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行政院衛生署九十年度委託研究計畫

以碳-13 尿素呼氣試驗建立正確的兒童及青少年幽門螺旋桿菌感染流行病學資料

委 託 研 究 成 果 報 告

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目　　錄

中文摘要：

幽門螺旋桿菌(Hp)，已被認為和上消化道多項病理變化有關。由於研究顯示，大多數地區的 Hp 感染大多發生在孩童及青少年時期，且年輕時候得到 Hp 感染會顯著增加成人時得到胃癌的機率，因此，孩童時期 Hp 感染準確的流行病學資料包括盛行率、感染途徑，受感染年齡及新感染獲得率等，就成為世界各國衛生保健及疾病預防非常重要的項目之一。雖然現今以孩童為對象之流行病學研究，仍大多以血清學檢查為主，但是血清學檢查用於偵測孩童及青少年 Hp 感染的準確度則尚未經過確認。我們發現對年齡較小的國小兒童，血清學檢查的誤差很大，會引起對以往相關流行病學資料準確性的懷疑。

本研究目的在於：1) 同時以碳 13 呼氣試驗及血清學來檢測與比較孩童及青少年 Hp 感染。前瞻性逐年調查及確認國內國小及國中 (7 至 15 歲) 之孩童及青少年 Hp 感染“真正的”盛行率，並探討 Hp 感染之獲得(Acquisition)及自發性清除(Spontaneous clearance)的比例與特質；2) 探討 Hp 感染在台灣地區傳播(transmission)之相關因子，做為國內制訂公共衛生政策及傳染病防治工作方針的參考。

我們選定羅東地區之一國小及國中為研究範圍。對每一例學生均以班級為單位，排定時間接受抽血及碳 13 尿素呼氣試驗。全部對象在四週內完成血液收集與編號及呼氣試驗。每一對象均被要求留下姓名、性別、學號、家庭住址、及電話，以便後續追蹤、訪談之用。每位參與研究學生之家長，均被要求填寫一份針對 Hp 感染流行病學相關之問卷，之後加以回收做統計分析。對收集之血液做血清學檢測，而收集之碳 13 尿素呼氣樣品則以質譜儀做 $^{13}C/^{12}C$ 之比值測定。將所得有關血清學檢驗及碳 13 呼氣試驗之結果，與問卷調查所得之流行病學相關資料，輸入統計研究所之電腦中，以 SAS system 分析之。

總共收錄國小（一至六年級）共 780 人，國中（一至三年級）共 629 人及老師 150 人完成本研究。血清學檢查在各年齡學童的靈敏度由 7 歲至 15 歲分別為 33, 41, 50, 59, 68, 63, 65, 66, 及 70%，而老師則可高至 90%。若以血清學來篩檢，則各年齡學童感染 Hp 的盛行率為 5.5, 8.6, 6.8, 11.8, 12.3, 15.3, 11.9, 14.5 及 15.2% , 而老師為 58.7%。若以碳-13 呼氣檢查為金標準來校正血清學的誤差，則真正感染 Hp 的盛行率便提高為 13.6, 14.5, 13.6, 16.7, 17.9, 18.8, 16.4, 20.4 及 20.7% , 而老師組則維持在 57.3%。此結果顯示血清學檢查在小孩群體的靈敏度是不夠的，會導致一些流行病學資料的誤差。若要得到較正確的資料，應該使用碳 13 呼氣試驗做進一步的確

