出國報告（出國類別：進修）

美國臨床磁振頻譜自動化定量分析系統設計架構及數據分析方法

服務機關：　行政院國軍退除役官兵輔導委員會台北榮民總醫院
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派赴國家：　美　國
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摘要

職赴美一年之任務為學習磁振頻譜之定量方法並將整套系統架構帶回國內，與臨床研究及服務接軌。頻譜的定量分析依職所見是使用開放源之 LINUX 系統平台上的線性組合模式為主要運算核心，但在醫院中的眾多醫療儀器及資訊系統間不見得使用相同的作業系統，故虛擬機器架構可利用於跨平台作業，也降低硬體系統資源的閒置。以今日的磁振儀器性能及電腦網路科技，磁振頻譜之分析結果可建立動態資料庫，以利實驗結果探討及醫師判讀。而除了氧氣之外，葡萄糖也是細胞存活及行使功能不可或缺的物質之一，且以磁振頻譜技術可以動態偵測葡萄糖代謝行為。若能再善加利用碳十三元素，則十分有潛力進行新方向的研究，甚至新的臨床應用。

關鍵字：

磁振頻譜、定量分析、線性組合模式、虛擬機器、動態資料庫、葡萄糖、碳十三

目次

一、 目的

核磁共振的科學技術在人體活體上之醫學應用自二十世紀以來已有數十年的時間，相較於其他醫學科學技術而言，可說是一種比較新興且目前在全球各先進國家仍持續快速發展中的科技。1945 年史丹佛大學的 Felix Bloch 教授與 1946 年哈佛大學的 Edward Mills Purcell 教授的研究團隊因分別進行了核磁共振的實驗而分享了 1952 年的諾貝爾物理學獎，這可說是科學界開始廣泛使用核磁共振現象來進行實驗的起源。而進入二十一世紀，2003 年美國伊利諾大學的 Paul C. Lauterbur 教授以及英國諾丁漢大學的 Peter Mansfield 爵士共同獲得了諾貝爾生理醫學獎，則為近代許多科學家紛紛投入核磁共振相關研究領域並應用於生物醫學上給予肯定並激勵。

核磁共振科技，簡稱磁振技術，於醫學上最為所知之應用為產生影像來探知疾病並作鑑別診斷；而磁振技術也可於活體產生頻譜，如同生物醫學檢驗及分析化學實驗一般，可以非破壞方式取得內容物質之化學成分比例及結構資訊，其實更有利於醫學上之疾病診斷及研究分析。然而非破壞性的活體頻譜其執行上的困難大約有二：其一為正確的空間定位及實驗重複步驟以確保其科學上的重現性；其二為各種微量化學成分的定性解析度及絕對定量。

目前，國內之各醫療機構與研究單位對於核磁共振技術於醫學上之應用與創新開發皆不遺餘力，在硬體及軟體方面的各種投資亦金額龐大。職於服務單位中負責核磁共振儀器之操作及各種檢查業務之執行已十餘年，期間除了以磁振技術完成碩士論文外，更一直積極參予各項磁振臨床研究及教學，發表數篇國際學術期刊論文並取得部定教職。而依照職於服務單位中的經驗：對於磁振系統的軟硬體投

資，無論從臨床服務、學術研究、及教學發展…等各方面來看都相當值得；並且就醫療業務經營管理的角度而言，確實為一項成本回收迅速的投資行為。

然而，由於醫療磁振系統涉及複雜的機電資訊系統整合、軟硬體專利或智慧財產權授予、及世界各國嚴格的衛生法令規範等，目前國內各醫療及學術單位所使用之世界各主要醫療儀器生產廠家所提供的系統皆或多或少將某些功能或系統資源加以設限保護，這使得進階的臨床應用開發及特殊檢查需求受到限制。其中，尤其以在既有系統中編寫特定軟體以求某種特殊檢查或實驗結果以高重現性自動輸出最為困難。

職之服務單位向來以「視病猶親、追求卓越」為最高宗旨。故此，對於臨床服務各種檢查診療需求一向要求高效率及高品質；且與各醫療部科及許多學術單位保持密切合作關係。為提供最有效率且最精準的服務以及最大的創新開發可能性，職服務單位向來要求各系統提供廠家以最精確且最具經濟效益方式提供年度保養維護服務；然而正因如此，大多數廠家不願意使用者任意撰寫或修改系統軟體環境及系統資源設定，以求系統運作穩定，縮短當機待修時間。雖然，職之服務單位與學術單位（如：國立陽明大學…等）進行合作研究時，可以使用離線方式，也就是將實驗結果轉存至其他電腦，再進行數據分析；但如此方式僅適用於學術研究及實驗，並不適用於臨床檢查服務及醫師判讀，且通常各個合作之研究團隊對實驗設計與數據分析的方法不同，無法一體適用，且分析軟體之智慧財產權大多屬於各個研究團隊，或僅供學術研究，無法適用於臨床服務。

是故，本次職研究進修的目的，即在於接受培訓養成為臨床磁振數據分析的專長人力，並且自國外引進整套臨床磁振數據及頻譜自動化分析軟體系統。藉由觀摩國外專門機構的診斷流程與作法，學習國外專家分析臨床磁振數據方法及實驗技

術，再融合職本身已具備的基礎背景，能夠達到此研究計畫的目的。

職此次進修的具體目的：

- 自國外引進整套臨床磁振數據及頻譜自動化分析軟體系統。
- 接受培訓以成為具臨床磁振數據分析專長的人力。

於國際上，磁振頻譜技術在絕大多數現代臨床磁振掃描儀上皆可獲得。尤其在於腦部，磁振頻譜已然是種強大的研究工具，且在許多種類的疾病上，如腦腫瘤、代謝性疾病、及全身性疾病等方面，也被證實可提供輔助診斷資訊。質子磁振頻譜（^{1}H，氫原子核 MRS）是最普遍被使用的，也是美國食品藥物管理局及台灣衛生主管官方認可的，當病情需要時，臨床醫師可開立的檢查項目。除此之外，氫原子核磁振頻譜不需要使用任何超出臨床磁振造影所使用的硬體配備。是故，質子的磁振頻譜技術完全主導了目前活體臨床磁振頻譜應用，也是職本次進修的主要內容。而其他種類原子核，如：磷三十一(^{31}P)、碳十三(^{13}C)、或氟十九(^{19}F)的頻譜，其實也已經成功地應用於人體上。但是由於臨床上磁振造〝影〞的重要性向來與日俱增，這些「很炫很潮」但需要冗長時間及人力的應用就被丟在一邊了，只剩下少數研究單位還在使用。

所謂磁振造影，簡單的說主要就是組織中水分子（H_2O，水的兩個氫原子）的空間分布或交互作用的圖譜；相較之下，質子磁振頻譜則是各種不同分子上的氫原子核之訊號分析。若說磁振造影是只標畫一個訊號波峰（主要是水）的空間位置圖，那麼磁振頻譜的輸出結果則為許多不同頻率的波峰代表著處於不同化學環境的質子，故以頻譜稱之。因為以磁振技術可測得且需要去量測的化學物質其實際濃度都很低，所以磁振頻譜的取樣區塊（ROI 或 voxel）不能太小，其體積尺寸遠大於磁振造影空間解析度的像素單元。磁振頻譜一般標準的空間解析度約 1 ~

10 立方公分，相較於一般磁振造影的空間解析度（約 1 ~ 10 立方公釐）可說是大了千倍。

除了少數的例外，如伽瑪丁氨基酪酸（gamma amino butyric acid, GABA）或天門冬胺酸（aspartate）…等，通常僅有〝小而具活動性〞的化學物質且濃度約 0.5 mM（μmol/gram）才可被磁振頻譜偵測。此外，大分子或磷酯類這些分子量大且〝不動性〞的物質，如：髓鞘質（myelin），蛋白質，核醣核酸，去氧核醣核酸等，對磁振頻譜而言是無法測得的。在大腦中，以頻譜技術可量測的，小分子量的氨基酸、碳水化合物、脂肪酸、及脂質等的作用架構是由各種輔酶（酵素、中間產物）所緊密控制的，且有數種主要關鍵物質分子（磁振上〝看不見〞的訊息產物與神經傳導物質）是被保持在相當程度的穩定濃度。這就是若以〝十分穩固〞的方法來擷取訊號並分析，則可以取得重現性極高的人體磁振頻譜之原因。從一慣連續性的正常健康成人群體的實驗經驗不難得知，磁振頻譜技術應用最大的變因並非生物個體性或生活飲食等環境群體因素，反而是如實際操作時無可避免的受試者擺放定位不準確、重複實驗時取樣位置一致性的確立問題、以及磁振硬體穩定度的不夠完美。當下列狀況發生：結構被破壞（如：外傷、腫瘤、退化性疾病、膠質增生…等）、生理狀況改變（如：供應血流被阻斷…等）、以及生化學上或基因上產生問題時，組織的磁振頻譜，也可稱為〝生化指紋〞就會發生異常。而即便是正常狀況，這代謝物的指紋也會隨不同的腦部取樣區域以及年齡增長而發生變異。

職此次赴美，除接受培訓養成能具備臨床磁振數據分析的專長人力，且自國外引進整套臨床磁振數據及頻譜自動化分析軟體系統外，在國外各大醫學中心，於放射線部科或醫學影像部門皆配置有專屬人力負責研發各種進階或新式的科技臨床應用，但職之服務單位目前仍未有如此人員配置或任務編組。故職此次到國外

具規模的醫學中心進修研究，除將國外之系統全套移植並建立於國內外，也必須參酌國外之制度並提出建議，供　長官們及服務單位參考。

磁振系統資源向來廣為國內各醫療及學術單位極力爭取且提倡使用，然而研究合作與臨床應用研發之間向來存在著許多差異。職忝不辱使命利用了此次赴外研究進修的時機，深入了解國外醫學中心核磁共振最新技術的使用情形以及相關的研究進行，敬提供將來學術研究與臨床創新服務之參考，並藉此機會建立國內外學術合作交流的管道。

二、 過程

職於民國九十九年十月初銜命動身前往本次研究進修之目的地美國洛杉磯兒童醫院（Children’s Hospital Los Angeles, CHLA）。該院為美國歷史悠久的大型專科教學醫院之一，也是南加州大學醫學院（University of Southern California, USC, Keck School of Medicine）的附設教學醫院，位於美國加州洛杉磯市，成立於西元 1901 年，目前合計約有 614 位主治醫師，以臨床醫療、教學、與科學研究聞名國際。該醫院之放射線部門有完善的設備，各項影像檢查均有專長醫師負責監督完整檢查程序與影像判讀；其磁振造影單位有專職資料及頻譜處理分析的人員配置，均為博士級磁振頻譜師，除了負責臨床檢查及研究實驗的數據分析外，更已開發了自動磁振頻譜分析及定量的系統。該軟體系統目前適用於世界各大廠牌所生產的磁振儀器。該院也提供完整的臨床研究醫師及各類醫事人員的進修研究訓練計畫；而放射專科類由該院醫學影像部門統一管理。該醫院該部門亦有多項臨床研究計畫，配合各類醫學研究的進行。

由於此次奉派為職生平第一次前往美國洛杉磯地區，且須工作、生活、及居住為期一年；故於抵達後，需首先熟悉附近環境、安置居所、並詢問打探一切生活起居事項並辦理完畢後，依本計畫規定向我國駐外單位及南加州大學醫學院辦理報到手續。而後向洛杉磯兒童醫院辦理到職手續，接受該院要求之醫療人員體檢及防疫注射，通過該院人體實驗委員會及資訊室之一切必要課程且測驗及格後，取得正式工作證件，開始進入該院醫學影像部之新式影像科技實驗室，進修學習。於此職之〝初來乍到〞期間，美方南加州大學醫學院、洛杉磯兒童醫院、該院醫學影像部、及新式影像科技實驗室之〝新〞同事們與相關接觸人士皆提供了熱心及友善的協助幫忙，外交部駐洛杉磯辦事處人員也提供了關懷與建議，使職能順

利即刻展開赴美進修，特在此致謝。

依照職原先之赴美研究進修計畫，首先，須了解國外磁振影像及磁振頻譜的檢查流程，例如：參數設定、特殊技巧、各種技術使用時機、整體檢查內容等。再則，學習磁振頻譜與數據資料傳輸分析自動化系統架構以及軟體寫作、除錯、及修改等，以及各種數值分析方法的科學理論基礎、運算方法、程式化方法等。當然，最重要的是藉此機會，將整套可為臨床應用的自動化頻譜絕對定量分析軟體系統帶回國內，建立於服務單位中，並於日後負責運作、維護、升級更新擴展功能、及教學等。而為達到這些目的，職實際參與了該機構各項檢查的實際作業，且希望藉由進一步參予該研究機構的研究計畫，於返國後能獲得學術上的具體成果，也提昇個人的研究指標。

