，其中部分患者腦部有海馬硬化(hippocampal sclerosis)的情形，在青少年或成年期發展為頑固性癲癇(intractable epilepsy)[9]。早期研究顯示熱痙攣長發癲癇的相關危險因子包括：家族有癲癇史、先前存在神經學方面的異常以及複雜型熱痙攣[10]，且緒發癲癇的熱痙攣兒童智力比例高達 26.9 % [11]。就目前所知，並無特別針對熱痙攣續發癲癇的族群進行智力特性缺損的研究，本研究之目的在於瞭解由熱痙攣續發的癲癇是否對學齡兒童智力功能有所影響外，亦希能描繪出該群兒童特殊的智力剖面圖。

材料與方法

研究對象

本研究採用個案對照的研究設計，樣本來源是 1997-2000 年間在成大醫院、嘉義基督教醫院小兒神經內科門診個案，收集年齡在 6-12 歲的學齡兒童，目前的診斷為癲癇，並在癲癇發生前曾有熱痉攣的情形(熱痉攣續發癲癇組)。並根據熱痙攣續發癲癇組的年齡選取另外兩對照組，其一：熱痙攣組，5 歲前曾發生熱痙攣，5 歲之後無復發，且目前無癲癇的診斷(與熱痉攣續發癲癇組的對照個案年齡相差在六個月內者)；其二：手足
對照組（sibling control），收集熱帶敲續發癲癇組個案之年任何抽歎史且年齡相近的兄弟姊妹。並收集兩組父母教育程度、家庭社經狀況、熱帶攬初發年疊與復發次數等資料。父母教育程度區分為三等級，低（國中、國小）、中（高中、五專）、高（大學以上）。家庭社經地位區分為低、中、高三等級[12]。

研究工具

本研究智力功能評估工具使用中國行為科較社在台灣發行的魏氏幼童智力測驗第三版中文版（The Wechsler Intelligence Scale for Children- Third Edition, WISC-III）為評估工具，依指導手冊標準程序進行施測。語文測驗包括常識（Information）、類同（Similarities）、算術（Arithmetic）、詞彙（Vocabulary）、理解（Comprehension）、記憶廣度（Digit Span）；作業分測驗包括圖畫補充（Picture Completion）、符號替代（Coding）、連環圖系（Picture Arrangement）、圖形設計（Block Design）、物型配置（Object Assembly）。結果可得語文智商（VIQ）、作業智商（PIQ）、全量表智商（FIQ）等三項智商分數，語文理解因素（Verbal Comprehension）、知覺組織因素（Perceptual Organization）、專心注意因素（Freedom of Distractibility）等三項因素分數，智商與因素分數平均值與標準差為 100±15，各分測驗則為 10±3。

磁振造影檢查（MRI）：利用 1.5T 光電子掃瞄裝置（Siemens Vision+, Erlangen, Germany），空間解析度為 0.59 x 0.78 x 2.0 mm³（TR/TE/NEX =9.7/4.0/2），所有腦切面是以海馬回結構長軸作垂直切面。使用 3D T1-weighted gradient-echo technique，取得腦部（特別是海馬回）高解析度的核磁共振影像。

資料分析

所有統計採用雙尾檢定（two-tailed tests），取 p 值小於 0.05 達到統計上的顯著意義。平均年齡、熱帶攬初發年疊與復發次數，以 independent t test 檢定分析兩組間的差異。以卡方檢定（χ² test）分析男女比例、父母教育程度、家庭社經地位、智障比例、特教比例等類別資料，比較兩組資料的比例分配的同質性。熱帶攬續發癲癇組與熱帶攬組，兩組智力測驗分數的比較以 paired-sample t test 進行分析。熱帶攬續發為癲癇組與手足對照組，兩組以 Generalized Estimating Equations (GEEs) 分析，考慮家庭配對的變項，在調整年齡變項下，分析各智力分數在兩組間的差異。
結果

本研究共收集 90 位學齡兒童，基本資料見表一。每組人數各 30 位，三組平均年
齡為接受測驗的實際年平均值±標準差依序如下：熱疫癲癇本癲癇 97.9±18.7 個
月、熱疫癲癇 98.7±18.1 個月、手足對照組 108.1±16.9 個月，性別比例(男/女)依序為
13/17、19/11、15/15，我們發現熱疫癲癇手癲癇組的年齡與手足對照組有顯著差異，熱
疫癲癇手癲癇組與其他兩組的男女比例在統計上無差異。

比較熱疫癲癇手癲癇與熱疫癲癇兩組的父母教育程度、社經地位以及熱疫癲癇初發年
齡與復發次數等資料，發現熱疫癲癇手癲癇組母親屬於低教育程度比例顯著較多，而父
親的教育程度則無顯著差異；兩組在家庭社經地位上無顯著差異。熱疫癲癇的初發年齡與
復發次數，雖然發現熱疫癲癇手癲癇組的初發年齡較早、復發次數較高，但兩變項皆未
達統計的顯著差異。

熱疫癲癇手癲癇兒童的癲癇發生平均年平均為 60.8±25.5 個月(年齡範圍 2-10 歲)，
其中 8 位屬於頑固性癲癇(26.7 %)；共 3 位未服抗癲癇藥物，服用 valproic acid 共 15
位，phenobarbital 共 2 位，carbamazepine 共 3 位，7 位服用兩種以上的抗癲癇藥物；頑
固性癲癇中有 6 位兒童使用多抗癲癇藥物治療。

比較智障(mental retardation，在此取 WISC-III 之 FIQ 低於 70 者)兒童在各組的比
例，熱疫癲癇手癲癇組智障比例顯著高於熱疫癲癇(p=0.005)與手足對照組(p=0.001)；並
且熱疫癲癇手癲癇組接受特殊教育的比例顯著多於熱疫癲癇組(p=0.011)與手足對照組
(p=0.002)。