認。

中文關鍵詞(至少三個)：幽門螺旋桿菌、碳-13尿素呼氣試驗、血清學、流行病學

Abstract

Because *H. pylori* infection is contracted primarily in childhood, epidemiological studies among pediatric populations are imperative. Serologic immunoassays based on *H. pylori* antigens require validation in the pediatric population under evaluation. The aims of this prospective study are: (1) to compare the suitability of serological test with ^{13}C-urea breath test as a epidemiological screening tool in children and adolescents; (2) to investigate the "true" prevalence rate of *H. pylori* infection in the population whose ages between six and fifteen; (3) to explore the risk factor of transmission of *H. pylori* infection in Taiwan. The study population included 780 students of one primary school, 629 students of one junior high school and 150 teachers. Blood samples were collected from each student and teacher for the serological test. ^{13}C-urea breath test was adopted as gold standard. Result: The sensitivity of serology in the students with age of 7, 8, 9, 10, 11, 12, 13, 14 and 15, were 33, 41, 50, 59, 68, 63, 65, 66, and 70%, respectively, while this value in the teachers were 90%. The "crude" prevalence was 5.5, 8.6, 6.8, 11.8, 12.3, 15.3, 11.9, 14.5, and 15.2% in each age group of students and 58.7% in the teachers. However, after corrected by the data of ^{13}C-urea breath test, the "true" prevalence raised to 13.6, 14.5, 13.6, 16.7, 17.9, 18.8, 16.4, 20.4, and 20.7% in each age group of students. The reference value in the teachers was 57.3%. Conclusion: The serological test is not sensitive enough as an epidemiological screening tool for *H. pylori* infection in children, especially below the age of nine.

Keyword: *Helicobacter pylori*, ^{13}C-urea breath test, serology, epidemiology

Introduction

Helicobacter pylori (*H. pylori*), a spiral microaerophilic Gram-negative bacterium isolated in 1983 [1], is now known as the most common gastrointestinal bacterial infection worldwide. It is the principal cause of chronic gastritis [2] and is strongly associated with peptic ulcer disease [3] as well as gastric lymphoma (MALT type) [4], and gastric cancer [5-6]. In developed countries, infection occurs in more than 50% of adults, whereas developing countries have infection rates reaching 90% [7-8]. Among those with *H. pylori* infection, eradication therapy alters the natural history of recurrences with attendant morbidity and death, which previously required lifelong maintenance therapy. Perhaps the greatest concern with regard to infection with *H. pylori* is the increased risk for the development of gastric cancers in adulthood. This is particularly relevant because infection dating from childhood appears to enhance the risk of carcinogenesis [5, 9-10]. Because *H. pylori* infection is contracted primarily during the childhood years, additional epidemiological studies among pediatric populations are imperative [11].

Two categories of diagnostic methods for *H. pylori* infection are distinguished: invasive tests to detect the microorganisms in a biopsied samples of the gastric mucosa obtained at endoscopy [12-15], and noninvasive tests to obviate the need for endoscopy[16-21]. These diagnostic tests have been applied to diagnose *H. pylori* infection in adults. Deep sedation or even general anesthesia is sometimes required for endoscopy in children, while this procedure remains valuable in pediatric patients with symptoms suggesting peptic ulcer. Noninvasive tests, such as urea breath test (UBT), have been proved to be equally accurate in diagnosing *H. pylori* infection in children. The validation of an inexpensive,

easy-to perform, sensitive, specific, and noninvasive diagnostic test for *H. pylori* infection in children and adolescents is of paramount importance to enhance our presently limited understanding of *H. pylori*-related diseases. Currently available tests for *H. pylori* infection in children may be not optimal tools for use in large-scale epidemiological research. Serologic immunoassays based on *H. pylori* antigens require validation in the pediatric population under evaluation [23-27].

The aims of this prospective study are: (1) to compare the suitability of serological test with ^{13}C-urea breath test as a epidemiological screening tool in children and adolescents; (2) to investigate the “true” prevalence rate of *H. pylori* infection in the population whose ages between six and fifteen; (3) to explore the risk factor of transmission of *H. pylori* infection in Taiwan.

Materials and Methods

Study population and study design

The study population included students of one primary school and one junior high school in Lo-Tong area. The teachers of these two schools were recruited as adult control. Participation in this study was voluntary. Informed consent of parents was obtained in each case. Blood sample was collected from each student for the serological test. ^{13}C-urea breath test was performed in each student, too. The parents of students were asked to answer a questionnaire concerning the basic epidemiologi-cal data and possible factors related to the transmission of *H. pylori*. All of these results were analyzed by a SAS system.