在美國的指導教授 Dr. Stefan Blüml，洛杉磯兒童醫院臨床主任磁振頻譜師同時也是南加州大學 Keck 醫學院的副教授及磁振科技界世界性知名專家，親自的指導教學下，職開始了在美進修的工作。首先，該部門由於執行且支援〝專科醫療業務〞，所以即便是規模、病床數、門診量與本院規模相較小了數倍，但其硬體配備、各項檢查流程設計安排、及人員素質等方面，雖國情及許多制度不同但卻值得本院借鏡參考。以磁振儀器數量而言，該部門總共配備五台（三台 1.5T、兩台 3T）全身型磁振造影儀。所有的〝MRI〞、〝MRA〞、〝MRS〞…等等與使用磁振設備相關的檢查項目均〝分開且獨立〞並同時能夠獲得各種醫療保險給付，以影像判讀為主的，如 MRI 和 MRA 等，由放射科專科醫師負責製發報告；而磁振頻譜 MRS，則由磁振頻譜師負責分析並製發報告。該院各臨床部科若有病患需使用到磁振設備則會開立會診醫囑，MRI、MRA、MRS…均可分別開立、收費、及或申請保險給付。而若單一項目的會診醫囑轉介至該單位，於執行時發現可能需要〝其他項目〞來做輔助診斷時，則放射科專科醫師可以立即開立醫囑，且同

時成立，以避免病患舟車勞頓。職於赴美期間幾乎每日皆目睹有數架次直升機載送病患至洛杉磯兒童醫院，而職進修工作之單位雖為醫學影像部門（放射科），但設有頗具規模的〝恢復室〞及麻醉科辦公室與值班室，並〝以病患為中心〞地考慮到病患狀況，將各項所需檢查儘量集中，〝一氣呵成〞。

洛杉磯兒童醫院所使用的院內電腦網路系統基本上為美國微軟（Microsoft®）公司的視窗 XP，32 位元的作業系統架構。而於實驗室內因工作內容不同於一般臨床部科，故各種廠牌的電腦軟硬體及作業系統都有，也都各扮演著重要角色。所以，跨作業系統平台的〝電腦使用方式〞一直是實驗室中所強調，也是工作的重點。從儀器端得到的數據檔案需跨平台傳輸至實驗室的工作站上分析結果，搭配上從醫院影像系統上擷取的磁振頻譜取樣位置影像，在實驗室的儲存設備上做備份儲存，然後把分析結果傳送至個人電腦並輸入資料庫中，比對完成後再送至磁振頻譜師的個人電腦上製發報告，確定後送至醫院的病歷系統中。這整個工作流程除了用多台電腦連接並個別編寫軟體之外，拜今日資訊科技大明之賜，除可用集中式的主機或伺服器，或者以單一台系統資源較豐富的電腦作不同作業系統的〝多重開機〞外，職在美國發現了〝虛擬機器（virtual machine）〞廣為盛行，可使得某一作業系統的電腦能夠以〝加開視窗〞的方式同時執行另一種作業系統。而原本電腦中的〝母作業系統〞與視窗中的〝子作業系統〞彼此間可以虛擬網路磁碟機架構作為〝及時〞檔案分享。

氫原子核的磁振頻譜，在各種類型及廠牌的磁振造影儀上皆可取得，且不需使用任何多於磁振造影需求的硬體配備。而要取得磁振頻譜，在儀器上其實有許多種的〝脈衝程序〞可以使用，且每個參數，例如：重複時間 TR、回訊時間 TE…等，都可以自行設訂，也會直接影響得到的頻譜。職在美期間，所參予的臨床檢查及學術實驗，在磁振頻譜方面所使用的參數方法〝十分固定〞，為〝單體取樣（single

voxel point resolve spectroscopy, SV-PRESS)″。若使用三特士拉的磁場，則主要參數為：TR=2000 ms，TE=35 ms，NEX=128；而在一點五特士拉的磁場，則為：TR=1500 ms，TE=35 ms，NEX=160。

職在美國也有許多難能可貴的機會，實際參予了正在執行中的研究計畫。以下就是職在美國的實驗記錄：

There were extraordinary experiences of actual and full participations in using 3T clinical MR scanner (Philips, Achieva 3.0T, Netherland) in CHLA/Radiology to practice oral glucose tolerance test (OGTT) without any vein-punctures required but through single voxel ^{1}H MRS. The methods were: normal volunteers as control studies, fast at least 6 hours and been consented by IRB regulation previously, 2 MRS voxels placed in gray matter and white matter respectively (Fig. 1, using an 8 channel head coil, and PRESS, TR: 2s, TE: 35ms, 128 averages, acquisition time: 4’56”), after the baseline scans 100g (for every volunteer’s body weight over 60kg, 50g for under, by the American OGTT suggestion for pregnancy) regular 100% glucose orally administered, and subsequently repeated (gray matter and then white matter, so the time resolution of the data points ≈ 10mins, 4'56" x2) MRS acquisitions. All the MR spectra acquisitions were up to 120mins after the glucose ingestion (i.e. every volunteer was not supposed to move inside the scanner up to 2 hours, which implied, as well in fact, the person fell asleep or was in resting state).

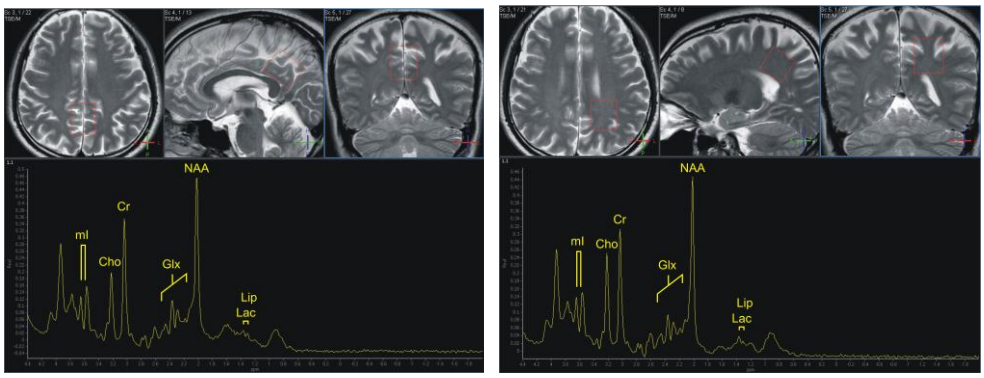


Figure 1.

As the technology continuously progressing, the quality of MRS, no matter the spectral resolution or the SNR, had been much more improved than years/decades ago. A simple OGTT could have been performed on clinical MR scanners 2 more decades ago but must with much more amount of glucose orally administered. On recently installed scanners, especially 3T clinical ones, MRS OGTT could be performed in the way very close to daily practice in clinics and the results could be robust. In the Fig. 1, 2 screenshots were shown on the Philips clinical MR scanner as the results of spectroscopy. In fact, most of the scanner manufacturers had provided similar software or function(s), for the graphic indications of the voxel location, the spectral result (through Fourier transform) from the time varying signal, and even some basic analysis (ex. some metabolites' peak height ratios to creatine...). Instead of just looking at the DICOM pictures on the local PACS, the raw data files were pulled from the scanner console (Windows PC) to another workstation (Linux PC) through network FTP. Then all the files were input on the Linux PC to the software LCModel® (S-Provencher INC., [S.W. Provencher: Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn Reson Med 30, 672, 1993]). The output results of this off-line spectra processing were graphic post script files for printing/displaying and data table files for archiving. All these data file transferring

and software processing jobs were done within 30mins after the end of each volunteer's scans, using preprogrammed Linux shell scripts.

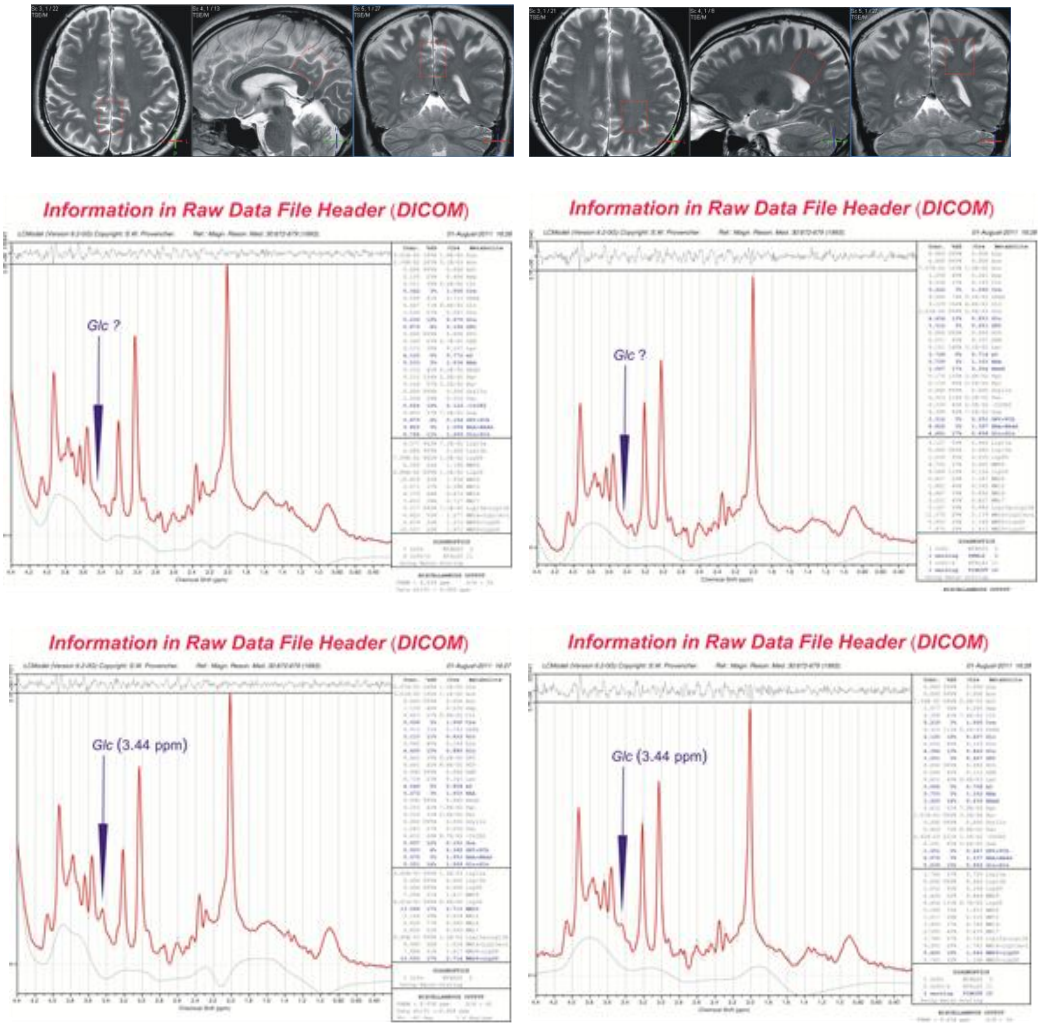


Figure 2.

In the actual clinical practice of MRS, the graphic localizer images indicating the voxel placement were as the same importance as the raw data and the processed data tables. There should be secure designs of the MRS database to store these images/screenshots for retrospective retrievals. Fig. 2 showed that at 3.44 ppm position and in both of the voxels (gray matter and white matter) glucose peak was not recognized on baseline spectrum yet became visible later in the end of the test.

Through the data processing using LCModel®, all the output data tables were assigned to a database, which could be accessed later for further analyses. Then on a MS-Windows® PC with Excel®, some data were retrieved and demonstrated using built-in function of scatter-gram (Fig. 3).