各組智力測驗分析的結果見表二。比較熱疫癲癇手癲癇組與熱疫癲癇組，我們發現
熱疫癲癇手癲癇組語文智商比後者約低 16 分(p=0.003)、作業智商約低 19 分(p<0.001)、
全量表智商約低 19 分(p=0.001)，除了記憶廣度分測驗外，兩組的三項因素分數以及其
餘 10 項分測驗分數皆達顯著差異，熱疫癲癇手癲癇組的各智力測驗的平均分數約低
0.7-1.3 個標準差左右。比較熱疫癲癇手癲癇組與手足對照組，我們發現熱疫癲癇手癲癇
組語文智商約低 18 分(p=0.0015)、作業智商約低 22 分(p=0.0001)、全量表智商約低 22
分(p=0.0002)，兩組的每一項智力測驗分數差異均達顯著，熱疫癲癇手癲癇組的平均測
驗分數約低 1-1.3 個標準差左右。

排除智障兒童，進一步分析三組內正常智力兒童的測驗表現。在熱疫癲癇手癲癇
組與熱疫癲癇組中，排除其中有智障的配對組後，共分析 18 對配對組，以無母數統計分
析中的 Wilcoxon signed-ranks test 檢驗，發現熱痙攣發癲癇組在符號替代 \((p=0.040)\) 分測驗顯著表現較差，而理解及連環圖系分測驗雖未達統計顯著，但其 \(p\) 值分別為 0.050 及 0.064 接近顯著水準。比較熱痉攣發癲癇組 \((n=19)\) 與手足對照組 \((n=29)\)，以 GEEs 分析兩組在測驗分數表現的差異，發現熱痙攣發癲癇組在算術 \((p=0.0224)\) 及符號替代分測驗 \((p=0.0245)\) 較顯著差異；而作業智商分數雖未達統計顯著差異，但其 \(p\) 值為 0.0502 接近顯著水準。

以自比式方式 (ipsative approach)，瞭解受試者本身能力水準的長處及弱處，描繪三組智力分測驗分數的剖面圖，計算每一位個案之所有分測驗的總平均，求其每一分測驗分數與分測驗總平均的差距值，分別計算各組每一分測驗的差距值，以 one-sample \(t\) test 檢定各組的差距值，若 \(p < 0.05\) 則達統計上的顯著。由熱痙攣發癲癇組的智力剖面圖 (見圖一)，我們發現該群兒童在作業分測驗上表現比語文分測驗相對要差，其中在符號替代分測驗相對於其他分測驗表現顯著差 \((p=0.001)\)。由熱痙攣組的智力剖面圖 (見圖二)，發現各分測驗表現並無特別趨勢。對照組的智力剖面圖 (見圖三)，發現以語文分測驗的算術分測驗分數顯著較高 \((p=0.004)\)。比較熱痙攣發癲癇組與其他兩組的智力剖面圖，我們發現該群兒童在符號替代分測驗表現上明顯較差。

熱痙攣發癲癇組兒童共有 21 位完成腦部 \(MRI\) 檢查，其中 11 位結果正常，10位結果異常 \((47.6\%)\)。其中海馬回病變或萎縮有 6 位 \((4\) 位病變發生在左側，2 位發生在右側)；其他病變包括 2 位白質病變 \((1\) 位甚至嚴重到白質空洞軟化症，涉及大腦區域為額葉及顳葉部位)，1 位左大腦萎縮合併鈣化，1 位左額葉良性腦瘤。由於樣本數較小，我們使用無母數分析中的 Mann-Whitney \(U\) test，比較熱痙攣發癲癇組中 \(MRI\) 異常 \((n=10)\) 與正常兩組兒童的智力表現，結果發現 \(MRI\) 異常兒童的全量表智商分數雖較低 \((66.5 \pm 25.4\) 與 \(76.7 \pm 23.6\))，但兩群兒童間無顯著差異 \((p=0.457)\)。比較 6 位海馬回異常與 15 位海馬回正常 (包括其他病變或 \(MRI\) 結果正常) 的智力表現，結果發現兩群的全量表智商分數分別為 \(70.2 \pm 29.3\) 和 \(72.5 \pm 23.4\)，並無顯著差異 \((p=1.000)\)。

討論

我們發現熱痙攣發發的癲癇對兒童智力發展有不良的影響，熱痙攣發癲癇的智商分數較熱痙攣組或手足對照組低約 16-22 分左右，且其智障比例較高。本研究的熱痙攣組的智障比例雖較人口研究要高 \([2,5,11]\)，但與過去醫學研究相比 \([3]\)，熱痙攣的智障比例在合理的範圍內；根據 WISC-III 手冊，台灣常模全量表智商 69 的百分等級為 2，推估人口的智障比例約為 2 %，本研究手足對照組的智障比例為 1/30，應是合理的。
抽象結果；因此推測本研究樣本的選擇方法並無偏誤存在，反推熱症肇續發癲癇組的智
商差、智障比例偏高有其特殊的意義存在。綜合過去研究結果[4,5]與本研究的數據顯
示：熱症肇兒童智力與一般兒童無差異，由此我們認為兒童早期的熱症肇對於智力發
展無顯著不良的影響，但是熱症肇續發的癲癇對智力卻有很大的影響。

由於疾病本身與環境和遺傳因素都可能影響兒童智力的發展，為考慮環境與遺傳
因素對兒童智力發展的可能性影響，本研究選擇將熱症肇續發癲癇組年齡相近的兄弟姊
妹作為手足對照組[4]，以控制其家庭社經地位、環境因素(親子互動、父母教養態度等)
與遺傳因素，比較兩組智力表現的差異，希望凸顯疾病因素的影響。文中以 GEEs 調整
年齡的差異後，比較兩組的智力表現，我們發現熱症肇續發癲癇的兒童與手足對照組在
智力測驗各分數表現均達顯著差異，意即控制了環境與遺傳因素的影響下，疾病本身(熱
症肇與癲癇)對兒童的智力發展的確造成相當不良的影響。

