MEDICAL PRACTICE

# Reversible posterior leukoencephalopathy syndrome in Chinese children induced by chemotherapy: a review of five cases

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**This is a retrospective review of the clinico-radiological features and neurological outcomes of reversible posterior leukoencephalopathy syndrome episodes in Chinese cancer children receiving chemotherapy in a regional hospital in Hong Kong from 1998 to 2008. Five children (3 males and 2 females) with a mean age of 7 years were identified, four of whom had acute lymphoblastic leukaemia and one had a central nervous system germ cell tumour. Presenting symptoms included seizures (100%), altered mental function (100%), headache (40%), and visual disturbance (60%). The mean systolic blood pressure at presentation was 158 mm Hg. Approximately 80% had typical radiological features of reversible posterior leukoencephalopathy syndrome. All showed complete recovery after the acute stage, but one subsequently developed epilepsy. Two patients ultimately died of refractory malignant disease. Two others were followed up for a mean of 6 years, and remained neurologically normal. This report was the first case review documenting reversible posterior leukoencephalopathy syndrome in Chinese cancer children. The clinico-radiological features and neurological outcomes were similar to those reported in western series. Early recognition of the syndrome is important to facilitate appropriate treatment. The central nervous system damage may not be reversible and thus long-term follow-up is warranted.**

## Introduction

Reversible posterior leukoencephalopathy syndrome (RPLS), also known as posterior reversible encephalopathy syndrome, was a term first used by Hinchey et al[1] in 1996 to describe a distinct clinico-radiological entity comprising headache, seizures, visual disturbance, and altered mental function associated with symmetrical posterior cerebral white matter oedema. The syndrome is thought to be reversible in the majority of the cases upon control of hypertension and the underlying precipitating factor.[1,2] Imaging of the brain typically shows symmetrical hemispheric oedema predominantly in bilateral parieto-occipital regions.[3] Other cortical regions, as well as the cerebellum, brainstem and basal ganglia, may also be affected.[4] The pathophysiology of RPLS is not fully understood, but is believed to be related to failure of cerebral auto-regulation leading to vasogenic oedema.[1,3-6] It has been associated with a number of clinical conditions including hypertension, eclampsia and immunosuppressive therapy.[1] While there is increasing awareness of RPLS and high-dose multi-drug cancer therapy, we reviewed its clinical presentation, initial and follow-up radiological features as well as the neurological outcome in Chinese paediatric patients who developed this syndrome while receiving cytotoxic chemotherapy for cancers.

**Key words**
Antineoplastic combined chemotherapy protocols; Child; Magnetic resonance imaging; Posterior leukoencephalopathy syndrome; Seizures

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## Methods

All children with cancers who received chemotherapy and diagnosed to have RPLS between 1 January 1998 and 31 December 2008 at Tuen Mun Hospital, Hong Kong were included. They were identified using Clinical Management System (CMS), out-patient records and the Clinical Development and Reporting System (CDARS). The latter used a text-retrieval system that searches the final diagnosis in the electronic clinic notes for coded text. We started recruiting patients by using both CMS and CDARS to identify all patients admitted to the paediatric unit with the following ICD-9 codes: 323.9 for leukoencephalopathy, 780.32 for convulsion, 780.09 for unconsciousness/loss of consciousness, 369.9 for drug-related visual impairment. We then narrowed down our search by only recruiting those patients who had previous admissions with the above codes and were admitted under the subspecialty code PHO which stands for paediatric haematology-oncology. Then the case summary of each patient was reviewed and cases were included if the corresponding

## 因化療引致的可逆性後部白質腦病綜合徵：五名華籍小兒患者的病例回顧

從1998年至2008年期間，於一所分區醫院內因癌症接受化療並確診患有可逆性後部白質腦病綜合徵的五名華籍小童，本研究對他們的臨床放射症狀及腦神經表現作病例回顧。五名小童分別為三男二女，平均年齡7歲。其中四人有急性淋巴細胞性白血病，一人有中樞神經系統生殖細胞瘤。他們的症狀包括癲癇發作（100%）、意識障礙（100%）、頭痛（40%）及視覺障礙（60%）；病發時平均收縮壓為158 mm Hg。約有八成患者出現可逆性後部白質腦病綜合徵的典型影像特徵。所有患者在急性期過後完全康復，只有一位患者隨後有癲癇發作。兩名患者最終因難治性惡性疾病死亡。其餘兩名患者的神經系統在六年的隨訪期內仍然保持正常。本文是對華籍小兒癌症患者的可逆性後部白質腦病綜合徵的首個病例回顧，患者的臨床放射症狀及腦神經表現與西方文獻相若。及時有效的治療對診治此症相當重要。此外，由於中央神經系統的破壞可以是永久性，因此長期的隨訪是需要的。

clinical picture matched the definition of RPLS.