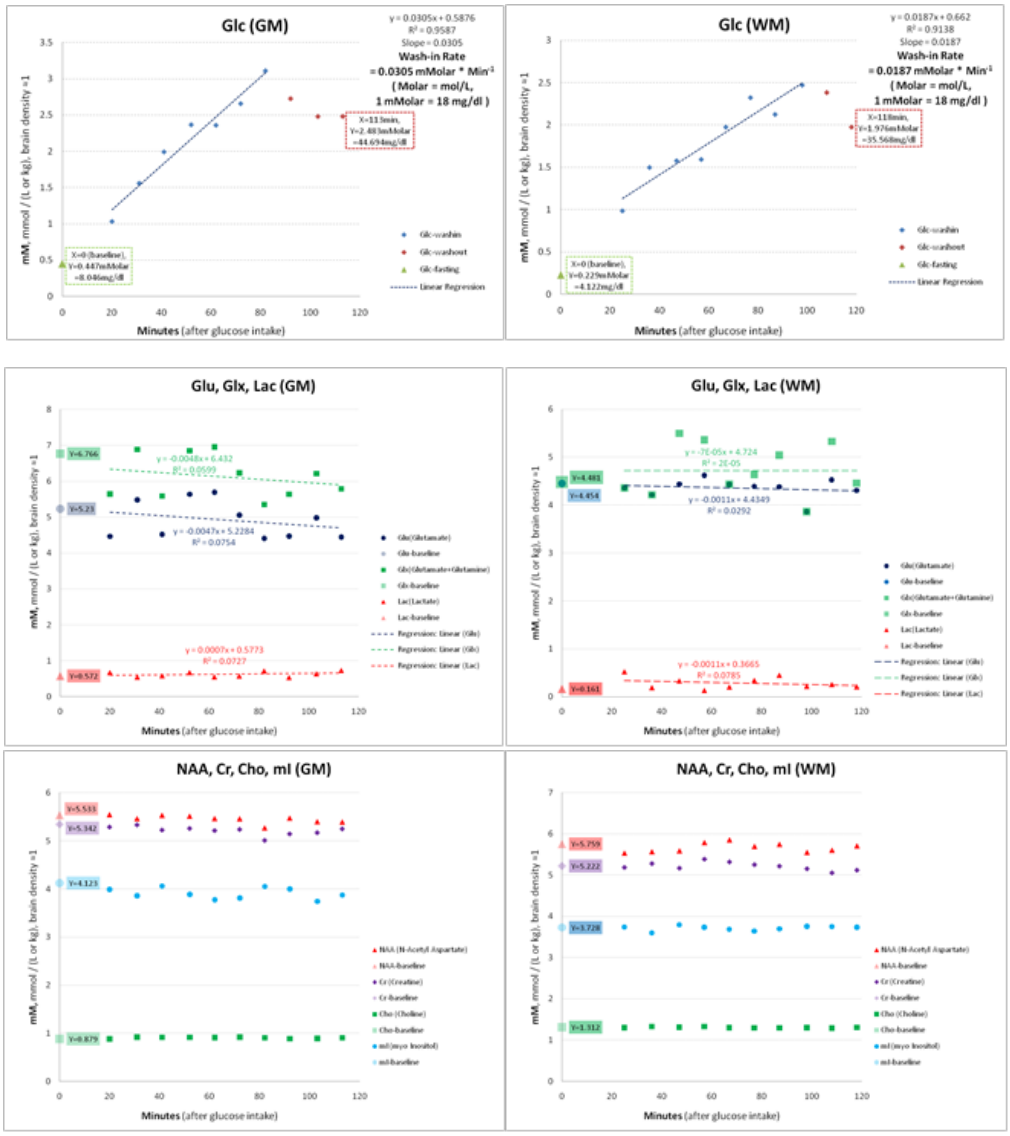


Figure 3.

LCModel® used the linear combination algorithm of the Basis files (different manufacturers' scanners had different Basis file-sets) to output the metabolites'

concentrations. In Fig. 3 upper row showed the ^{12}C OGTT results, where the baseline glucose concentration in GM and WM was 0.446 mM (8.046 mg/dl) and 0.229 mM (4.122 mg/dl) respectively. The final glucose concentration in GM and WM was 2.483 mM (44.694 mg/dl) and 1.976 mM (35.568 mg/dl). According to WHO diabetes criteria - interpretation of oral glucose tolerance test 1999:

a. Fasting plasma glucose (measured before the OGTT begins) should be below 6.1 mM (110 mg/dl). Fasting levels between 6.1 and 7.0 mM (110 and 125 mg/dl) are borderline "impaired fasting glycemia". Fasting levels repeatedly at or above 7.0 mM (126 mg/dl) are diagnostic of diabetes.
b. The 2 hour OGTT glucose level should be below 7.8 mM (140 mg/dl). Levels between this and 11.1 mM (200 mg/dl) indicate "impaired glucose tolerance". Glucose level above 11.1 mM (200 mg/dl) at 2 hours confirms a diagnosis of diabetes.

Also from the National Institute of Health, United States website (Medline Plus) [http://www.nlm.nih.gov/medlineplus/tutorials/hypoglycemia/htm/index.htm]:

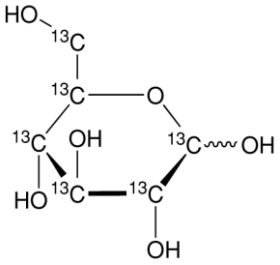
The normal range for blood sugar is about 3.33-6.67 mM (60-120 mg/dl), depending on when the person being tested last ate. If the person is fasting, the blood sugar level could fall below 60 mg/dl and not indicate a serious abnormality or disease. Blood sugar levels below 2.5 mM (45 mg/dl) usually indicate disease.

If the conclusion was made without previous experiences of BOTH IN VIVO AND IN SITU YET TOTALLY NON INVASIVE MRS quantification, it would definitely be “a person with severe and life threatening hypoglycemia”. But in fact, the volunteer was fasting, known to be normal, stood well (symptom free) thru the whole procedure, and still a little higher baseline glucose level in comparison with other volunteers.

The simple linear regression (built-in function of Excel®) was used, tentatively instead of the Michaelis-Menten kinetics, to represent the glucose wash-in rate (slope, Radiological commonly used "perfusion"), which was 0.0305 mM/min of gray matter and 0.0187 mM/min of white matter. The wash-out of glucose (somatic circulation, insulin, glycolysis …etc.) was also detected, started at 82 minutes (GM) and 98 minutes (WM) after the glucose ingestion. The witnessed schedule of glucose transportation/metabolism was compatible with conventional OGTT result, which the glucose concentration in the brain of normal fasting subject would reach to the maximum at about 90 minutes after oral administration. On the middle row of Fig. 3, glutamate (Glu), glutamine (Gln, Glu+Gln=Glx), and lactate (Lac) were evaluated for the possible influences on astrocyte/neuron function (Gamma Amino-Butyric Acid was omitted tentatively). The surge of regular glucose did not seem to change, in this short term of 2 hours, the concentrations of the 3 metabolites significantly, nor the NAA, Cr, Cho, and mI, on the lower row of Fig. 3.

The purpose of this ^{1}H MRS OG(^{12}C)TT was not just to see the feasibility. There were 6 carbon atoms in the glucose molecule and carbon itself had 15 known isotopes, from ^{8}C to ^{22}C, 2 of which (^{12}C of 98.93% natural abundance and ^{13}C of 1.07% natural abundance) were stable. Isotopes of carbon were atomic nuclei that contain six protons plus a number of neutrons (varying from 2 to 16). The ^{13}C atom, which having 1 more neutron than ^{12}C, was a non-radioactive isotope of carbon and had been used in clinical stomach exam as ^{13}C urea breath test for 2 more decades. Not only the ^{13}C had been approved to be used clinically, but also in the field of MRS studies, owing to its physical property to produce MR signal. Some research groups worldwide had been working on ^{13}C MR spectroscopy, yet the techniques were not easy as proton (^{1}H) spectroscopy. In bio systems, carbon and hydrogen were 2

abundant and important elements. Nevertheless, ^{13}C and ^{1}H, both producing MR signals, would undergo nuclear energy exchange (the physical phenomenon called Nuclear Overhauser Effect, NOE), if they were structurally close (in the same molecule). That was to say, if some specific ^{12}C positions of a metabolite were substituted with ^{13}C, then instead of measuring ^{13}C spectrum, the ^{1}H spectrum of the metabolite would change in pattern accordingly, and physically be called the indirect detection of ^{13}C. After acquiring regular glucose ^{1}H MRS previously, the same volunteer was once again recruited as a pilot study subject of OG(^{13}C)TT. The methods modified (different from previous MRS OGTT) were: 75g 99% Dexter ^{13}C glucose $C_{1\text{-}6}$ uniformly labeled (D-Glucose ul-$^{13}C_6$) orally administered, and the voxel placements in medial/parietal gray matter, left hippocampus, and cerebellum (Fig. 4).



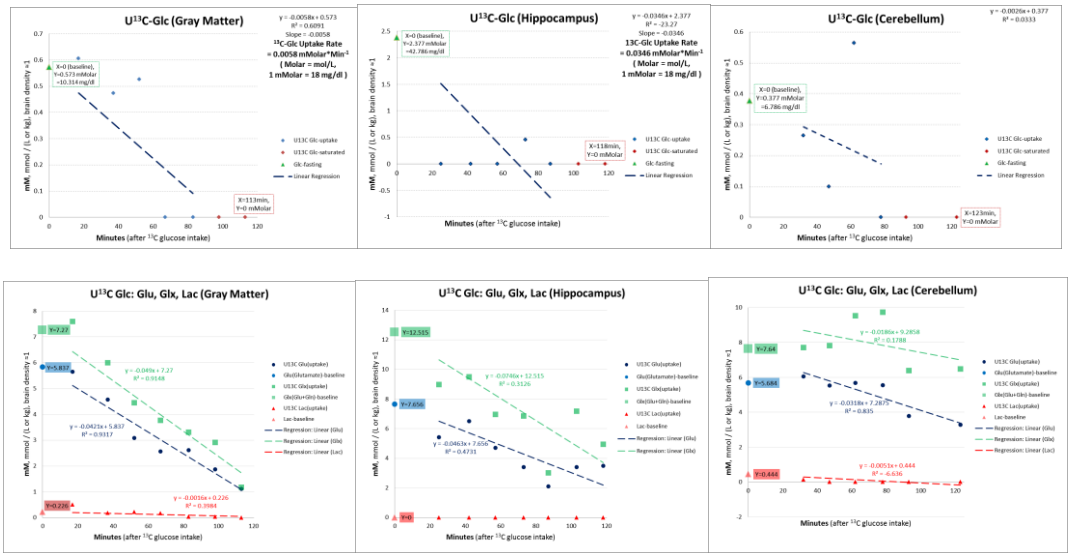


Figure 4.

三、 心得

在國內，氫原子核的磁振頻譜在許多的醫療機構中，比較像是〝磁振造影檢查的附帶選項〞，而非一項獨立的磁振檢查。雖然也有許多的與磁振頻譜技術相關的研究被提出，但所使用的方式與得到的結果比較適用於各個研究團隊，在未來不見得可以支援其他臨床解讀。且在絕大多數的教學醫院中，磁振儀器的硬體都被〝很忙碌的〞使用著，而磁振檢查的結果報告也被要求有效率的製發，以符合許多〝醫療品質〞的指標。

在國際上，磁振頻譜技術數十年來早已是一種〝成熟且強大〞的，放射線醫學界的診斷工具。磁振頻譜使用與磁振造影相同的硬體工具，來產生組織或器官某一區塊部位的頻譜，每個不同〝化學位移〞處的波峰代表著不同的化學物質或代謝物，而波峰的高度比值代表著這些物質的〝濃度比例〞。藉由許多〝濃度比例式樣〞，很多的疾病，如：腦腫瘤、阿茲海默症、癲癇、頭部受傷、代謝異常、精神異常…等等，可以獲得準確的診斷。

四、 建議事項

職赴美返國，建議由服務單位做起，由職來主動負責推廣介紹：〝磁振造影加上磁振頻譜，將絕對大於只有磁振造影〞的觀念。而為了推廣磁振頻譜的臨床應用與增加數據分析判讀的正確性，磁振頻譜定量分析的資料庫將由職來負責建立與維護。此外，此次訪美除增廣見聞外，更獲得許多國外友人及學者的友誼與支持。職將繼續維持與這些友人的合作交流，將服務單位介紹給他們，讓他們更加了解我們。

職將協助服務單位推動之專科醫療任務包括:

一、 建立自動化磁振數據及頻譜絕對定量分析系統。

二、 對各項磁振檢查內容最佳化。

三、 建立進階磁振臨床服務平台。

四、 磁振學術研究之數據分析絕對定量平台。

五、 最新進階磁振臨床應用教學。

附錄

- 附錄內容為職於美國進修期間，幫忙指導教授 Dr. Stefan Blüml 整理之磁振頻譜臨床病例報告之小部分內容草稿。
- 附錄中所有文字內容、圖表、影像、及頻譜…等皆已依照美國洛杉磯兒童醫院人體實驗委員會之規範，全面匿名化。
- 附錄內容純粹為臨床病例經驗報告，無影射任何單一病例，也不建議任何軟硬體或方法技術。
- 附錄之版權，全依照我國政府相關法令規範。

病例一：非常見的磁振影像－腦膜瘤及丙胺酸 ***Meningioma, Alanine, Unusual MRI***

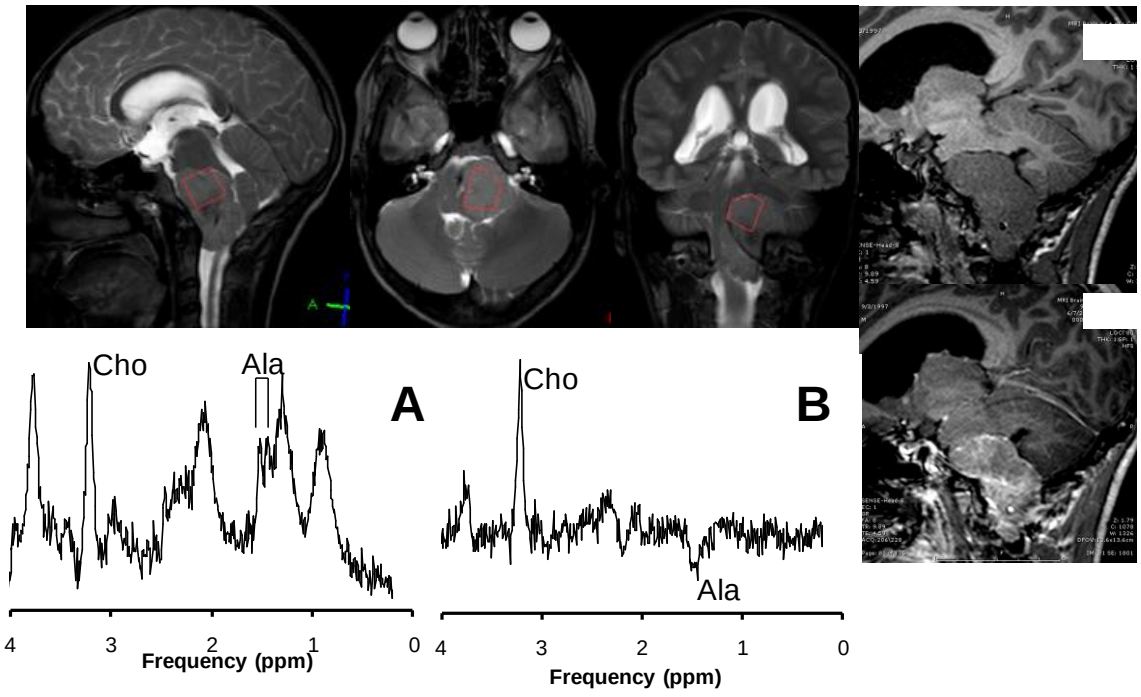
Background:

12 years-old previously healthy male with left sided lower CN dysfunction. MRS was carried out to improve initial lesion characterization.