使用熱症肇續發癲癇組與年齡配對熱症肇組的研究設計，試圖瞭解熱症肇續發的
癲癇對智力造成的影响。熱症肇續發癲癇組母親的教育程度較低，雖然主要照顧者母親
的教育程度對兒童智力發展可能有影響，但仍不至於造成智商差距高達 15-20 分左右，
尤其熱症肇續發癲癇手足的智商與常模無差別，母親較低的教育程度並非造成熱症肇続
發癲癇兒童智力下降的主要原因。過去文獻研究熱症肇初發年齡及復發性對智力的影
響，正反結果均有[4-6]，我們比較此兩組發現其初發年齡及復發次數未達統計顯著差
異，此兩因素無法解釋兩組智商間如此大的差距。因此我們認為續發的癲癇對熱症肇兒
童的智力發展是相當重要的因素。

本研究熱症肇續發癲癇兒童的平均智力分數在邊緣智障範圍，比 Bourgeois 研究
癲癇兒童的智力分數(101.0±20.5)來得低[13]，可能源於 Bourgeois 的樣本具備選擇性，
排除智商低於 40 及癲癇重積症(status epilepticus)的患者，且頑固性癲癇的比率较低(11.1
%)，樣本的選擇可能包括較多的良性癲癇。文獻認為癲癇兒童中約有 20-30% 屬頑固性
癲癇[1]，本研究頑固性癲癇的比率在合理範圍內，且選樣標準也並未排除較不良的癲
癇。本研究熱症肇續發癲癇的智力分數與 Bulteau 研究中 6 到 11 歲的智力分數(76.5±19.5)
相近[14]，但由於該研究的樣本年齡範圍較廣，智力測量的工具不只一種，兩研究結果
的比較上仍須小心。有興趣的現象是發現本研究作業智商顯著低於語文智商的情形
(p=0.04)，與 Bulteau 發現相同[14]，推測癲癇可能對右腦功能的影響比左腦更為明顯，
未來可利用神經心理測驗再進一步研究。本研究與其他癲癇研究最大的不同處在於我們
的研究樣本為熱症肇續發癲癇的個案，使用單一智力測量的工具，並根據熱症肇續發癲
癲癇，收集年齡配對的熱瘡脹及年齡相近的手足分別對照比較，可更加格出熱瘡煩續
發的癲癇對智力的影響。

抗癲癇藥物對認知功能的影響仍有許多爭議，藥物的種類與服用的數目對認知功
能的影響有差異[15]．過去研究發現服用抗癲癇藥物愈多愈可能造成智力分數的降低[13,
14]，Timble 回顧文獻中認為 phenytoin 會造成兒童認知損害，而 valproic acid 及
carbamazepine 造成認知損害較少[16]，長期服用 phenobarbital 患者相較於服用 valproic
acid 者的智商分數較低，valproic acid 對認知有輕微不良的影響[17]，但 Mandelbaum 研
究發現抗癲癇藥物治療對於認知功能損害並無顯著影響，認為癲癇兒童本身或環境的因
素對認知功能的影響較抗癲癇藥物明顯[18]，且多重迴歸分析結果也認為抗癲癇藥物與
癲癇兒童的智力表現無明顯相關[14]。本研究熱癆煩續發癲癇兒童大部分曾長期服用抗
癲癇藥物，我們的病人中無人使用 phenytoin，2 位使用 phenobarbital；半數以上兒童使
用 valproic acid 或 carbamazepine，此兩種藥物對認知的影響輕微。但 8 位癲癇型癲癇其
中有 6 位使用多種抗癲癇藥物治療，過去研究結果認為使用愈多的抗癲癇藥物對智力的
影響愈不良，我們不排除抗癲癇藥物對我們病人智力的影響，但可能不至於造成如此廣
泛全面性的損害，使得熱癆煩續發癲癇組的智力分數比其他兩對照組低 16-22 分，我們
認為影響兒童的智力損害，最大的可能來源為熱癆煩續發的癲癇本身或其腦部構造異常
的因素。

造成海馬回硬化的可能原因為抽搐的影響(熱癆煩與癲癇)或先天性腦部異常[1]，
過去研究發現海馬回硬化的顯葉癲癇患者中 22% 的比例過去曾發生熱癆煩[9]，研究認
為癲癇病人腦部先天性細微的海馬回異常(hippocampal malformation)可能促使熱癆煩發
生與海馬回硬化的發生[19]。我們認為腦部結構異常可能影響熱癆煩續發癲癇兒童的智
力發展，本研究特別針對熱癆煩續發癲癇兒童進行腦部 MRI 檢查，就目前所得 21 位腦
部 MRI 影像，顯示約有半數的兒童腦部結構有異常的現象，包括白質病變與海馬回病
變，海馬回病變的比例不低(28.6 %)，熱癆煩續發的癲癇與海馬回病變間似乎有不低的
關連性。熱癆煩續發癲癇 MRI 異常兒童的智商雖比 MRI 正常兒童低，但未達統計的顯
著差異，且海馬回異常與非海馬回異常兒童的全量表智商無顯著差異。未來研究方向可
再增加樣本數作比較，試圖釐清腦部結構異常對熱癆煩續發癲癇兒童智力的重要性。

排除智障兒童，進一步分析智力正常熱癆煩續發癲癇兒童的測驗表現，我們發現
熱癆煩續發癲癇兒童在符號替代分測驗表現明顯地較其他兩組差，且算術分測驗表現也
較對照組差，有數個智力分數差異 p 值落在 0.05-0.10 之間，可能在增加樣本數後，分
數的差異可能達到顯著。由於本研究在排除智障後樣本人數更少，未來可再持續增加樣本數，更清楚描繪癲癇兒童的心智特性。

分析智力剖面圖，我們發現癲癇兒童智力測驗表現全面下降，但符號替代分測驗表現相對更差，其他兩組的智力剖面圖並無呈現類似結果。符號替代分測驗與心理動作速度(psychomotor speed)、工作記憶(working memory)、持續注意力(sustained attention)等認知能力有關，且對腦部器質性或功能性損害相當敏感，腦部任
何部位的損害均可能降低此分測驗的分數[20]。由於研究工具的限制我們無法精確解釋

