行政院國家科學委員會專題研究計畫　成果報告

罹患惡性苯丙酮尿症兒童之白質擴散張度影像研究

計畫類別：個別型計畫
計畫編號：NSC92-2320-B-002-107-
執行期間：92 年 08 月 01 日至 93 年 07 月 31 日
執行單位：國立臺灣大學醫學院放射線科

計畫主持人：彭信逢
共同主持人：胡務亮，曾文毅，廖漢文

報告類型：精簡報告

處理方式：本計畫可公開查詢

中　華　民　國 93 年 11 月 3 日

國科會專題研究計畫成果報告撰寫格式

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行政院國家科學委員會補助專題研究計畫
▓ 成 果 報 告
□期中進度報告

罹患惡性苯丙酮尿症兒童之白質擴散張度影像研究

計畫類別：▓ 個別型計畫　　□ 整合型計畫
計畫編號：NSC　92－　2320－B －002－107－
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計畫主持人：彭信逢
共同主持人：曾文毅 胡務亮 簡穎秀 廖漢文
計畫參與人員：

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行政院國家科學委員會專題研究計畫成果報告

罹患惡性苯丙酮尿症兒童之白質擴散張度影像研究

Diffusion tensor imaging of children with malignant phenylketonuria

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主持人：　　彭信逢

共同主持人：曾文毅　胡務亮　簡穎秀　廖漢文

一、中文摘要

本研究應用擴散張度影像以彰顯罹患惡性苯丙酮尿症兒童之大腦白質變化。

本研究對象為十二例經早期治療且穩定的罹患惡性苯丙酮尿症兒童，評估其擴散張度影像變化包括 **first, second and third eigen values (EVs), apparent diffusion coefficients (ADCs), and fractional anisotropy (FA) in the fronto-parietal, parieto-occipital, frontal and central white matter, and the anterior as well as posterior corpus callosum** 以及智力商數並與年齡相當知健康兒童比較。本研究發現大於三歲的研究群與對照群在 **EV2, EV3 and FA of the parieto-occipital white matter areas** 有明顯差異。此外，在 **parieto-occipital** 白質的 **EV3 and ADC of the parieto-occipital white matter** 與 **verbal intelligence quotient (VIQ; r = -0.79, p = 0.04), and performance intelligence quotient (r = -0.93, p = 0.03),** 分別有顯著負相關**.** 然而， **FA of the parietal central white matter** 則與 **VIQ** 有正相關**(r = 0.75, p = 0.05)**。

關鍵詞：擴散張度影像　腦部 惡性苯丙酮尿症 兒童 磁振掃描

Abstract

Purpose: Diffusion tensor images (DTIs) are used to demonstrate the supratenorial white matter changes of malignant phenylketonuria (PKU) patients.

Materials and Methods: The intelligence and diffusion tensor imaging parameters (including first, second and third eigen values (EVs), apparent diffusion coefficients (ADCs), and fractional anisotropy (FA) in the fronto-parietal, parieto-occipital, frontal and central white matter, and the anterior as well as posterior corpus callosum were assessed in 12 early-treated, chronic, stable malignant PKU patients.

Results: Our findings indicated that EV2, EV3 and FA of the parieto-occipital white matter areas were significantly different in study and control groups of patients older than three years of age. In addition, EV3 and ADC of the parieto-occipital white matter were significantly negatively correlated with verbal intelligence quotient (VIQ; r = -0.79, p = 0.04), and performance intelligence quotient (r = -0.93, p = 0.03), respectively. FA of the parietal central white matter was positively correlated with VIQ (r = 0.75, p = 0.05).

Conclusion: Though treated early, these chronic, stable malignant PKU patients still had abnormal DT tensor imaging findings in the parieto-occipital central white matter. EV2, EV3 and FA maps are potential tools for demonstrating brain changes stemming from malignant PKU.