Data collection

Self-administered questionnaire

The parents of the children were asked to fill out a standardized questionnaire, which contained questions about sociodemographic factors, housing and living conditions, and other factors that was suspected to be potentially related to *H. pylori* infection.

Serology test

HEL-p II test kit (Amrad, Boronia, Victoria, Australia) for determination of *H. pylori* IgG antibody was used in this study. The HEL-p II test is an indirect ELISA immuno-assay involving four separate steps. Initially, test serum or plasma is diluted in specimen diluent buffer and allowed to react with *Helicobacter pylori* antigen bound to the microtitre well. Removal of the unreacted antibodies by washing allows the specifically bound antibody to be detected by an enzymatic method. Conjugated sheep anti-human IgG-HRPO reacts with this bound patient IgG. Unreacted conjugate is removed with a

subsequent washing step. Tetramethylbenzidine (TMB) substrate is converted enzymatically to a blue color with the rate of conversion of this substrate from colorless to a blue color being proportional to the amount of specific antibody bound. H_2SO_4 is used to terminate the enzymatic reaction converting the blue to a yellow color which is measured spectrophotometrically. According to the manufactory's statement, the sensitivity of the HEL-p II test is 96% and the specificity is 93%.

^{13}C-urea breath test

^{13}C-urea breath test modified from European standard protocol was performed in each case. Briefly, a baseline sample of expired breath in a 20 ml vacutainer was obtained by using a disposable plastic straw. Patients then drank 100 ml milk intended to delay gastric emptying. After 10 minutes, 100 mg of ^{13}C-urea (99% pure, Isotech, USA) in 50 ml of tap water was swallowed and distributed within the stomach by turning the patient to the left then, the right decubitus position. One point breath sample was collected, 30 min post ingesting the ^{13}C-urea, in an identical manner to the baseline sample. All samples were taken in duplicate and sent to INER where an isotope ratio mass spectrometer (Bureau of Stable Isotope Analysis Ltd. England) was used for analysis. The technician performing the analysis was unaware of the results or the status of *H. pylori* in the patients. The results were expressed as excess δ $^{13}CO_2$ excretion per mil by subtracting the baseline pre-^{13}C-urea breath sample result. The positive breath test was defined as excess δ $^{13}CO_2 >$ 5 per mil. The ^{13}C-UBT was adopted as gold standard in this study for the evaluation of the "true" prevalence.

Statistical analyses

In this study, statistical analyses were performed using on SAS system. The stepwise logistic regression analysis was performed with various items

affecting the *H. pylori* infection.

Results

Totally, 780 students of the primary school (LT), 629 students of one junior high school (TK) and 150 teachers were enrolled into this study. The variation of sensitivity of serology and the prevalence of *H. pylori* in the different age of students and teachers are summarized in the table 1. The sensitivity of serology in the students with age of 7, 8, 9, 10, 11, 12, 13, 14 and 15, were 33, 41, 50, 59, 68, 63, 65, 66, and 70%, respectively, while this value in the teachers were 90%.

The “crude” prevalence was 5.5, 8.6, 6.8, 11.8, 12.3, 15.3, 11.9, 14.5, and 15.2% in each age group of students and 58.7% in the teachers. However, after corrected by the data of ^{13}C-urea breath test, the “true” prevalence raised to 13.6, 14.5, 13.6, 16.7, 17.9, 18.8, 16.4, 20.4, and 20.7% in each age group of students. The reference value in the teachers was 57.3%.（Table 2）

When logistic regression analysis was applied on some variables for the serology-based prevalence of H. pylori infection in children, age and number of children living together were two significant positive coefficients at 5% level. However, age was not a significant positive coefficient for the UBT-based prevalence rates in this study, because the UBT-based prevalence rates reached a much higher level than the serology-based prevalence in the age groups of 7~9.