MRS method:

3T, single-voxel PRESS with TE=35ms (A) and TE=144ms (B), centered in lesion without partial volume of surrounding tissue.

Results:



Discussion:

On MRI an enhancing extraaxial posterior fossa lesion was seen. A nerve sheath

tumor was suggested as the most likely tumor type due to the growth pattern. The MRS showed elevated lipids. A doublet consistent with ***alanine*** was noted. Creatine appeared depleted whereas choline was the most prominent peak. The long TE spectrum confirmed the presence of ***alanine***. MRS was suggestive for meningioma as the most likely tumor type since alanine has frequently been reported in these tumors. This was subsequently confirmed.

*病例二：退行性星狀細胞瘤－疾病監測與代謝發展 **Anaplastic Astrocytoma, Disease Monitoring, Metabolic Progression***

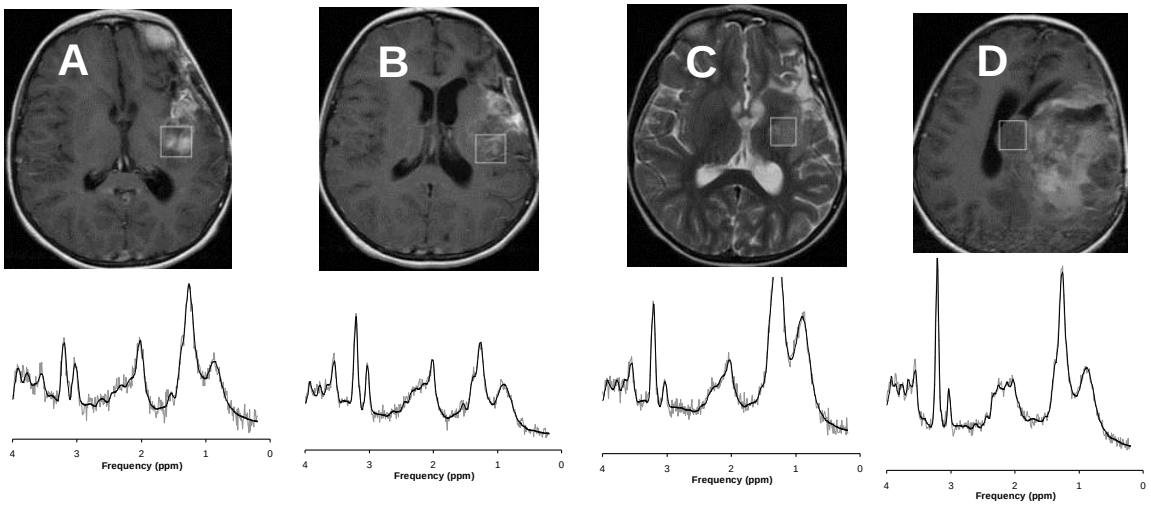
Clinical background:

Nine years-old girl with history of recurrent anaplastic astrocytoma post gross total resection. MRS was carried to distinguish between treatment related changes versus residual/recurrent disease.

MRS method:

1.5T, repeated single-voxel PRESS, TE 35ms, of enhancing tissue adjacent to site of resection 2 days (A), 1 month (B), 2 ½ months (C), and 7 months (D) after surgery. Spectra are scaled to present absolute concentrations to allow direct comparison.

Results:



Discussion:

The MRI at 1 month (B) suggested "…*interval decrease of ... edema, enhancement ... probably due to resolution of post-op changes and ongoing therapy*…". In contrast, MRS demonstrates increased levels of Cho and reduced NAA suggesting

recurrent/residual disease already at one month after surgery. The subsequent MRI at 2 ½ months (C) was consistent with disease progression. MRS at that time was interpreted as likely grade IV glioblastoma. The MRI performed at seven months (D) shows dramatic disease progression.

Conclusions:

Increasing levels of choline in serial MRS studies may indicate recurrent disease.

病例三：新生兒－非乳酸而是丙二醇 **Newborn, Propylene Glycol (Pgc), *NOT* Lactate**

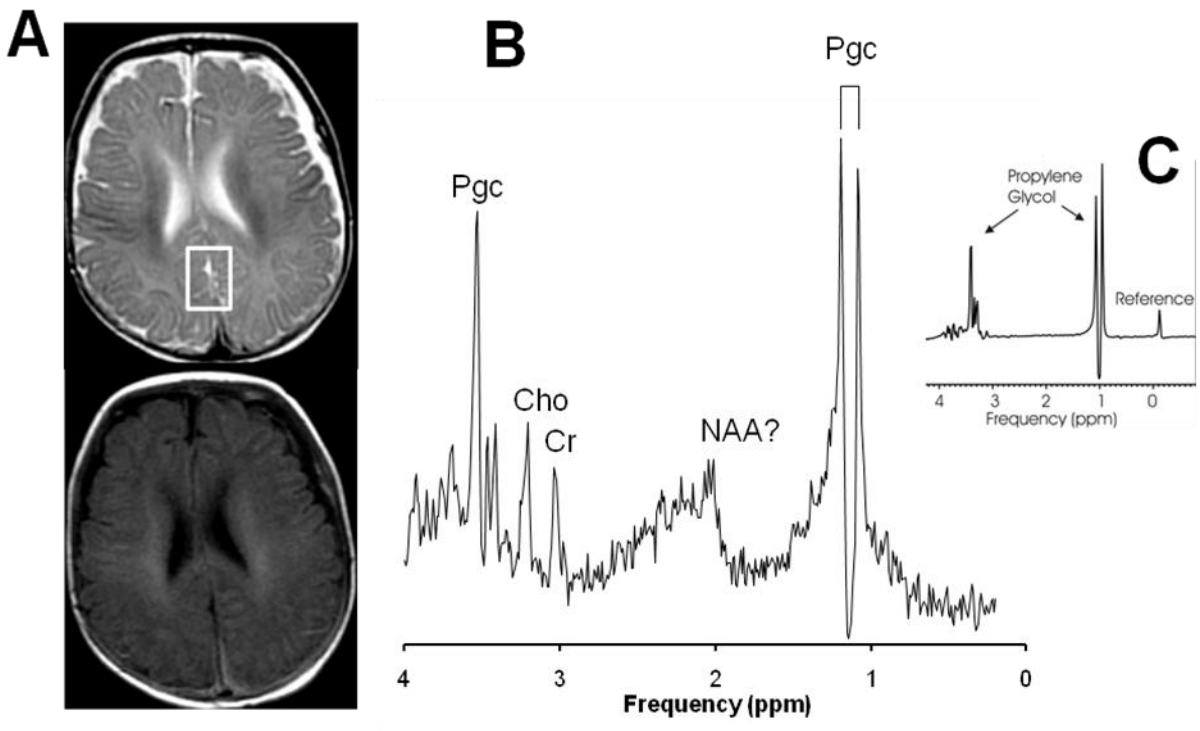
Clinical background:

Two months-old with hemorrhage and suspected head trauma. MRS was performed to rule out axonal/neuronal injury.

MRS method:

1.5T, single-voxel PRESS, TE = 35 ms, occipital grey matter.

Results:



Discussion:

On MRI the brain parenchyma appeared normal on all sequences and the ventricles were of normal size. An acute subdural hemorrhage along the falx and tentorium was

noted (A). A prominent signal from propylene glycol (Pgc), also known as propan-1,2-diol, was detected in the MR spectrum (B). Pgc presents with a doublet that can be confused with the lactate doublet. A spectrum obtained from a model solution of Pgc is shown for comparison (C). The concentration of Pgc in brain tissue was ≈ 20 mmol/kg. Additionally, NAA was reduced in this patient indicating significant brain damage. A later CT scan revealed shrunken gyri and ventriculomegaly suggesting parenchymal volume loss in both hemispheres.

Conclusions:

To ensure proper identification of lactate and/or propylene glycol the chemical shift of the downfield doublet needs to be checked carefully. Note that the Pgc doublet is centered at ≈1.2 ppm whereas the double from lactate is centered at ≈ 1.3ppm. Propylene glycol is often used as a solvent for drugs (anti-seizure drugs) and its accumulation in brain tissue of small babies has been reported by several groups[1]. It is unknown whether Pgc by itself can cause brain damage.

1. Cady EB, Lorek A, Penrice J, et al. Detection of propan-1,2-diol in neonatal brain by in vivo proton magnetic resonance spectroscopy. *Magn Reson Med.* Dec 1994;32(6):764-767.

2. Seymour ZA, Panigrahy A, Finlay JL, Nelson MD, Jr., Bluml S. Citrate in pediatric CNS tumors? *AJNR Am J Neuroradiol.* May 2008;29(5):1006-1011.

病例四：檸檬酸與退行性星狀細胞瘤 **Citrate, Anaplastic Astrocytoma**

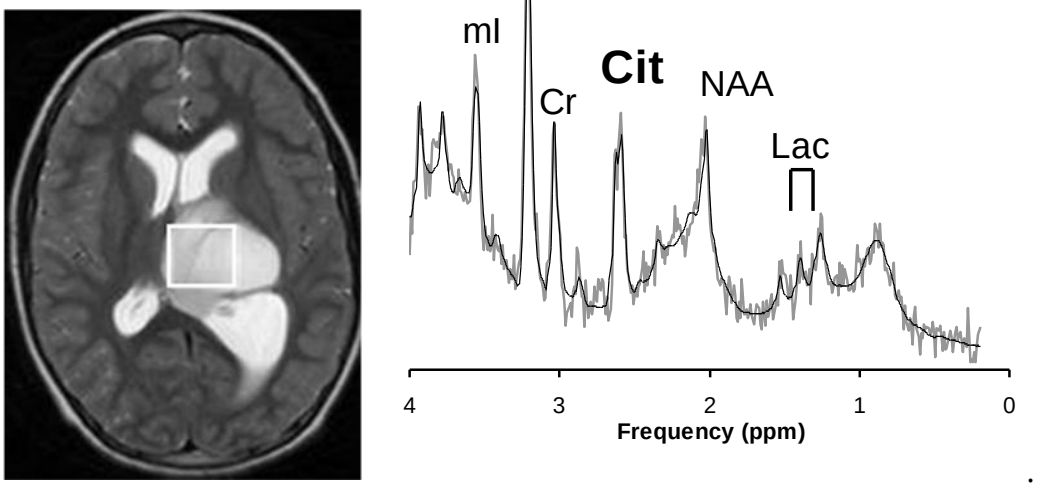
Clinical background:

Seven years-old female with brain lesion. MRS was performed for lesion characterization.

MRS method:

1.5T, single-voxel PRESS, TE 35 ms.

Results:



Discussion:

On MRI a left thalamic/left intraventricular solid-cystic hypocellular mass most likely presenting a pilocytic astrocytoma was reported. Perfusion MRI was also performed and indicated a hypoperfused tumor. MRS was not consistent with pilocytic astrocytoma and a regular glial tumor was suggested. Subsequent resection revealed an anaplastic astrocytoma. The unusual peak at ≈ 2.6 ppm was consistent with citrate

which has previously been observed most consistently in diffuse brainstem gliomas but also in other grade II and grade III gliomas. Despite surgical resection and chemotherapy, disease progression was noted at 5 months after initial diagnosis and the patient died within one year after diagnosis.