Keywords: diffusion tensor, brain, magnetic resonance (MR), pediatric, phenylketonuria

二、緣由與目的

Phenylketonuria (PKU) is the most frequent inborn error of amino acid metabolism. The primary neuropathologic findings of PKU are diffuse abnormalities in cerebral white matter (Pietz, 1998; Malamud, 1966). Even with dietary control starting early in life, PKU patients of all ages have neuropsychological deficits, including deficient abstract reasoning, executive functioning, and information processing (Smith et al., 1991; Feldmann et al., 2002). MRI T2-weighted images can help reveal symmetrical hyperintense lesions present in the periventricular white matter of classic PKU patients (Philips et al., 2001; Schmidt et al., 1998; Surgita et al., 1990; Brismar et al., 1990; Budinchet et al., 1992; Pietz et al., 1996b; Cleary et al., 1995). These MR abnormalities seem to correlate most strongly with blood phenylalanine level within one year of MR imaging examination but not with intelligence quotient (Thompson et al., 1990; Cleary et al., 1994; Pearson et al., 1990; Bick et al., 1991; Pietz et al., 1996a). MR abnormalities are less marked in malignant PKU patients whose blood levels of phenylalanine are usually not elevated (Schmidt et al., 1998; Surgita et al., 1990; Brismar et al., 1990; Gudinchet et al., 1992; Pietz et al., 1996b; Cleary et al., 1995).

Previous PKU studies, using cerebral MR spectroscopy as a noninvasive modality to measure brain metabolite levels, revealed normal metabolite levels except for increase of phenylalanine (Pietz et al., 1996a; Johannik et al., 1994; Chien et al., 2002; Huttenlocher, 2000). Studies using diffusion-weighted MR imaging have shown changes in trace apparent diffusion coefficients (ADCs) and tortuosity (Philips et al., 2001; Deortova et al., 2001) in PKU patients. Diffusion tensor (DT) images can provide information about the nature of white matter changes and provide additional quantitative MR parameters for assessing and monitoring patients with malignant PKU. However, reports of DT imaging of PKU patients are scarcely found in literature. The purpose of this study is to evaluate 1) brain changes in malignant PKU patients using DT images and 2) their relationship to the intellectual development of patients older than three years of age.

三、結果與討論

Conventional MR

MR images disclosed focal high signal intensity in the bilateral parieto-occipital and central white matter on T2WI in all four patients younger than three years of age. These signal changes in the parieto-occipital and central white matter were not discrete and were similar to those found in unmyelinated parieto-occipital white matter of children. In the other eight patients, no definite signal changes were found on the axial FSE T2-weighted images.

DTI

None of the malignant PKU patients had decreased ADC as compared with the ADC of the control group. In the eight malignant PKU patients older than three years of age, EV2 (0.5961 ± 0.0483) and EV3 (0.4006 ± 0.0545) of the parieto-occipital and central white matter were significantly larger than the EV2 (0.5263 ± 0.0449) and EV3 (0.3473 ± 0.0503) in the control group ($p < 0.05$) (Table 1). FA of the parieto-occipital and central white matter (0.3206 ± 0.0528) was significantly smaller in the older PKU group than the control group (0.3954 ± 0.0788). However, no significant difference of EV1 and ADC in the parieto-occipital and central white matter existed between the study and control groups of

patients older than three years of age. In the frontal, fronto-parietal, and central white matter, and the anterior and posterior portions of the corpus callosum, the difference in all DTI parameters was not significant between PKU patients and controls older than three years of age. In the four patients younger than three years of age, DTI indices did not differ significantly between PKU patients and patients in the control group (Table 2).

Correlation between IQ test and DTI

For the seven patients receiving assessment of intelligence, VIQ (81 $\pm$ 18), PIQ (75 $\pm$ 18) and FSIQ (76 $\pm$ 19) were subnormal except for one patient. EV3 and ADC of the parieto-occipital, white matter were significantly correlated with VIQ ($r = -0.79$, $p = 0.04$) and PIQ ($r = -0.93$, $p = 0.03$), respectively. ADC and FA in the parieto-occipital white matter borderline correlated with FSIQ ($r = -0.76$, $p = 0.05$) and VIQ ($r = 0.75$, $p = 0.05$), respectively. No significant correlation existed between DTI indices at the other ROIs and all IQ tests.