Discussion

At present, precise details concerning the bacterial, host, and environmental factors that lead to the development of disease complications are lacking. Because *H. pylori* infection is contracted primarily during the childhood years, additional epidemiologic studies among pediatric populations are imperative. To achieve this, accurate diagnosis of *H. pylori* infection in children is essential. At present, diagnosis of *H. pylori* infection in children still largely depends on the endoscopic biopsy of the gastric tissues for culture and urease test. These methods are previously regarded as the gold standard. However, the invasive nature limits its wide use in children, especially for the young children and infants. This invasive method has made it impossible to perform proper epidemiologic studies in this important population. The availability of a safe, valid, noninvasive test in children is essential if the epidemiology of *H. pylori* is to be properly evaluated. Noninvasive diagnostic tests, including ^{13}C-UBT and serology, were recently developed and shown to be promising in establishing the diagnosis of *H. pylori* infection in children.

Serologic immunoassays based on *H. pylori* antigens require validation in the pediatric population under evaluation because cutoff values established in adult subjects are often higher than antibody levels present in infected children [31]. In addition, commercially available serologic tests demonstrate lower accuracy compared with testing in the research setting [32-33]. Most commercially available IgG antibody to *H. pylori* kits performed equally. It must be used carefully as a test for diagnosis and therapeutic monitoring in children. Probably due to the duration of infection and the difference in immunity and bacterial load, the antibody levels in children are different from the adults. Moreover, spontaneous clearance of *H. pylori* may occur in some children with persistent antibody, thus results in false positive serological

tests.

In adults the carbon 13-labeled urea breath test has been shown, initially by Graham et al. [18] and subsequently by other groups, to be a safe and reliable method for the diagnosis of *H. pylori* infection [19]. Rowland et al. reported the sensitivity and specificity of ^{13}C-UBT may be as high as 100% and 97.6% if the subjects were fasting [30]. ^{13}C-UBT is of good diagnostic accuracy in children. It offers a feasible way for diagnosing *H. pylori* infection, screening of asymptomatic population, and monitoring the therapeutic effects in children who can successfully follow the procedure of ^{13}C-UBT.

Currently, serological test is the most popular epidemiological screening tool in adult. However, it must be used with caution in the childhood years. In this study, we found the sensitivity of the serological test became decreasing to only about 30 ~ 50% in the young children which age between 7 ~ 10.

It is concluded that the serological test is not sensitive enough as an epidemiological screening tool for *H. pylori* infection in children, especially below the age of nine.

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Table 1. Variation of sensitivity of serology and the prevalence of *H. pylori* in the different age of students and teachers:

Student age	7	8	9	10	11	12	13	14	15	Teacher
Total number (T)	110	186	132	102	106	144	312	172	145	150
Positive (P)	5	11	8	10	13	17	33	23	21	77
Negative (N)	94	154	114	82	87	112	257	135	114	53
False positive (FP)	1	5	1	2	0	5	4	2	1	11
False negative (FN)	10	16	9	7	6	10	18	12	9	9
Sensitivity (%)	33.3	40.7	50.0	58.5	68.4	63.0	64.7	65.7	70.0	89.5

Table 2. Prevalence rates of *H. pylori* infection in the different age groups of students and teachers

Student age	7	8	9	10	11	12	13	14	15	Teacher
Prevalence 1 (%)*	5.5	8.6	6.8	11.8	12.3	15.3	11.9	14.5	15.2	58.7
Prevalence 2 (%)†	13.6	14.5	13.6	16.7	17.9	18.8	16.4	20.4	20.7	57.3

* prevalence 1 (P+FP/T) means the result is base on serological data only
† prevalence 2 (P+FN/T) means the result is corrected by the data of ^{13}C-urea breath test.