Conclusions:

Citrate may be observed in subgroups of pediatric brain tumors, mostly likely in glial tumors. The significance of citrate is currently being investigated.

病例五（甲）：檸檬酸－三特士拉、短回訊時間 **Citrate, 3T, Short TE**

Clinical background:

Seven years-old male with brain lesion. MRS was performed for lesion characterization.

MRS method:

3T, single-voxel PRESS, TE 35 ms, lesion

Results:

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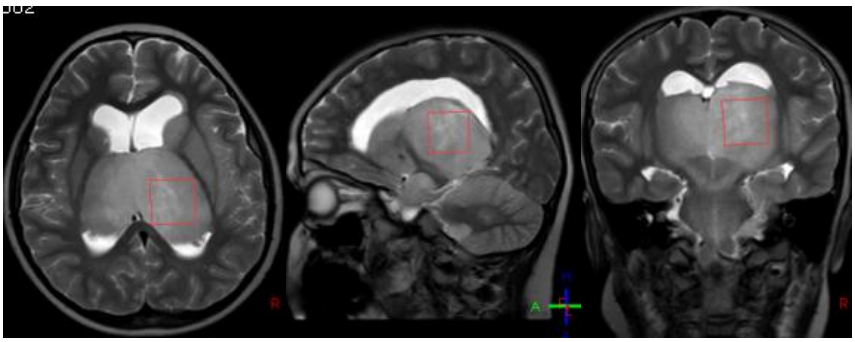
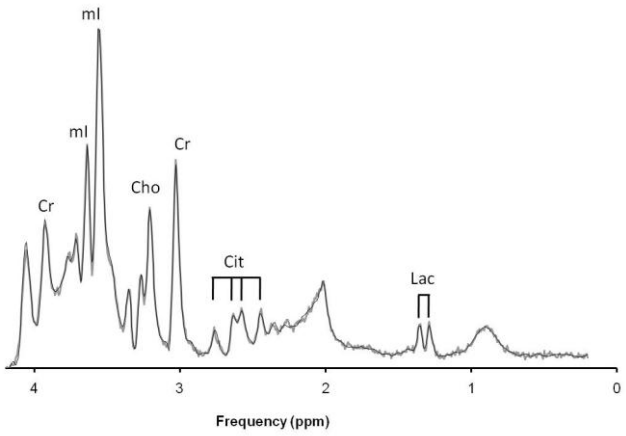




Discussion:

On MRI a bithalamic/left non-enhancing lesion was detected. Subsequent biopsy

revealed a low-grade (WHO II) astrocytoma. Perfusion MRI was also performed and indicated a hypoperfused tumor. MRS was consistent a low-grade glioma. Moderate levels of choline are more typical for lower grade lesions albeit there is a significant overlap. The unusual signal at ≈ 2.4 – 2.8 ppm was consistent with citrate.

Conclusions:

Note that the citrate signal at 1.5 and 3T are substantially different even when the same acquisition method is used.

病例五（乙）：檸檬酸－三特士拉、長回訊時間 **Citrate, 3T, Long TE**

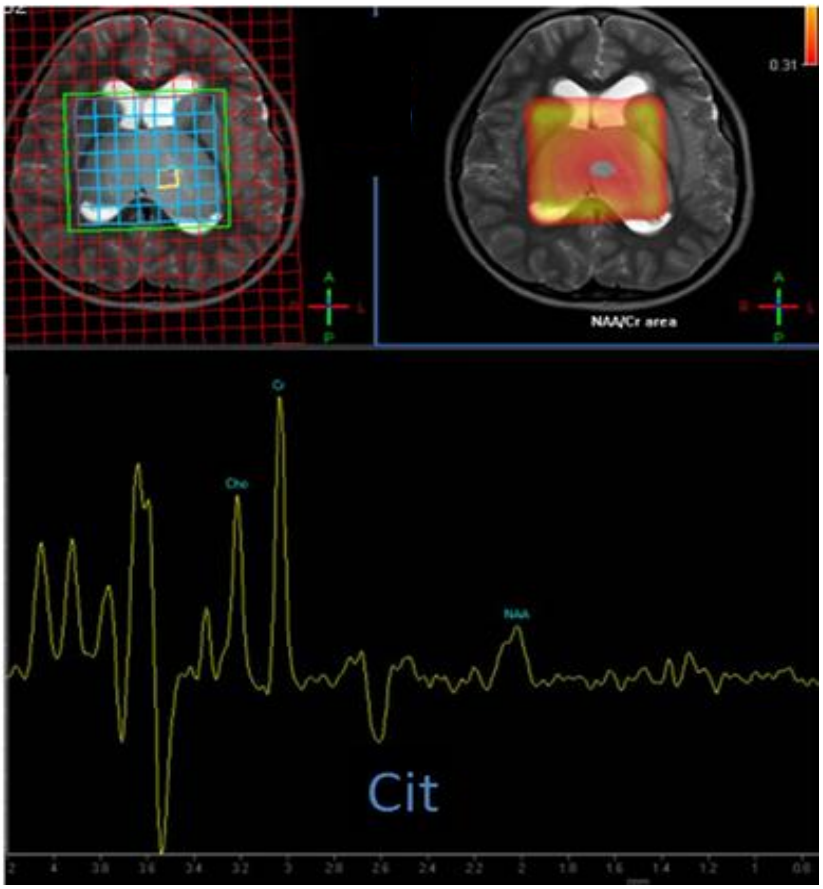
Clinical background:

Seven years-old male with brain lesion. MRS was performed for lesion characterization.

MRS method:

3T, 2D-CSI, TE 85ms, lesion and surrounding tissue. A TE of 85 ms was selected as citrate is inverted at this echo time at 3T.

Results:



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Discussion:

Multi-voxel MRS confirms moderate levels of choline throughout lesion (not shown in detail). An inverted peak consistent with citrate was observed.

Conclusions:

病例六：極端早產兒－正常影像與頻譜 **Extreme Prematurity, Normal MRI, Lactate**

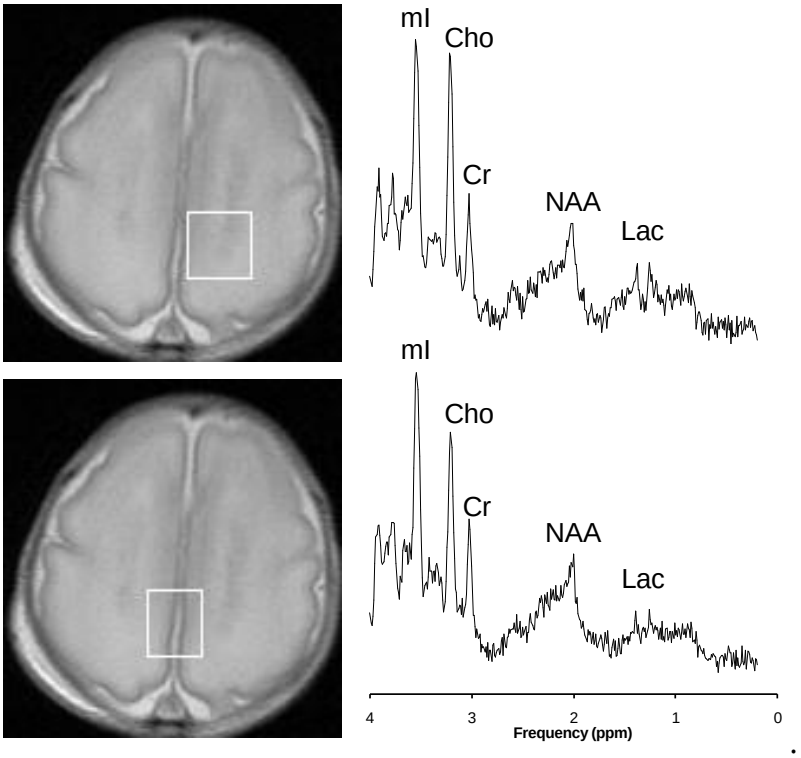
Clinical background:

14 weeks premature baby with respiratory distress. Gestational age at birth was 25 weeks. The patient was studied 1 week after birth.

MRS method:

1.5T, single-voxel PRESS, TE 35 ms, two locations in undifferentiated brain tissue.

Results:



Discussion:

MRI was reported to be within normal limits and clinical follow-up of more than 4

years after the study was unremarkable for this patient. Lactate is present in both spectra. NAA is very low, whereas myo-inositol is the most prominent peak.

Conclusions:

Lactate detected at very early brain development does not necessarily indicate brain injury. Similarly, very low NAA levels are normal at this age.

病例七：瓜胺酸血症第一型 **Citrullinemia I**

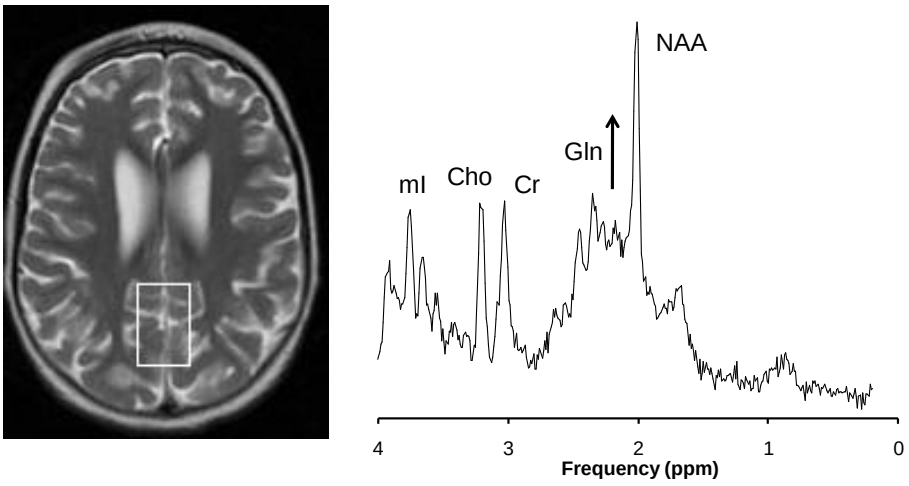
Clinical background:

Seven years-old boy with new-onset seizures and tremors, prior diagnosis of citrullinemia.

MRS method:

1.5T, single-voxel PRESS, TE 35 ms, occipital mostly grey matter containing tissue.

Results:



Discussion:

Citrullinemia is an autosomal recessive urea cycle disorder that causes ammonia to accumulate in the blood. The MRI showed moderate diffuse volume loss and hyperintensity on FLAIR images in subcortical and periventricular white matter. MRS of normal appearing occipital grey matter was strikingly abnormal with prominent glutamine and depleted myo-inositol. These changes are consistent with acute hyperammonia and accumulation of glutamine. NAA was only slightly reduced in this patient.

病例八：腦幹神經外胚層母細胞瘤－頻譜誤解為膠質瘤 **Brainstem Primitive Neuroectodermal Tumor (PNET), Glioma, MRS Interpretation Incorrect**

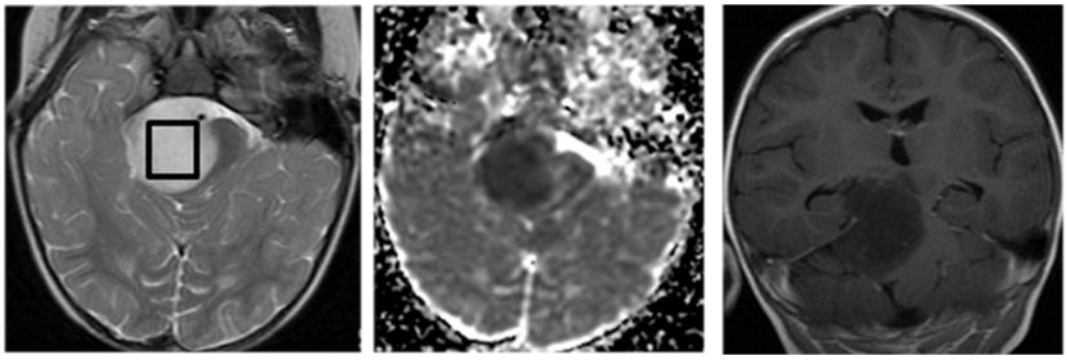
Clinical background:

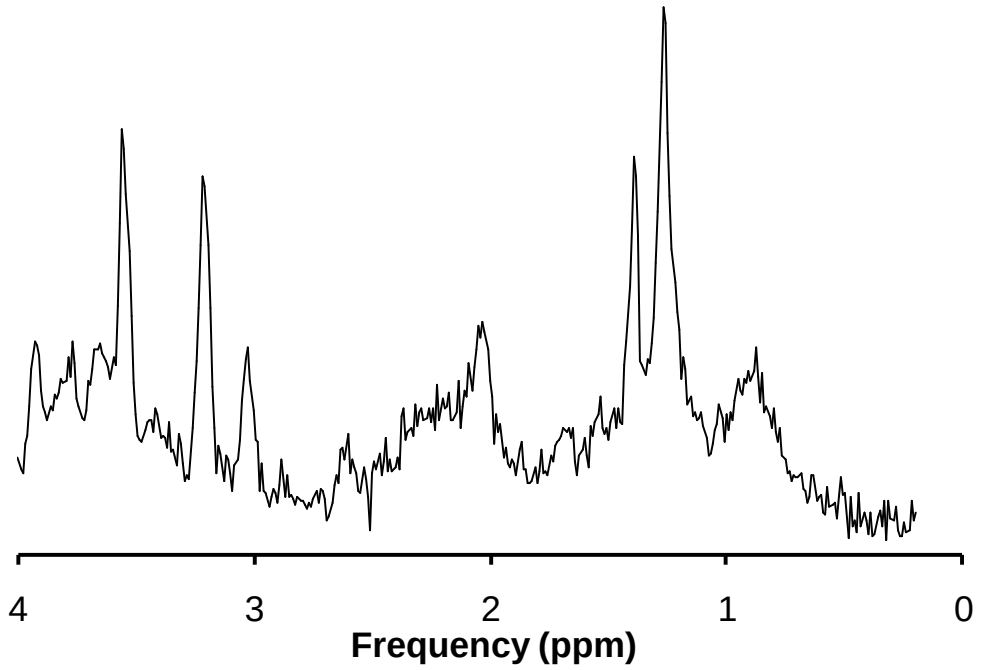
15 months-old boy with left-sided weakness.