熱症與癲癇的關係對特定認知功能或腦部區域造成的損害，未來可考慮以較為精細的神
經心理測驗為工具，期待以神經心理的角度分析熱症與癲癇兒童的發展情形，精確

描繪熱症與癲癇的關係對各項認知功能是否有不同的影響。過去研究癲癇患者的智力剖
面圖顯示：特別的認知缺損與癲癇發作的部位有關[14]，抽筋類型也為認知損害重要的
指標[18]。由於樣本數的限制，無法根據癲癇特性作分類，未來研究可朝向將熱症與癲
癇的癲癇分成同質性更高的亞群作更細緻的比較。

本研究結果發現熱症與癲癇的關係對學齡兒童智力有全面不良的影響，幾乎所有智
力分數均顯著降低，特別是符號替代分測驗的分數更差，臨床工作者若發現早期熱
症與癲癇兒的情形，對於這些兒童的智能發展需要更加地關注，建議能進行早期定
期的追蹤檢查，以便能及早進行神經復健計畫。
参考文献


13. Bourgeois BFD, Prensky AL, Palkes HS, Talent BK, Busch SG: Intelligence in epilepsy:


表一: 三組兒童的人口學與家庭背景資料

<table>
<thead>
<tr>
<th></th>
<th>癫癇組 (n=30)</th>
<th>癲癇組 (n=30)</th>
<th>對照組 (n=30)</th>
<th>p^a</th>
<th>p^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>平均年齡(月)</td>
<td>97.9±18.7</td>
<td>98.7±18.1</td>
<td>108.1±16.9</td>
<td>0.872</td>
<td>0.031</td>
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<tr>
<td>年齡範圍(月)</td>
<td>76-129</td>
<td>77-131</td>
<td>78-143</td>
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<tr>
<td>性別 (男/女)</td>
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<td>19/11</td>
<td>15/15</td>
<td>0.121</td>
<td>0.605</td>
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<td>父親教育等級</td>
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<td>高</td>
<td>5 (17%)</td>
<td>9 (30%)</td>
<td>5 (17%)</td>
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</tr>
<tr>
<td>中</td>
<td>13 (43%)</td>
<td>17 (57%)</td>
<td>13 (43%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>低</td>
<td>11 (37%)</td>
<td>4 (13%)</td>
<td>11 (37%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>不知道</td>
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<td>0</td>
<td>1 (3 %)</td>
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<td>高</td>
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<td>6 (20%)</td>
<td>3 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>中</td>
<td>13 (43%)</td>
<td>19 (63%)</td>
<td>13 (43%)</td>
<td></td>
<td></td>
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<tr>
<td>低</td>
<td>14 (47%)</td>
<td>5 (17%)</td>
<td>14 (47%)</td>
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<td>家庭經濟地位</td>
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<tr>
<td>高</td>
<td>4 (13%)</td>
<td>6 (20%)</td>
<td>4 (13%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>中</td>
<td>5 (17%)</td>
<td>10 (33%)</td>
<td>5 (17%)</td>
<td></td>
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</tr>
<tr>
<td>低</td>
<td>19 (63%)</td>
<td>14 (47%)</td>
<td>19 (63%)</td>
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<tr>
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<td>2 (7%)</td>
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</tr>
<tr>
<td>熱病癱初發年齡(月)</td>
<td>24.9±19.1</td>
<td>29.5±18.2</td>
<td>無</td>
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<tr>
<td>熱病癱復發次數</td>
<td>3.27±3.6</td>
<td>1.97±1.9</td>
<td>無</td>
<td>0.087</td>
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</tr>
<tr>
<td>智障人數(比例)</td>
<td>11 (36.7 %)</td>
<td>2 (6.7 %)</td>
<td>1 (3.3 %)</td>
<td>0.005</td>
<td>0.001</td>
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<tr>
<td>接受特殊教育人數</td>
<td>8 (26.7 %)</td>
<td>1 (3.3 %)</td>
<td>0 (0 %)</td>
<td>0.011</td>
<td>0.002</td>
</tr>
</tbody>
</table>

數據以平均值±標準差表示
p^a: 熱病癱續發癲癇組 vs 癲癇組
p^b: 熱病癱續發癲癇組 vs 對照組
### 表二：魏氏兒童智力測驗結果

|                | 腦癱嬰長發
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<td>語文智商</td>
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<td>全量表智商</td>
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<td>知覺組織</td>
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<td>專心注意</td>
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<td>常識</td>
<td>7.03±3.7</td>
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<td>項同</td>
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<tr>
<td>算術</td>
<td>6.73±4.3</td>
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<td>詞彙</td>
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<td>理解</td>
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<td>記憶廣度</td>
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<td>圖畫補充</td>
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<td>符號替代</td>
<td>5.10±4.0</td>
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<td>速記圖指</td>
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<td>圖形設計</td>
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<td>物型配置</td>
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<table>
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所有分數以平均值+標準差表示

$p^a$：熱痲癇續發癲癇組 vs 熱痲癇組

$p^b$：熱痲癇續發癲癇組 vs 對照組
圖一：熱座奪發癲癇組的智力剖面圖。*表示 $p < 0.05$
圖二：熱症療組的智力剖面圖。
圖三：對照組的智力剖面圖。*表示 $p < 0.05$
2001 年 4 月底到 5 月初美國小兒科醫學會在 Maryland 州 Baltimore 市近 Inner harbor 之有名的 Convention Center 舉行，開會場地寬廣，視野明朗，大會依照以往極有 organized 之各大小會場舉行不同 subspecial 之 Topic symposium，Subspecialities themes，Workshops，Special interest groups 以及不少場次之 poster sections。並且大會也邀請了現階段 state of art 之研究者現身說法，特別是邀請現炙手可熱 Celera 之 JC. Venter 演講”sequencing the human genome”更是大會高潮。

台灣此次也去了不少醫師，包括成大醫院葉院長、林其和、林毓志及我本人，新樓醫院王藍浣醫師，林口及高雄長庚之 8 位以及台北婦幼醫院新生兒醫師，也發表了 7 個 posters（包括了我自己的 2 個 posters），算是成績不錯的一次，因為美國小兒科醫學會對接受口頭或 poster 發表之標準很高，這也代表台灣兒科在研究方面有向上提高之現象。