附錄

附錄一

幽門螺旋桿菌問卷調查表

※請確實填寫下列資料並交回學校，以便將幽門桿菌檢驗結果直接寄至家裏，或以電話聯絡方式通知，並安排以後追蹤及診療時間。

- 姓名_____ ◎ 年班級_____年_____班 ◎ 學號_____
- 性別：□男 □女 ◎ 出生年月日_____年____月____日(_____歲)
- 血型：□O □A □A B □B □不確定
- 身高：_____公分；體重：_____公斤
- 本籍：①□閩南人②□客家人③□原住民④□廣東福建⑤□其他省籍。
- 聯絡地址：_____
- 聯絡電話：_____
- 家長教育程度：父親①□不識字②□小學③□國(初)中④□高(職)中⑤□專科⑥大學⑦□研究所以上。

  母親①□不識字②□小學③□國(初)中④□高(職)中⑤□專科⑥大學⑦□研究所以上。
- 家長職業：父親_____ (職位 _____)

  家長職業：母親_____ (職位 _____)
- 家庭收入每月共約①□2 萬元以下②□2~5 萬元③□5~10 萬元④□10~15 萬元 ⑤15 萬元以上。
- 家裡小孩總數_____人 (本人在家排行第幾？_____)

家有哥哥_____人、姊姊_____人、弟弟_____人、妹妹_____人

- 家中屋內大小，一共約為_____坪 (或_____平方公尺) ；共有幾間臥室？_____間
- 家中目前共有幾人同住？_____人(包括大人_____人，小孩_____人)。
- 平常作息及睡眠，是否與人共用一個房間？①□是，和誰？_____；②□否。
- 嬰兒時期餵過母乳嗎？①□有，餵過_____個月，或_____天

  ②□沒有，直接餵牛奶。
- 現在是否有喝牛奶的習慣？①□無②□有，每天_____杯(一杯約為 200cc)。
- 家中飲用水為①□自來水②□井水或地下水③河水或溪水④□其他_____。
- 吃飯時是否有飯前洗手的習慣？①□總是②□經常③□少用④□不用。
- 家長洗手時，是否常用肥皂？①□總是②□經常③□少用④□不用。
- 家中吃飯時，夾菜或喝湯是否先使用公筷母匙後再用自己的筷子及湯匙？ ①有②□無。
- 喝水時，是否用共同之茶杯？①□有②□無，家人各自用自己的茶杯。
- 家中所用廁所之形式為①□有沖水設施，坐式②□有沖水設施，蹲式

  ③□沒有沖水設施④□其他_____。
- 家中所用廁所距離洗手處約為①□10 公尺內②□10~20 公尺③□20~30 公尺 ④大於 30 公尺。
- 家中有無飼養動物？①□有，貓、狗、雞、鴨、鵝、豬、牛(請圈選之，可複選)，其他_____ ②□無。
- 最近一個月內有無服用抗生素或消炎藥？①□有②□無。
- 以前有無經常服用抗生素或消炎藥？①□有，最長一次服用_____天，②□無。

- 最近一個月內有無胃腸不舒服？①□無；②□有，包括如下：上腹痛、下腹痛、腹脹感、溢酸水、打嗝、噁心等 (請圈選之，可複選)，其他_____
- 以前有無經常胃腸不舒服？①□無；②□有，包括如下：上腹痛、下腹痛、腹脹感、溢酸水、打嗝、噁心等 (請圈選之，可複選)，其他_____
- 家中親人中，是否有人罹患下列腸胃疾病？

. 胃或十二指腸潰瘍①□無；②□有，①□(外)祖父母②□父③□母④□兄弟 ⑤姊妹⑥□自己⑦□其他_____。

. 胃或十二指腸手術①□無；②□有，①□(外)祖父母②□父③□母④□兄弟 ⑤姊妹⑥□自己⑦□其他_____。

. 胃癌 ①□無; ②□有, ①□(外)祖父母②□父③□母④□兄弟 ⑤□姊妹⑥□自己⑦□其他_____。

全文完