MRS method:

1.5T, repeated single-voxel PRESS, TE 35ms, lesion, at presentation

Results:





Discussion:

Well circumscribed non-enhancing lesion which is bright on T2w images. The diffusion signal is hyperintense with low ADC value. The lesion was hypointense on T1w images but nevertheless considered to be consistent with large epidermoid tumor. MRS was not consistent with epidermoid where previous studies have shown mostly lactate. The MR spectrum shows prominent lactate and a small residual signal from NAA. Both choline and myo-inositol are elevated relative to creatine. However, absolute choline and myo-inositol are below normal tissue levels. There is no evidence for taurine. The MRS pattern fits best the pattern of a glial tumor. Due to the absence of taurine, the low concentration of choline, and relatively prominent myo-inositol it was felt that MRS was not consistent with a primitive neuroectodermal tumor (PNET). However, the tumor was biopsied/partially resected and the pathologist classified the tumor as a PNET.

病例九：典型髓母細胞瘤— **Classic Medulloblastoma, Typical and Atypical**

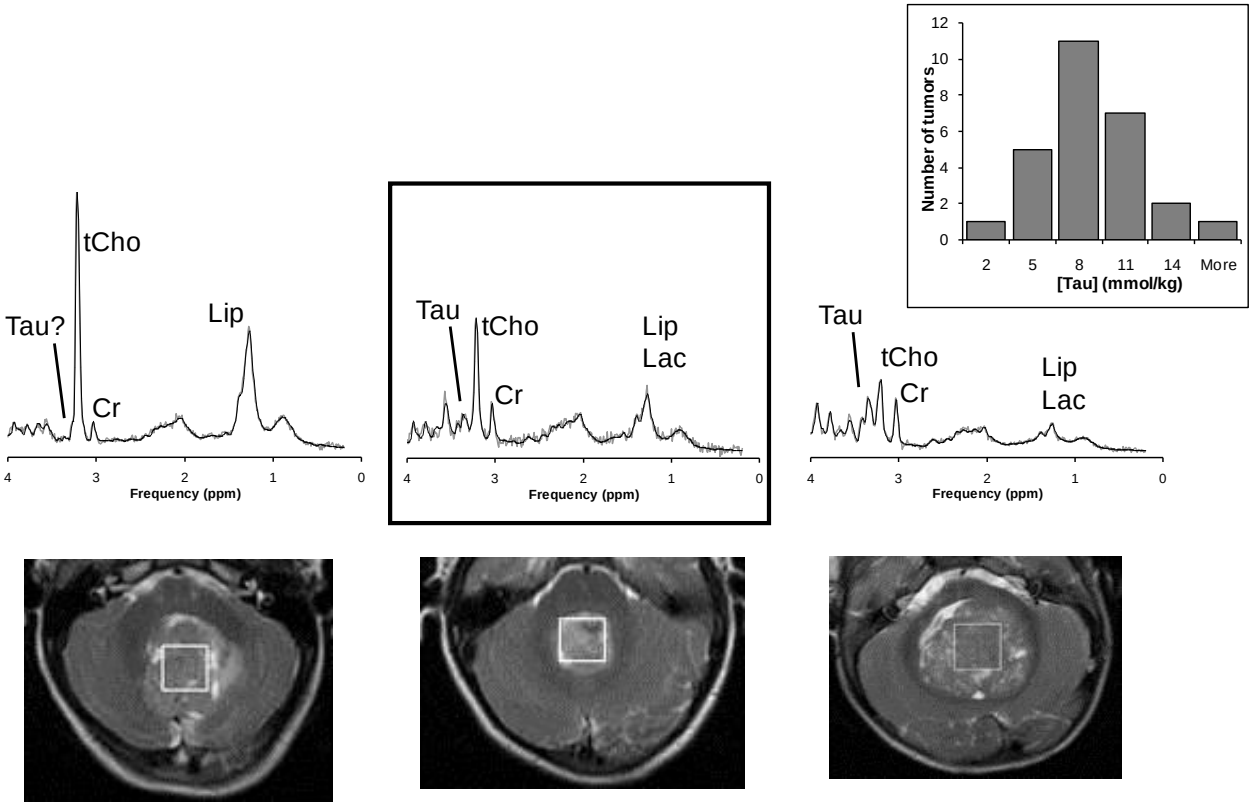
Clinical background:

Three pediatric patients with newly diagnosed, untreated tumors of the posterior fossa.

MRS method:

1.5T, single-voxel PRESS, TE 35 ms, lesion.

Results:



Discussion:

All three lesions were subsequently resected and the tissue samples were interpreted to be consistent with *classic medulloblastoma.* These cases are shown to illustrate the metabolic/biologic heterogeneity even within medulloblastomas of the *same subtype*. The framed spectrum in the center is the most typical and most likely appearance of a

classic medulloblastoma. But it is possible to observe spectra that are substantially different. Here medulloblastoma spectra with very low and very high taurine are shown. The insert shows the histogram of taurine concentrations measured at Childrens Hospital LA in classic medulloblastoma. As expected it follows a normal (Gaussian) distribution. As several groups have shown{Moreno-Torres, 2004, Taurine detection by proton magnetic resonance spectroscopy in medulloblastoma: Contribution to noninvasive differential diagnosis with cerebellar astrocytomas}{Kovanlikaya, 2005, Untreated Pediatric Primitive Neuroectodermal Tumor in Vivo: Quantitation of Taurine with MR Spectroscopy}, the elevated taurine is very good indicator for medulloblastoma, however, not in 100% of the cases. But, despite the low taurine of the spectrum on the left, this tumor was nevertheless correctly diagnosed as the very high Cho is not typical for ependymoma (or pilocytic astrocytoma). It is worth noting that these three patients all fell in the same risk class and were treated equally. One may wonder whether the quite different metabolic profile correlates with different biological behavior which could (some day in the future) be exploited to optimize therapies.

Conclusions:

The metabolic profiles of medulloblastoma can vary significantly.

病例十： 纖維狀細胞型星狀細胞瘤 **Pilocytic Astrocytoma (WHO I) With Aggressive Behavior**

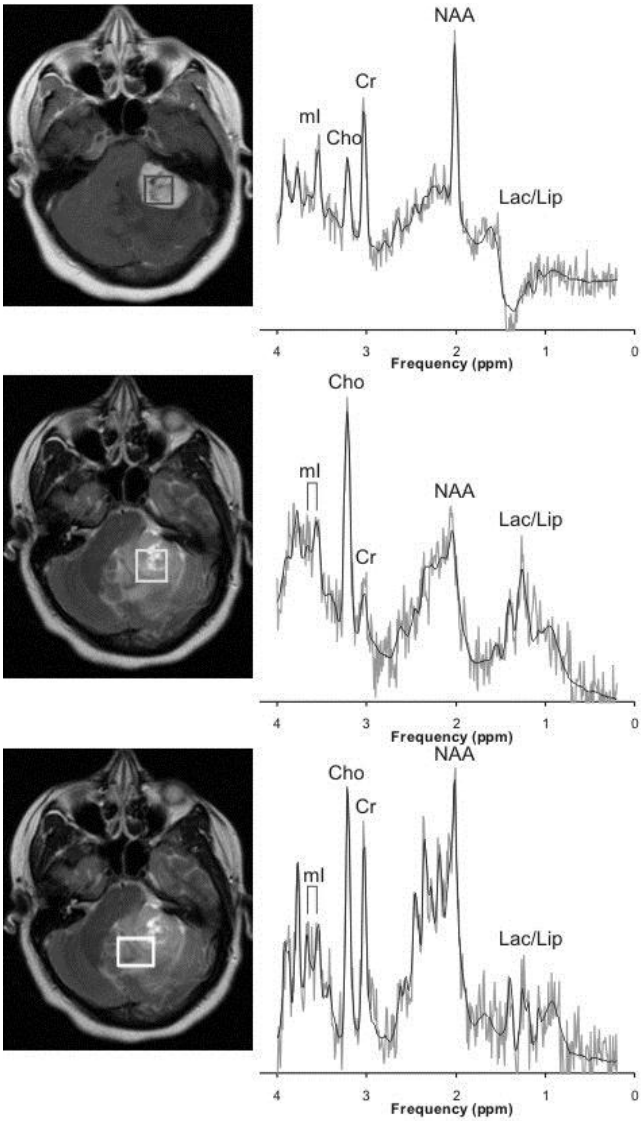
Clinical background:

16 year old female with vertigo and vomiting, assess for intracranial mass.

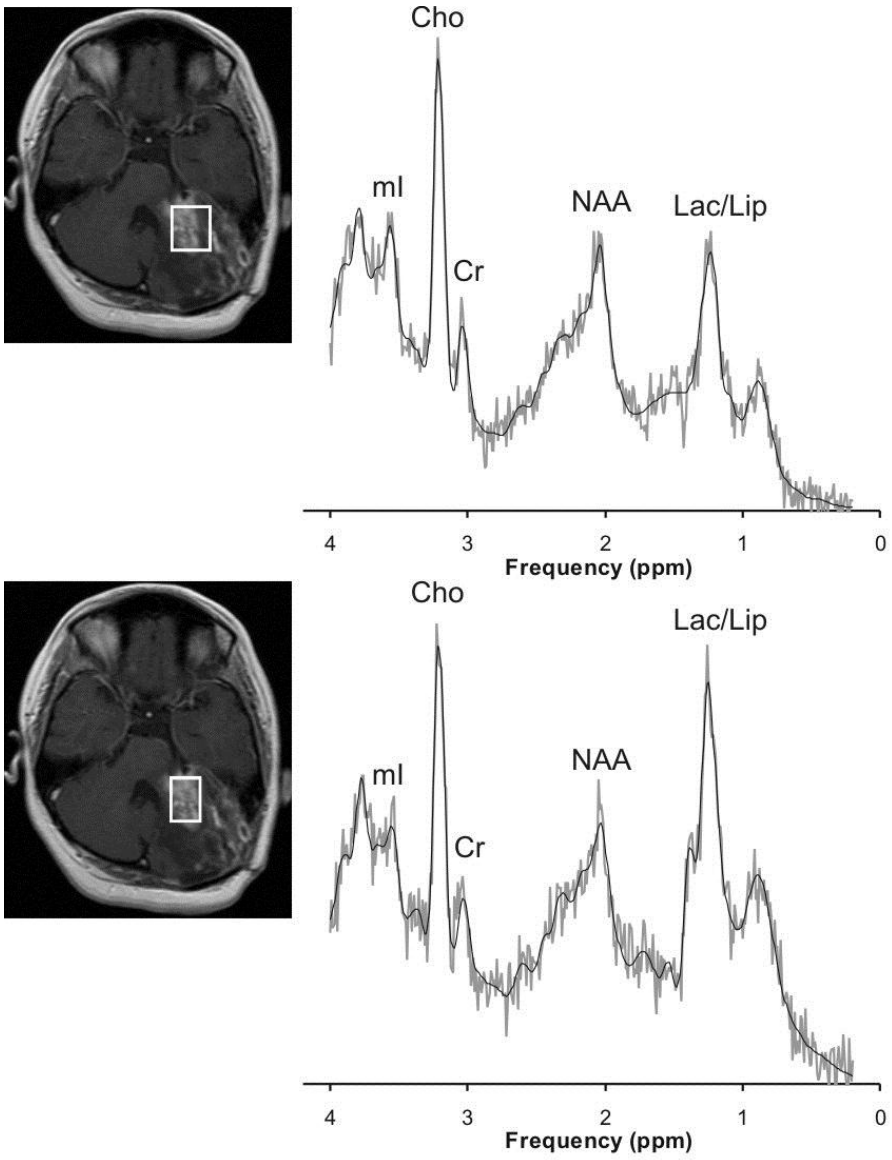
MRS method:

1.5T, single-voxel PRESS, TE 35 ms, of lesion and surrounding tissues.