Discussion

Our results indicate EV2, EV3 and FA of the parieto-occipital white matter were significantly different between the study and control groups of patients older than three years of age. The EV2 and EV3 were significantly larger and the FA smaller in the older malignant PKU patients than in controls. Although treated early, these chronic, stable malignant PKU patients still had abnormal findings in the parieto-occipital central white matter on DT images. In addition, EV3 and ADC of the parieto-occipital white matter were significantly negatively correlated with VIQ and PIQ, respectively. FA of the parietal and central white matter was positively correlated with VIQ. However, the trace ADC of the parieto-occipital and central white matter was negatively correlated with FSIQ. Similar studies applying DT images to evaluate PKU patients were difficult to find in literature.

PKU is an autosomal recessive disorder causing a broad spectrum of clinical and metabolic phenotypes, from classical PKU to mild hyperphenylalaninemia (Mallolas et al., 2000; Scriver, 1995; Lou et al., 1985; Pratt, 1979). Malignant PKU is a rare variant caused by dihydropteridine reductase deficiency, which induces hyperphenylalaninemia and deficiency in neurotransmitters such as 3,4-dihydroxyphenylalanine (DOPA) and 5-hydroxytryptophan. A defect in biopterin synthesis not only prevents the transformation of phenylalanine to tyrosine but also blocks the biosynthesis of dopamine, norepinephrine, and serotonin, causing severe neurological disturbances (Pietz et al., 1996b). Retarded development and intellectual impairment are the most consistent clinical findings in patients with PKU, although no single clinical risk factor is sufficient by itself to explain the brain manifestations (Longhi et al., 1987).

MR imaging studies on early, late and untreated classic PKU patients disclose frequent findings of white matter abnormalities even in neurologically asymptomatic patients (Thompson et al., 1990; Cleary et al., 1994; Pearsen et al., 1990; Bick et al., 1991; Pietz et al., 1996b; Lou et al., 1992). White matter changes seen on MR images in classic PKU patients seem to correlate most strongly with blood phenylalanine level when the MRI is performed (Thompson et al., 1990; Cleary et al., 1994). In spite of severe clinical findings, MR findings in malignant PKU patients are usually normal or almost normal (Brismar et al., 1990). However, subtle or quite different MR imaging findings, including subcortical cyst-like lesions and abnormal signal intensities in the periventricular white matter, are also found (Schmidt et al., 1998; Surgita et al., 1990; Brismar et al., 1990; Gudinchet et al., 1992; Pietz et al., 1996b; Chien et al., 2002). Most of our malignant PKU patients, like well-treated PKU patients, had subtle findings on FSE T2-weighted images. It was usually difficult to distinguish these findings from unmyelinated areas found normally in young children. In comparison, diffusion tensor images are more sensitive than FSE T2-weighted images for detecting abnormalities in the normal-appearing white matter of PKU patients. In addition, DT images can provide additional quantitative MR parameters for assessing and monitoring patients with malignant PKU. MR spectroscopy is another promising method for assessment of malignant PKU patients (Pietz et al., 1996a; Johannik et al., 1994; Chien et al., 2002). DT images can provide an overview of the changes in DT indices and help to guide MR spectroscopic sampling by localizing the most markedly changed areas.