此次大會中，Kernicterus symposium 發表了近年來美國足月兒腦部因核黃膽受傷之人數有上升的趨勢，並且令人動心地提出數例個案報告並請父母現身參與。另外對於腦傷之機制，腦部發育與行為認知以及早期之腦傷對認知之影響等題目均開了很好受歡迎之 symposium。

我們也另外去了 Johns Hopkins 之克雷格-甘乃迪兒童發展中心參訪，特別是與 Neuroimaging Center 之 Dr. Kauffman 討論了以後可能合作於 proteonomics 之研究，也談及了他最近發現在 fragile X 病人身上有另外一種與心智功能有關之 biochemical marker。

總之，此次 2001 年美國小兒科醫學會之行，對於一位小兒神經科醫師而言，此次大會內容也包括了不少與腦部發育、腦傷有關之特別演講，故也收穫頗大。
Urinary Interleukin-6 is Elevated in Newborns at Risk for Hypoxic-Ischemic Encephalopathy

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Running head title: Urinary IL-6 and neonatal hypoxic-ischemic encephalopathy

33 references, 1 table and 3 figures

Word Count: 3111
Abstract

It is crucial to identify newborns at risk of developing hypoxic-ischemic encephalopathy (HIE) shortly after birth. This study investigates whether urinary tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) predict the occurrence of HIE. Urinary TNF-α and IL-6 at \( \leq 6 \) and 48-72 hours after birth measured in 46 normal newborns (Group 1) and 38 newborns with perinatal asphyxia were correlated with the development of HIE. Among newborns with asphyxia, 22 had no HIE (Group 2) and 16 developed HIE (Group 3).

Within 6 hours after birth, the median urinary IL-6 of Group 3 (30.0 pg/mg-creatinine, range 15.7-679.4) was significantly higher than that of Group 1 (1.6, 0.3-17.7) \( (p < 0.001) \) or Group 2 (6.0, 0.6-21.7) \( (p < 0.001) \). The median TNF-α of Group 3 (2.8, range 0.6-309.6) was also higher than that of Group 1 (0.8, 0.2-6.7) \( (p < 0.001) \), but was not different from Group 2 (1.7, 0.3-18.6). Cut-off value set at 20 pg/mg-creatinine for IL-6 had 92% positive predictive and 81% negative predictive value for HIE occurrence. Compared with IL-6, TNF-α had a much larger overlap between Groups 2 and 3. By 48-72 hours of age, these two parameters had a much lower ability in distinguishing between Groups 2 and 3.

Infants with adverse outcomes at age one year had higher IL-6 or TNF-α levels (median, 47.5, 4.3, respectively) than those with favorable outcomes (7.7, 1.6, respectively) \( (p < 0.001, \ p = 0.006, \) respectively). These finding suggests that urinary IL-6 measured within 6 hours after birth could help to identify newborns at risk for HIE.
Perinatal asphyxia is an important cause of neonatal mortality or neurological handicaps among survivors.\textsuperscript{1-3} Despite the fact that majority of newborns having asphyxia may recover with a low likelihood of neurological sequelae, a significant percentage of them develop hypoxic-ischemic encephalopathy (HIE). Neither Apgar score nor degree of fetal distress could accurately predict the occurrence of HIE or neurodevelopmental outcome.\textsuperscript{1,3} Although continuous electroencephalography (EEG) monitoring can be of help in assessing the severity of neurological insult soon after asphyxia,\textsuperscript{4} interpretation of neonatal EEG requires considerable experience. Thus, a sensitive biochemical marker is valuable in order to early identify newborns who need neuroprotection for HIE.\textsuperscript{5}

Most prior studies of biochemical markers have focused on cerebrospinal fluids (CSF) examination.\textsuperscript{6-12} Since CSF is not always available in neonates without encephalopathy, a search for alternations in the body fluids readily available for clinical diagnosis appears more desirable. We know that one of the initial responses to perinatal asphyxia is preferential redistribution of cardiac output to the cerebral, coronary and adrenal circulations, with a concomitant decrease of renal perfusion. By measuring the degree of oliguria, Perlman reported a striking association between disturbances of renal function and cerebral abnormalities in newborns with perinatal asphyxia.\textsuperscript{13} But at least 36 hours were required to record the degree of oliguria, an interval not suitable for early diagnosis. Previous studies demonstrated that biochemical derangements induced by perinatal asphyxia could be detected in the urine.\textsuperscript{14-16} For example, we showed that urinary lactate:creatinine ratio measured by proton nuclear magnetic resonance (\textsuperscript{1}H-NMR) spectroscopy within 6 hours of birth could identify newborns with asphyxia who eventually developed HIE with poor outcome.\textsuperscript{16} Nevertheless, the \textsuperscript{1}H-NMR spectroscopy is not always available in every hospital, thus a alternative urinary parameter is needed for practical purpose.
The metabolic response to pathological stress consists of an orderly and tightly controlled series of reactions, called acute-phase response. It is an important pathophysiologic phenomenon replacing the normal homeostatic mechanisms with new set points that may presumably contribute to defensive or adaptive capabilities. Among the mediators involved in this process, tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) stimulate the production of acute-phase response proteins in response to varied stimuli. This study thus was performed to test the hypothesis that whether urinary levels of IL-6 and TNF-α, measured by immunoassay within 6 hours after birth following perinatal asphyxia, are sensitive markers for neonatal HIE and adverse neurodevelopmental outcome.