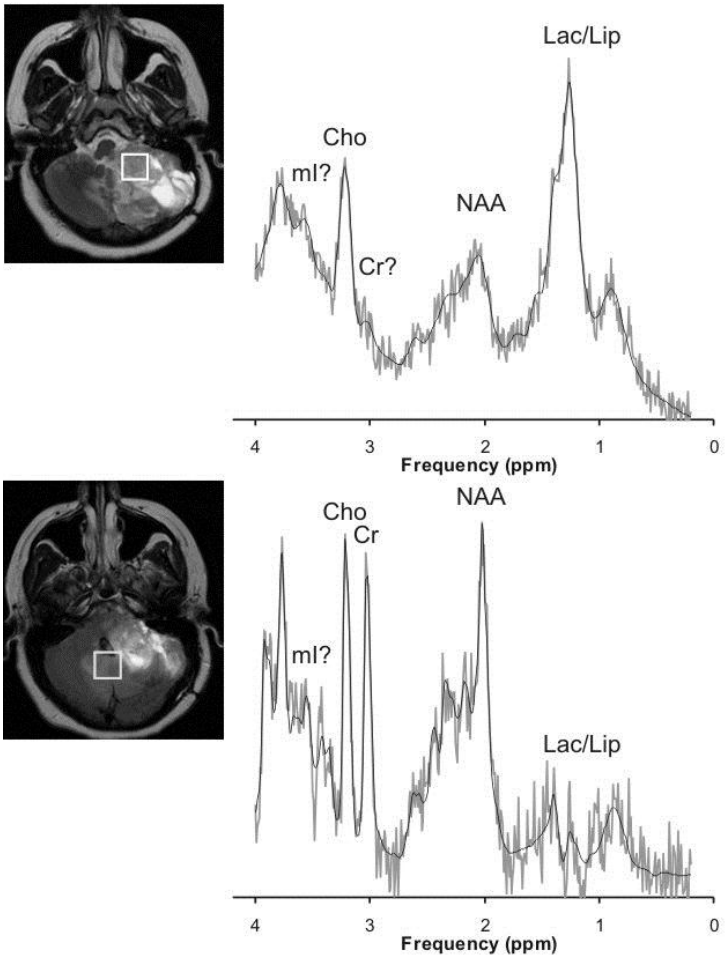
Results:



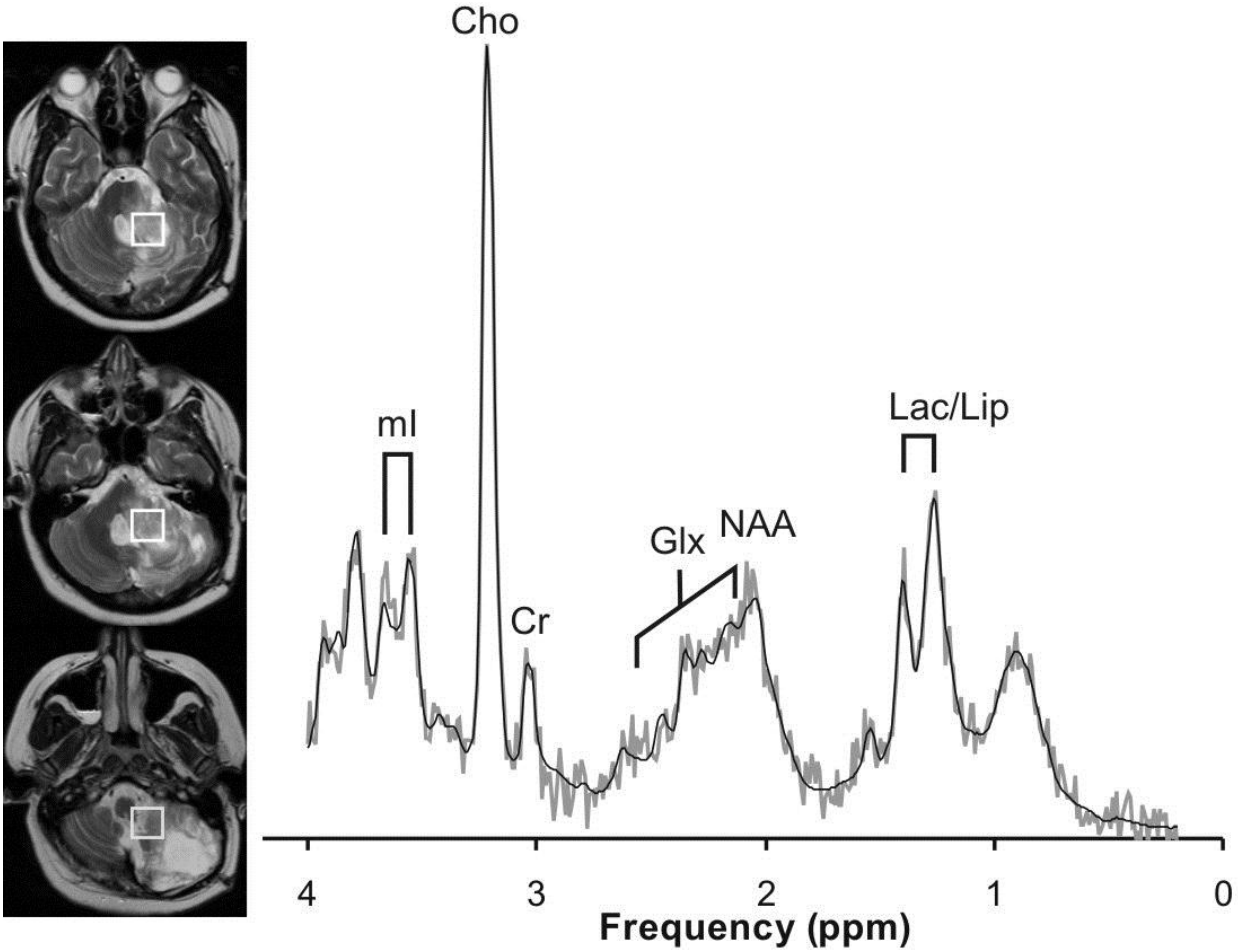
2/9/2004, 1.5T — MRI IMPRESSIONS: Left cerebellar mass with central necrosis and a moderate amount of edema and mass effect, likely a glioma, probably anaplastic astrocytoma. There is mild hydrocephalus of the third and lateral ventricles. NO MRS CONCLUSIONS.



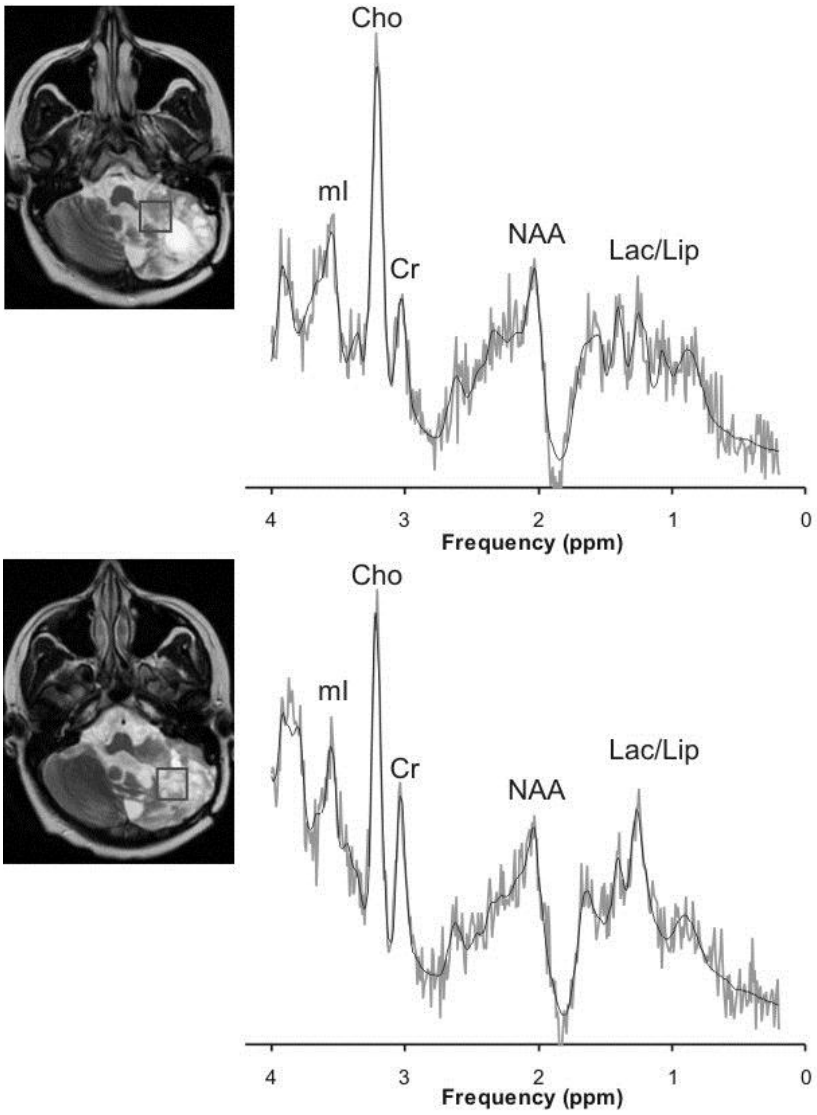
2/14/2005, 1.5T — MRI IMPRESSIONS: No interval change in the size of the residual enhancing tumor seen in the left cerebellar pontine angle region as described above compared with 11/15/04. Again, there is necrosis noted within the lesion. NO MRS CONCLUSIONS.



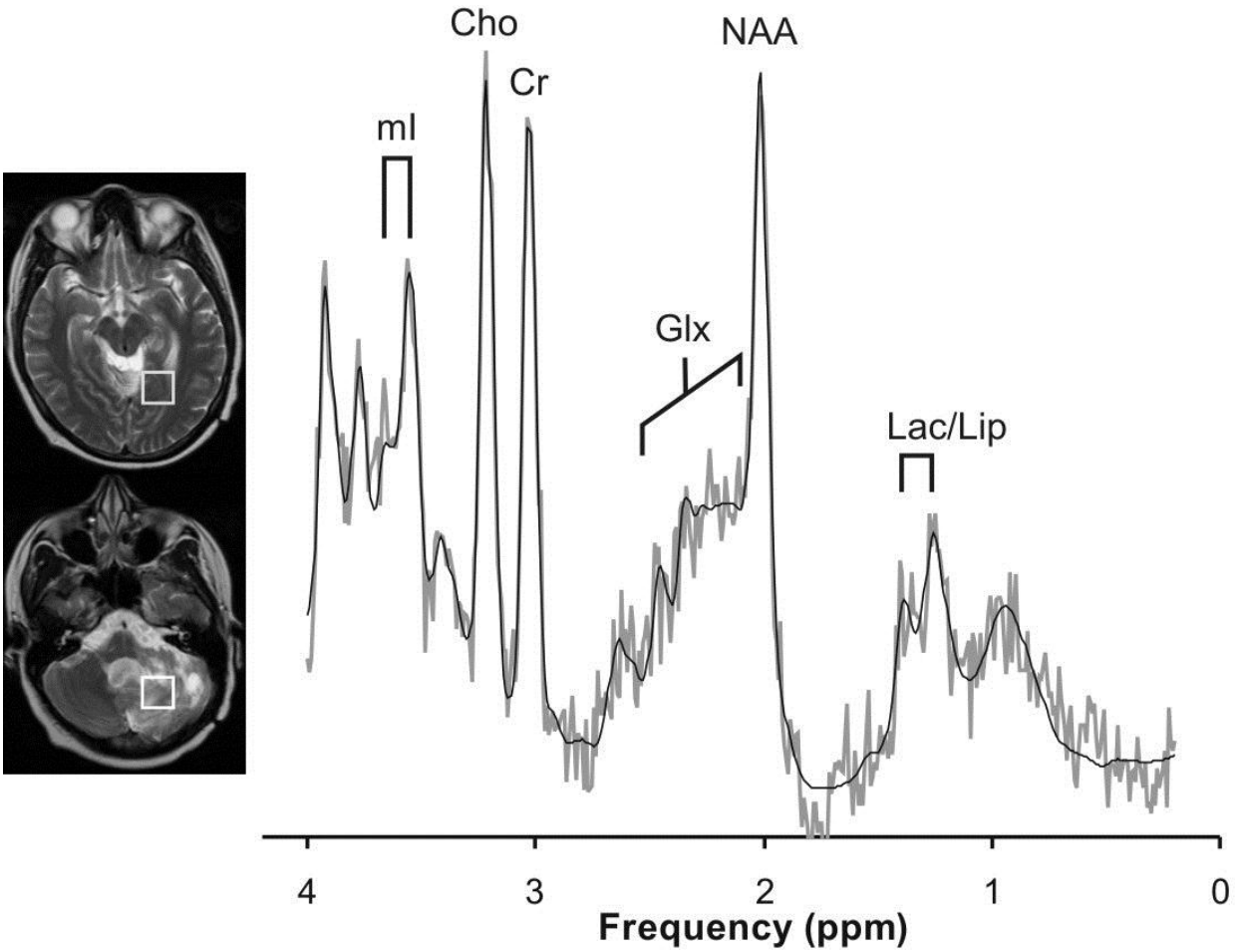
4/6/2006, 1.5T — MRI IMPRESSIONS: No interval change in the enhancing portion of the tumor seen in the left cerebellar peduncle, left cerebellum and left brainstem as described above. There has been slight increase in non-enhancing edema in the right side of the pons. NO MRS CONCLUSIONS.