Previous studies applying DT images to PKU patients were difficult to find, though DT images can provide information about the nature of parenchymal changes seen in T2-weighted images. The pathologic changes including impaired myelination, intramyelinic vacuoles, and gliosis (Huttenlocher, 2000) disclosed by previous studies in the brain of PKU patients do not suggest the typical demyelination (Malamud, 1966; Poser et al., 1959). Myelin proteins degrade more rapidly, especially at the regions, mostly at the parietal-occipital areas that myelinate late in life (Poser et al., 1959). Previous studies of diffusion-weighted images have shown that collisions between water molecules in PKU lesions are more distant than in controls (Dezortova et al., 2001). Water molecules may be forced to move by tortuous paths around obstacles such as a changed myelin structure (Dezortova et al., 2001), which hinders their motion. In comparison, DT images provide more diffusion parameters that help to disclose the underlying microscopic structural changes. The main pathway of free water molecule diffusion in the axonal direction did not change significantly, and no significant difference in EV1 was observed in malignant PKU patients. However, the path of free water molecules moving sideways could be much longer than the straight path. The significant increase in EV2 and EV3 in PKU lesions corresponds to an increased diffusion, but not along the main direction of diffusion. Although water molecules are not confined to the intracellular spaces in either PKU patients or control subjects, sideways diffusion is more prominent in PKU patients than controls. In the white matter of controls, diffusion tensor images showed strong anisotropy. However, the FA decreased in phenylketonurics, and water molecules in the parieto-occipital areas were more mobile than those of controls. The changes in EV2, EV3, and FA might be explained by changes in structures of myelin sheaths, which, presumably, have a different geometry in PKU patients than in control subjects. Changes of ADCs can be important in revealing acute changes including relatively recent increases in intracellular water content. The changes of DT indices were not apparently related to the elevation of blood levels of phenylalanine. None of our patients had high blood levels of phenylalanine, although changes in DTI indices were significant in malignant PKU patients older but not younger than three years of age. The failure to find significant changes in DTI indices in the younger PKU group could be due to small number of patients and smaller DTI parameters, including anisotropy in these patients.

MR image abnormalities seem not to correlate with intelligence quotient (Cleary et al., 1994; Pearsen et al., 1990; Bick et al., 1991). Several studies have shown no correlation between either IQ or the clinical stage of patients and MR findings (Cleary et al., 1994; Pearsen et al., 1990; Bick et al., 1991). Whether the cognitive loss in PKU can be explained by these MR image changes is unclear. Our results indicate that changes in DT indices including EV2, EV3 and FA are significant in patients without remarkable conventional MR imaging findings. In addition, our data also indicate that changes of VIQ, PIQ, and FSIQ are related to alterations of diffusion indices in the parieto-occipital white matter. These correlations probably reflect the diffuse pathologic white matter abnormalities, which may exert their effect through disruption of long corticocortical pathways. EV3 of the parieto-occipital white matter was particularly more sensitive than conventional MR images in demonstrating white matter changes in PKU patients and significantly correlated with their intellectual impairment.

Color schemes demonstrating the anisotropy of white matter are helpful to distinguish adjacent tracts with the same signal intensity on conventional MR images. However, some technical problems still exist in the present study. To compare PKU patients and controls, ROIs were chosen using anatomic landmarks shown on color maps of DTI rather than the corresponding T2-weighted abnormalities. Consequently, some ROIs inevitably contained both normal and abnormal tissue on color maps. In addition, the ROIs selected were limited to the supratentorial and central white matter because DTIs are greatly distorted within the posterior fossa owing to inhomogeneity of magnetic fields.

Conclusion

Our findings indicate that EV2, EV3, and FA maps are more sensitive tools than conventional MR images for demonstrating brain changes in PKU patients. DT images can also provide overview images helpful in guiding localization of MR spectroscopy and quantitative imaging follow-up of malignant PKU patients. However, the pathogenesis and clinical correlation of the lesions identified by this study certainly warrants further investigation.

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四、、計畫成果自評

1. This is the first study to find out the DTI changes of white matters in malignant PKU patients although the conventional MR imaging findings in these patients are quite subtle. The study can be a hint of applying DTI to several metabolic disorders involving the white matters.
2. The DTI findings are interestingly and possibly validated by the correlation with results of IQ tests.

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