Subjects and Methods

Subjects

Consecutive term-birth newborns admitted from June 1996 to October 1997 and diagnosed with perinatal asphyxia, according to the criteria described previously, were enrolled if at least three of these conditions were met: 1) intrapartum distress as indicated by fetal bradycardia with heart rate below 100 beats/minute, late decelerations, or an absence of heart-rate variability, 2) thick meconium-stained amniotic fluids, 3) 5-minute Apgar score ≤6, 4) requirement of more than 1 minute of resuscitation with positive pressure ventilation and oxygen, 5) arterial-blood pH value of ≤7.20 or a base deficit of at least 14 mmol/L within first hour after birth. Exclusion criteria were maternal drug addiction, congenital infections, perinatal infections including chorioamnionitis, neonatal sepsis, urinary tract infection, or lack of parental consent. The control group (Group 1) consisted of 46 normal full-term newborns meeting the following criteria: 1) no maternal illness, 2) normal fetal monitoring, 3) Apgar score ≥8 at 1 and 5 minutes, and 4) normal
postnatal course for the first week of life. Part of cases in this study was included in our prior investigation on the measurement of urinary lactate:creatinine ratio by \( ^1 \text{H}-\text{NMR} \) for early diagnosis of HIE.\(^{16} \)

Neonatal assessment and neurological examinations were performed daily for the first week after birth. HIE severity was categorized according to Sarnat's staging system.\(^{19} \)
Neurological evaluations were performed by a single investigator who was without knowledge of the urinary cytokine results. Asphyxiated newborns who did not develop seizures or other neurological signs were categorized as Group 2; those who subsequently developed HIE as Group 3. Mild HIE was diagnosed when hyperexcitability without seizures persisted for at least 72 hours after birth. Moderate HIE was diagnosed in the presence of lethargy, hypotonia, weak primitive reflexes and seizures. A diagnosis of severe HIE resulted from frequent seizures, apnea, flaccid weakness or coma.\(^{1,13} \) The study was approved by the Review Committee of National Cheng Kung University Medical Center, and written informed consent was obtained from the parents.

**Cranial sonography and electroencephalography**

Sonography, obtained with real-time ultrasound (Aloka SSD-630, Japan) equipped with a 5- or 7.5-MHz sector transducer, was performed in Groups 2 and 3 within 24 hours, 48-72 hours, and at 10 days old.\(^{20} \) Sonograms showing increased echogenicity within cerebral parenchyma, basal ganglia and thalamus, and the presence of encephalomalacia, were considered abnormal. EEG was performed at 36-52 hours after birth and repeated when necessary, and the background abnormalities were interpreted according to the criteria of Lombroso.\(^{1} \)
Neurodevelopmental outcome

All surviving patients in Groups 2 and 3 and 41 patients from Group 1 were available for follow-up examination at age one year, which included Amiel-Tison's neuromotor examination and the Bayley Scale of Infant Development II (BSID II). Neurodevelopmental outcome was classified as favorable (normal development or mild abnormalities in muscle tone and reflexes) or adverse. Adverse outcome was defined as death, severe cerebral palsy (hemiplegia, quadriplegia, diplegia, severe impairment of daily activities associated with hypertonicity), developmental delay (BSID II score below -2 standard deviation for age), blindness or deafness.11,16,21,22

Urine samples

Spot urine samples were collected within the first 6 hours and at 48-72 hours after birth. They were immediately centrifuged, aliquoted and stored at -80°C for later assay. Creatinine contents were determined using an autoanalyzer (Beckman Astra-8), and the levels of TNF-α and IL-6 were corrected for hydration status by creatinine concentration (pg/mg-Cr).

TNF-α and IL-6 immunoassay. Urine samples were assayed for TNF-α and IL-6 using Quantikine ELISA kits (Research and Diagnostics Systems, Inc., Minneapolis, MN), which are based on a sandwich technique. Briefly, a microtitre plate was precoated with murine monoclonal antibody specific for TNF-α or IL-6. Both standards and urine samples were pipetted into the wells and incubated for 2 hours on a horizontal microplate shaker at room temperature. After thorough washing, an enzyme-linked polyclonal antibody specific for TNF-α or IL-6 conjugated to alkaline phosphatase was added to the wells. Following removal of unbound antibody-enzyme
reagent, a substrate solution and an amplifier solution was added consecutively. Color intensity was read within 30 minutes using a spectrophotometer (Molecular Device Corp., Sunnyvale, CA) set at 490 nm, and the concentrations of TNF-α and IL-6 were determined. Each case was analyzed in duplicate, and the mean values were used as the final concentration.

Statistics

Unless indicated otherwise, the centrality of all the continuous data is expressed as median and the spread as range. Urinary TNF-α and IL-6 within 6 and 48-72 hours of life were compared between different groups using Kruskall-Wallis statistics. The differences between TNF-α and IL-6 data at the two time intervals were examined by the median test due to skewness of the data.

Results

Patient Characteristics

There was no difference among the 3 groups in birth-weight, gestational age or gender (Table 1). Among the 38 asphyxiated newborns, 22 had no HIE (Group 2), and 16 developed HIE (Group 3). The mean age at which the first urine sample was obtained for Groups 1, 2 and 3 was 4.4±1.1 hours, 4.5±1.2 hours and 4.5±1.2 hours, respectively. No statistical significance was found in Apgar scores, first arterial pH and base deficits between Groups 2 and 3. There was no difference in the incidence of oliguria between the two asphyxia groups. Transient oliguria (urine output <1 ml/kg/hr during the first 24 hours of life) was observed in three patients of Group 2 and four of Group 3, while persistent oliguria (urine output <1 ml/kg/hr for at least the first 48 after birth) found in only one patient in Group 3. In Group 3, 4 newborns developed mild HIE, 5 moderate HIE, and 7
severe HIE. Ultrasound examination showed none in Group 2 had abnormal lesions; however, in Group 3, 5 newborns had marked brain edema, 5 had hyperechogenecity in the bilateral basal ganglia and thalamus, 1 unilateral middle cerebral artery infarction, and 1 multicystic encephalomalacia. In Group 3, diffuse and severe EEG abnormalities (a burst-suppression pattern, unreactive traces, or marked voltage suppression) were found in 8 newborns, and multi-focal epileptiform discharges in 4.