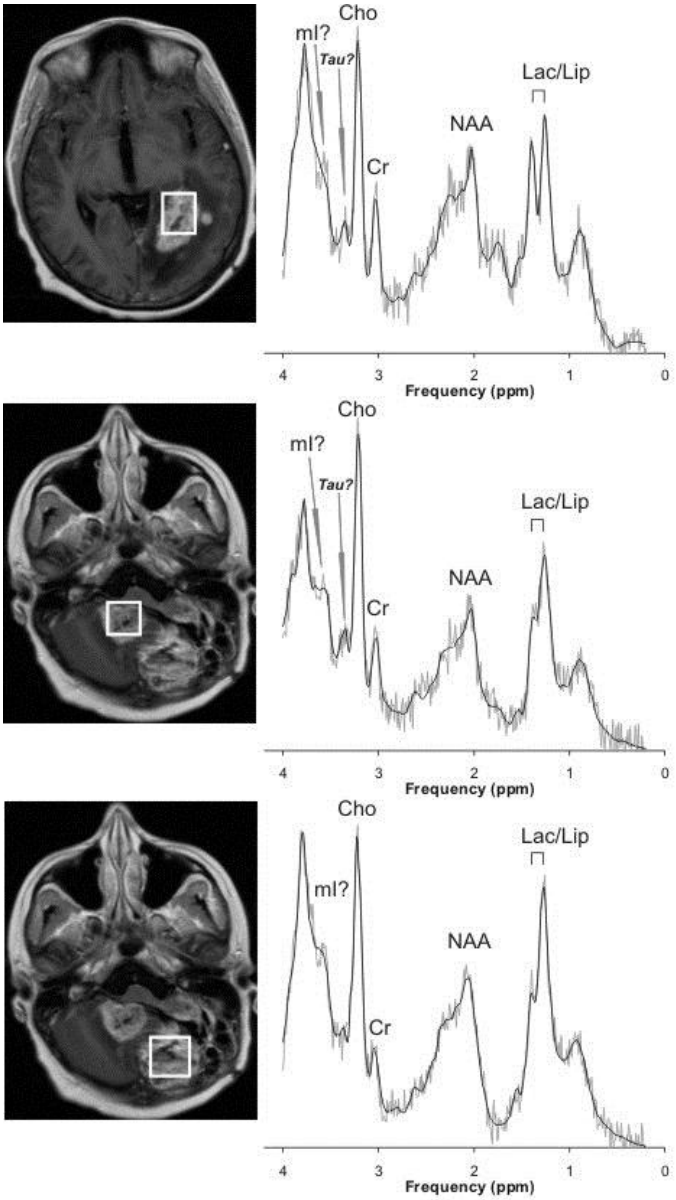
5/9/2006, 1.5T — MRI IMPRESSIONS: Large residual left cerebellar mass with no significant change in size since the MR of 4/11/2006. Mild ventriclur enlargement, slightly increased in size since 4/11/2006. The cystic component of the mass causing the left occipital bulging has decreased in size since the CT of 5/3/2006. NO MRS CONCLUSIONS.



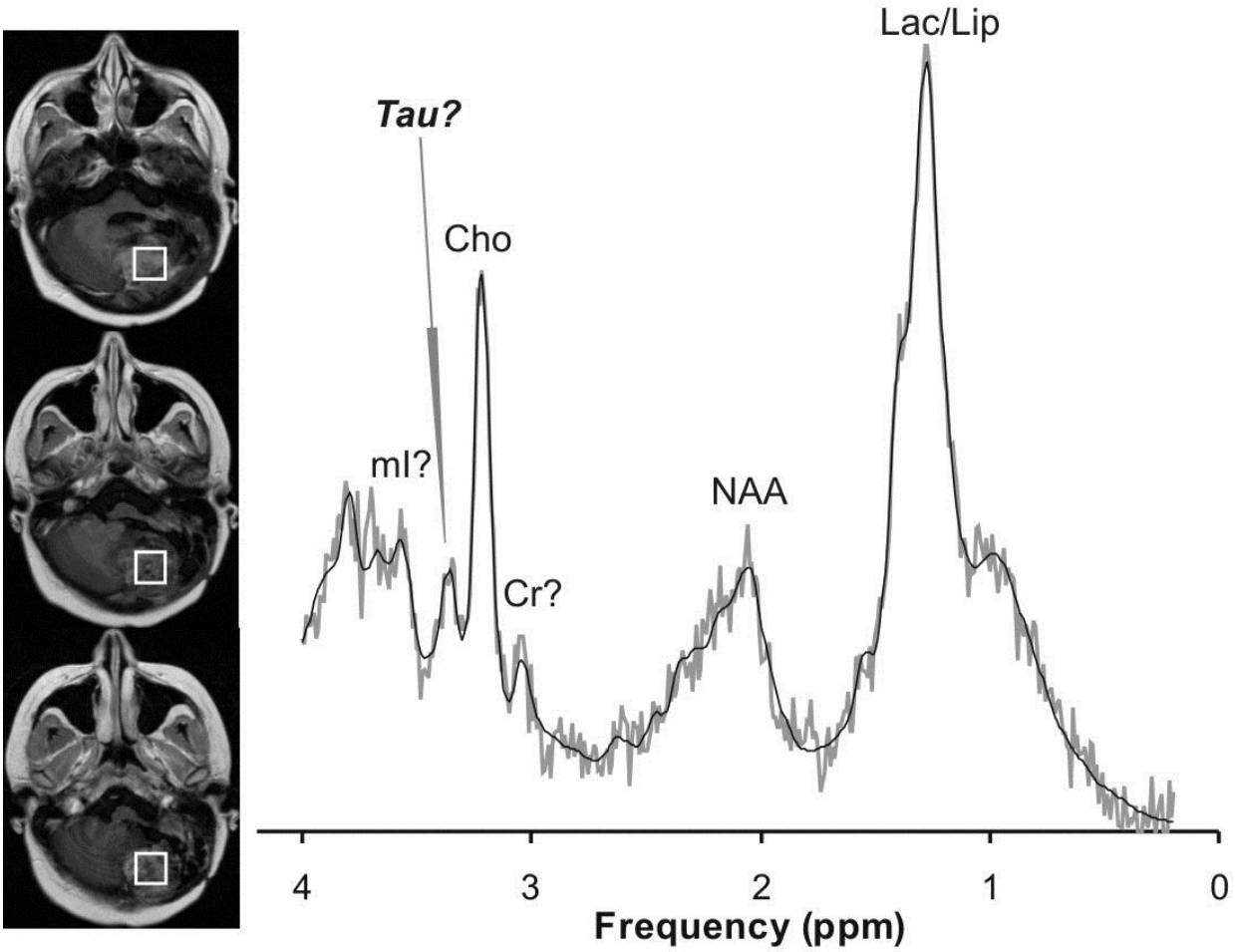
1/18/2007, GE — MRI IMPRESSIONS: (1) Large residual left cerebellar mass with no significant change in size since the prior MR. Slight decrease in the largest of the cerebellar cysts. (2) No change in the diffuse leptomeningeal disease involving the brainstem, suprasellar region and the bilateral insular region. NO MRS CONCLUSIONS.



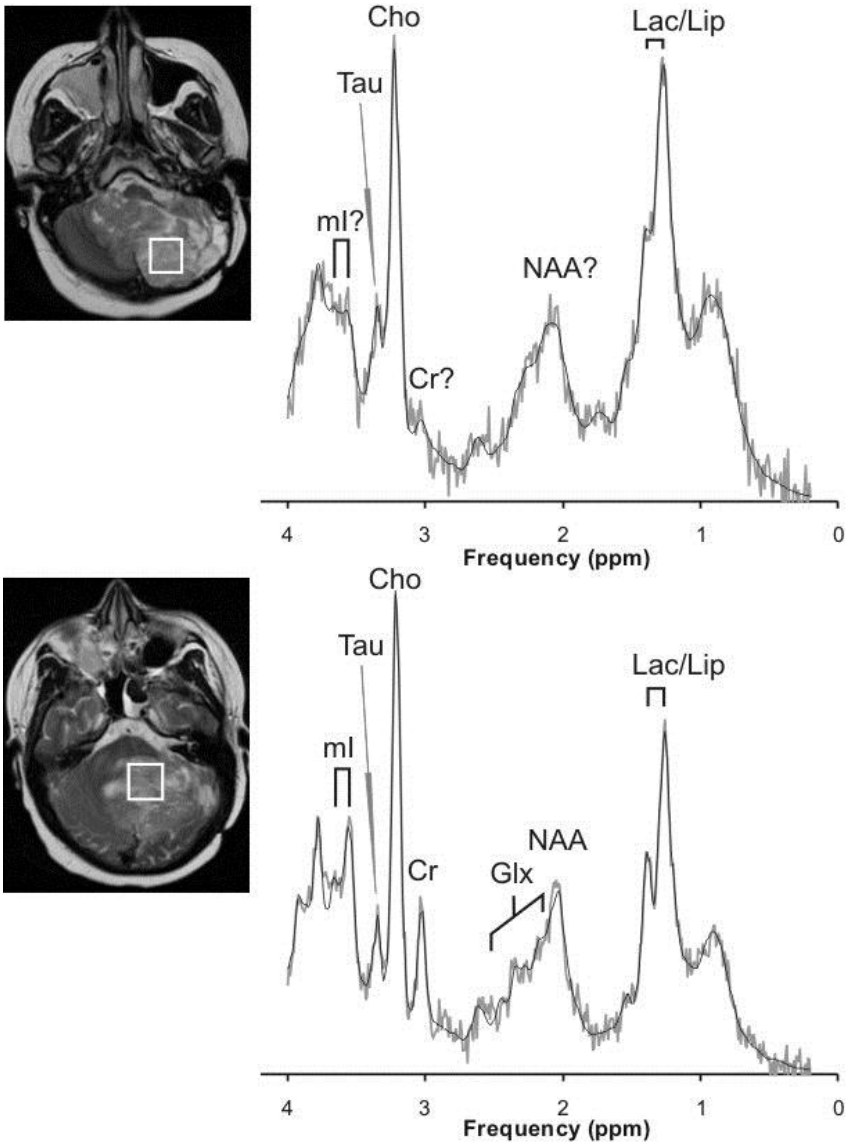
7/16/2007, GE — MRI IMPRESSIONS: Large residual left cerebellar mass with with new areas of contiguous involvement in the right medial inferior cerebellum abutting the fourth ventricle. There are also a few new nodular areas of enhancement in the left posterior temporal region. NO MRS CONCLUSIONS.



8/30/2007, GE — 20-year-old female with cerebellar astrocytoma, complains of emesis, headache, and imbalance. Please evaluate progression of disease. TECHNIQUE: SV-MRS of enhancing lesions (3 regions). FINDINGS: All spectra: elevated lactate and lipids. Creatine levels low or depleted. Myo-inositol below normal levels and choline elevated. CONCLUSIONS: MRS typical for pilocytic astrocytoma in all regions examined.



10/18/2007, GE — Progressive cerebellar astrocytoma and right distal radius osteosarcoma. MRI IMPRESSIONS: Interval decrease in residual astrocytoma and leptomeningeal disease as described above compared with 8/30/07. The lateral ventricles are small, but slightly increased in size from before. NO MRS CONCLUSIONS.



12/10/2007, GE — Cerebellar pilocytic astrocytoma. TECHNIQUE: SV-MRS of lesion. ROI1: left cerebellum. ROI2 : adjacent to pons/brainstem. FINDINGS: elevated lipids and lactate. NAA reduced or depleted. Creatine reduced. Myo-inositol increased in ROI2 but reduced in cerebellar ROI. Choline prominently elevated. CONCLUSIONS: MRS consistent with tumor. Overall pattern is consistent with pilocytic astrocytoma. However choline in this tumor is unusually high for pilocytic astrocytoma (two standard deviation above mean choline in pilocytic astrocytoma).

Discussion:

To be edited…

Conclusions:

To be edited…