**Urinary levels of TNF-α, IL-6 and neonatal HIE**

**Within 6 hours of life.** Figure 1 depicts urinary IL-6 and TNF-α at age ≤6 hours from each study group. Significant differences were noted in urinary IL-6 and TNF-α among 3 groups ($p < 0.001$, $p = 0.003$, respectively). The median IL-6 level of 30.0 pg/mg-Cr (range 15.7-679.4) in Group 3 was 19 times higher than the 1.6 (0.3-17.7) in Group 1 ($p < 0.001$), and 5 times higher than the 6.0 (0.6-21.7) in Group 2 ($p < 0.001$). The 3.7-fold difference between Groups 1 and 2 was also significant ($p = 0.027$). The median TNF-α level of 2.8 pg/mg-Cr (range 0.6-309.6) in Group 3 was 3.5 times higher than the 0.8 (0.2-6.7) in Group 1 ($p < 0.001$), but no significance was found when compared to the 1.7 in Group 2 (0.3-18.6) ($p = 0.069$). The 2-fold difference between Groups 1 and 2 was significant ($p = 0.008$). Urinary IL-6 levels ≥ 20 pg/mg-Cr, chosen post hoc, had 92% (11/12) positive predictive value and 81% (21/26) negative predictive value in predicting the occurrence of HIE. Compared with IL-6, TNF-α had a much larger overlap between Groups 2 and 3.

Within Group 3, there was a non-significant trend ($p = 0.062$) for urinary IL-6 to increase as HIE severity increased. For mild HIE, the median was 24.9 pg/mg-Cr (range 17.3-30.2); for moderate HIE, the median was 24.3 (15.7-242.7); for severe HIE, the median was 49.7 (15.8-79.4).

**At 48-72 hours of life.** Compared with measurement at age ≤6 hours, urinary IL-6 levels
at 48-72 hours revealed no significance in Group 1 (median, 1.6 vs. 2.3, \( p = 0.118 \)) and Group 3 (30.0 vs. 87.9, \( p = 0.121 \)). However, a significant alteration occurred in Group 2 (6.0 vs. 15.9, \( p = 0.002 \)). Significant increases in urinary TNF-\( \alpha \) was found in Group 1 (0.8 vs. 4.9, \( p < 0.001 \)) and Group 2 (1.7 vs. 5.5, \( p = 0.007 \)), but no significant change in Group 3 (2.8 vs. 12.2, \( p = 0.561 \)). By 48-72 hours after birth, significant differences in IL-6 and TNF-\( \alpha \) was observed among 3 groups (\( p < 0.001 \), \( p = 0.025 \), respectively) (Figure 2). The median IL-6 level of 87.9 pg/mg-Cr (range 8.6-491.2) in Group 3 was 38 times higher than the 2.3 (0.7-28.4) in Group 1 (\( p < 0.001 \)), and 5.5 times higher than the 15.9 (2.2-159.5) in Group 2 (\( p = 0.001 \)). The 7-fold difference of IL-6 between Groups 1 and 2 was also significant (\( p < 0.001 \)). The median TNF-\( \alpha \) level of 12.2 pg/mg-Cr (0.8-165.3) in Group 3 was 2.5 times higher than the 4.9 (0.7-15.7) in Group 1 (\( p = 0.003 \)), but no significance was found as compared to the 5.5 (0.9-79.9) in Group 2 (\( p = 0.102 \)). No significant difference in TNF-\( \alpha \) was found between Groups 1 and 2 (\( p = 0.229 \)). Compared with the value at \( \leq 6 \) hours, TNF-\( \alpha \) or IL-6 in Groups 2 and 3 had a much larger overlap at age 48-72 hours, resulting in much lower discriminatory power.

**Urinary levels of TNF-\( \alpha \), IL-6 and neurodevelopmental outcome**

None of Group 1 showed abnormal neurodevelopment at age one year. In Group 2, 1 infant had mild impairment and the rest were normal. In Group 3, 6 had favorable outcome (normal neurodevelopment in 5 infants, and mildly impaired in 1 infant), and 10 had adverse outcomes (5 died within 4 months of life, and 5 had severe neurodevelopmental sequelae). All 7 newborns with IL-6 \( \geq 31 \) pg/mg-Cr at age \( \leq 6 \) hours were either dead or had severe neurodevelopmental sequelae; only 3 of the 10 infants with adverse outcomes had IL-6 below 20 pg/mg-Cr. Figure 3 shows the relationship between IL-6 and TNF-\( \alpha \) within 6 hours after birth and neurodevelopmental outcome at age one year in 38
perinatally asphyxiated infants (Groups 2 and 3). Asphyxiated infants with adverse outcomes (median 47.5, range 15.9-679.4) had significantly higher level of IL-6 than those with favorable outcome (7.7, 0.6-30.2) \((p < 0.001)\). Urinary level of TNF-\(\alpha\) was also significantly different between infants with adverse outcomes (4.3, 0.8-309.6) and those with favorable outcomes (1.6, 0.3-21.7) \((p = 0.006)\).

**Discussion**

Conventional indicators, e.g., fetal heart rate, meconium-stained amniotic fluids, Apgar score and arterial blood gas, could not predict the occurrence of HIE. In this study, 74% of newborns with the criteria of perinatal asphyxia had favorable outcome (22 infants in Group 2, and 6 in Group 3). Most earlier studies of biological markers in perinatal asphyxia have focused on blood and CSF abnormalities, but these tests are usually performed days after birth when the patients may already have full-blown HIE.\(^{1,6-12}\) Our study demonstrates that urinary levels of IL-6, an acute phase protein, assayed within 6 hours after birth has a high predictive value in identifying newborns with perinatal asphyxia who eventually develop HIE, and even with an adverse outcome.

Acute phase responses are metabolic responses to hypoxia or infection. The finding that CSF IL-6 levels correlated well with the severity of HIE and neurological outcome supports the concept in the context of neonatal asphyxia.\(^{10-12}\) Clearly, a simple and non-invasive test is more acceptable than CSF study in newborns with asphyxia prior to the onset of full-blown encephalopathy. The association of urinary IL-6 levels with HIE, shown in this study, supports the potential utility of this test for fingerprinting the degree of brain injury in newborns with perinatal asphyxia. Although both TNF-\(\alpha\) and IL-6 levels measured within 6 hours or 48-72 hours of life showed group differences, only the urinary IL-6 values within 6 hours after birth was effective in discriminating asphyxiated
newborns with HIE from those without HIE. By using cut-point value at 20 pg/mg-Cr, urinary IL-6 levels within 6 hours after birth had 92% positive predictive and 81% negative predictive values in predicting the occurrence of HIE. Furthermore, the IL-6 level is positively related with the degree of neonatal HIE. Of particular importance is the relationship between urinary IL-6 levels and adverse neurodevelopmental outcome at age one year, supporting both diagnostic and prognostic implications of urinary IL-6 measurement.

One consideration, however, deserves comment here. Although urinary lactate:creatinine ratios detected by ^1^H-NMR spectroscopy has a higher sensitivity (94%) and specificity (100%) in predicting the occurrence of HIE compared with IL-6 immunoassay,^16^ the complexity of the technique and the cost required for the measurement may significantly hamper the application of ^1^H-NMR spectroscopy for diagnostic purpose. IL-6 urine test, in this respect, provides an important alternative to ^1^H-NMR spectroscopy with immediate clinical impact as a routine screening test.

It is well known that kidneys are very sensitive to ischemic stress. Monitoring of urine excretion has been demonstrated to detect the renal damage associated with perinatal asphyxia. Substances that have been examined so far include uric acid, vasopressin, prostacyclin metabolites, prostaglandin E2, hypoxanthine, organic acids, N-acetylglucosaminidase, β2-microglobulin and lactate.^3,13,14,23-27^ Although some of these molecules appear to be related to the severity of perinatal asphyxia, definite sensitivity and specificity in predicting HIE occurrence have not been reported.

IL-6 is a multifunctional cytokine involved in inflammatory and immunological responses,^17,28^ and is also the chief modulator of most acute-phase proteins. It reaches peak concentrations rapidly after the onset of infection, hypoxia, trauma, surgery, burns, and
tissue infarction. It has been reported that IL-6 levels in the CSF after perinatal asphyxia is related to the severity of neonatal HIE and to the neurologic outcome.\textsuperscript{10,11} Although serum IL-6 has been used as an indicator of neonatal sepsis,\textsuperscript{29} no clinical study has yet been conducted in the urine as an early marker for neurological outcome in asphyxiated newborns.

Currently, we have no complete rationale to explain the modulation of IL-6 excretion in urine. It could be derived from systemic circulation and/or produced by the kidneys in response to perinatal asphyxia. Since serum IL-6 was not determined simultaneously, the possible contribution of serum contents to urinary excretion cannot be assessed. However, the excretion by kidney appears to be more likely. Elevated urinary IL-6 has been observed in urinary tract infection, pyelonephritis, glomeronephritis, acute rejection of allografts or renal tumors.\textsuperscript{30-33} Since dysfunction of renal tubules commonly occurs in perinatal asphyxia, renal tubular cells, mesangial cells and/or monocytes/macrophages are plausible sources of urinary IL-6. Nevertheless, the biological role of IL-6 excretion in the urine after perinatal asphyxia remains to be clarified.

In conclusion, the magnitude of IL-6 response in the urine has a high predictive power for early identification of newborns at risk for HIE, and is also significantly associated with neurodevelopmental outcome at age 1 year. We believe that immunoassay of urinary levels of IL-6 provides a highly-predictive alternative to the measurement of the lactate:creatinine ratio, where $^1$H-NMR assay is not available. Application of this urinary test may be of value in the development of neuroprotection strategies for newborns with perinatal asphyxia.
Acknowledgments: This work was supported by a grant from the National Science Counsel, Taiwan, Republic of China (NSC: 89-2314-B006-017).
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### Table 1. Perinatal Characteristics and Urinary Levels of Tumor Necrosis Factor α and Interleukin 6 within 6 Hours and at 48 to 72 Hours after Birth in the Three Groups of Newborns.*

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<td>≤ 6 hrs</td>
<td>1.6 (0.3-17.7)</td>
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<td>30.0 (15.7-679.4)</td>
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</tr>
<tr>
<td>Urinary TNF-α (pg/mg-Cr)</td>
<td></td>
<td></td>
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<tr>
<td>≤ 6 hrs</td>
<td>0.8 (0.2-6.7)</td>
<td>1.7 (0.3-18.6)</td>
<td>2.8 (0.6-309.6)</td>
<td>0.069</td>
</tr>
<tr>
<td>48-72 hrs</td>
<td>4.9 (0.7-15.7)</td>
<td>5.5 (0.9-79.9)</td>
<td>12.2 (0.8-165.3)</td>
<td>0.102</td>
</tr>
</tbody>
</table>

TNF-α: tumor necrosis factor α, IL-6: interleukin 6

*Plus-minus data are mean ± SD values, and other data are expressed as median (range).
†Values denote comparisons between Group 2 and Group 3.
ND: not done
**Figure Legends**

**Figure 1.** Urinary levels of IL-6 and TNF-α within 6 hours after birth for 3 groups of newborns. Panel A shows levels of urinary IL-6, and Panel B levels of urinary TNF-α. Median, interquartile ranges, and largest and smallest values of IL-6 and TNF-α in normal control newborns (Group 1), asphyxiated newborns without hypoxic-ischemic encephalopathy (Group 2), and asphyxiated newborns with hypoxic-ischemic encephalopathy (Group 3) are shown. Interquartile ranges extend from 25th to 75th percentile, with horizontal line at median (50th percentile).

**Figure 2.** Urinary levels of IL-6 and TNF-α at 48-72 hours after birth for 3 groups of newborns. Panel A shows urinary IL-6, and Panel B urinary TNF-α. Median, interquartile ranges, largest and smallest values of IL-6 and TNF-α in normal control newborns (Group 1), asphyxiated newborns without hypoxic-ischemic encephalopathy (Group 2), and asphyxiated newborns with hypoxic-ischemic encephalopathy (Group 3) are shown. Interquartile ranges extend from 25th to 75th percentile, with horizontal line at median (50th percentile).

**Figure 3.** Urinary levels of IL-6 and TNF-α within first 6 hours of birth and neurodevelopmental outcome at age one year for 38 infants with perinatal asphyxia. Neurodevelopmental outcome was classified as favorable (normal development or mild
abnormalities in muscle tone and reflexes), and adverse (hemiplegia, quadriplegia, diplegia, marked developmental delay, blindness, or deafness). Median, interquartile ranges, and largest and smallest values in infants with favorable outcome and adverse outcome are shown. Interquartile ranges extend from 25th to 75th percentile, with horizontal line at median (50th percentile).