The demographic data, underlying malignant diseases, chemotherapeutic agents used, presenting symptoms, blood pressure values, initial and follow-up electroencephalograms and neuroimaging findings, and neurological outcomes were collected for each patient.

## Results

We identified five episodes of RPLS in 5 patients (3 males) with a mean age of 7 (range, 4-11) years at presentation (Table). Four patients had acute lymphoblastic leukaemia (ALL) and one had a pituitary germ cell tumour. Three of those with ALL developed RPLS while receiving re-induction chemotherapy according to the I-BFM 2002 protocol. Re-induction chemotherapy (protocol II) was given approximately 5 months after diagnosis and lasted 7 weeks. It consisted of dexamethasone, vincristine, doxorubicin and L-asparaginase in protocol IIa; and cytarabine, cyclophosphamide and 6-thioguanine in protocol IIb. These three patients developed symptoms during the protocol IIa phase of their chemotherapy. The remaining patient with ALL was receiving consolidation chemotherapy (High Risk Block 1) according to the I-BFM 2002 protocol, which lasted 11 days and consisted of dexamethasone, vincristine, L-asparaginase, methotrexate and cytarabine, and was given at week 12 after the diagnosis. The patient with the pituitary germ cell tumour was treated with BEP (cisplatin, etoposide and bleomycin).

Clinical seizures occurred in all five patients; in two of them the onset was focal. Altered mental state was also present in all five patients, two of whom had headaches and three had visual disturbance. The mean peak systolic blood pressure at presentation was 158 mm Hg (range, 148-165 mm Hg).

Magnetic resonance imaging (MRI) of the brain was performed for all the patients within 1 week of presentation. Typical RPLS findings were found in four of the cases, and consisted of bilateral symmetrical grey matter and subcortical white matter lesions in cerebral hemispheres, in particular at parietal and occipital lobes (Fig a), and one had abnormal T2-weighted hyperintense bilateral frontal lobe white matter lesions (Table).

All of the patients had a complete clinical

TABLE. Case summary of patients with reversible posterior leukoencephalopathy syndrome*

| Patient No. | Sex/age (years) | Cancer type | Chemotherapy | Clinical symptoms | BP (mm Hg) | Time of resolution of clinical features |
|---|---|---|---|---|---|---|
| 1 | F/7 | Pituitary germ cell tumour | Cisplatin, etoposide, bleomycin | Seizure, HA, VD, AMF | 158/100 | Seizure ceased: 1 hour<br>Normal vision: 6 hours<br>Full consciousness: 2 hours<br>Normal BP: 2 days |
| 2 | M/4 | ALL | Dexamethasone, doxorubicin, vincristine, L-asparaginase | Seizure, HA, AMF, hyporeflexia | 148/90 | Seizure ceased: 5 min<br>Full consciousness: 2 hours<br>Normal BP: 1 day |
| 3 | M/11 | ALL | Dexamethasone, vincristine, methotrexate, cytarabine, L-asparaginase | Seizure, AMF, VD | 165/101 | Seizure ceased: 10 min<br>Normal vision: 2 days<br>Full consciousness: 3 days<br>Normal BP: 3 days |
| 4 | F/8 | ALL | Dexamethasone, doxorubicin, vincristine, L-asparaginase | Seizure, AMF, hyporeflexia | 165/108 | Seizure ceased: 30 min<br>Full consciousness: 3 hours<br>Normal BP: 3 days |
| 5 | M/4 | ALL | Dexamethasone, doxorubicin, vincristine, L-asparaginase | Seizure, AMF, VD | 155/106 | Seizure ceased: 20 min<br>Normal vision: 3 days<br>Full consciousness: 1 day<br>Normal BP: 2 days |

* ALL denotes acute lymphoblastic leukaemia, AMF altered mental function, BP blood pressure, EEG electroencephalogram, HA headache, MRI magnetic resonance imaging, NA not available, VD visual disturbance

recovery upon receiving antihypertensive therapy, anti-epileptic therapy, and discontinuation of the possible offending drugs. Follow-up MRI of the brain was performed within 1 month of presentation. Complete resolution of the grey matter and subcortical white matter lesions (Fig b) was observed in three patients (Nos. 1, 2, and 4). While residual abnormal T2-weighted hyperintense signal changes were noted in patients 3 and 5, who had no further follow-up MRIs; patient 3 died shortly afterwards due to refractory disease, and patient 5 had no clinical neurological deficit.

No patients had recurrence of RPLS, despite subsequent continuation of chemotherapy. However, patient 4 went on to develop refractory epilepsy; an MRI of the brain performed 7 years later revealed right mesial temporal sclerosis. Two patients (Nos. 1 and 3) later died of refractory malignant disease.

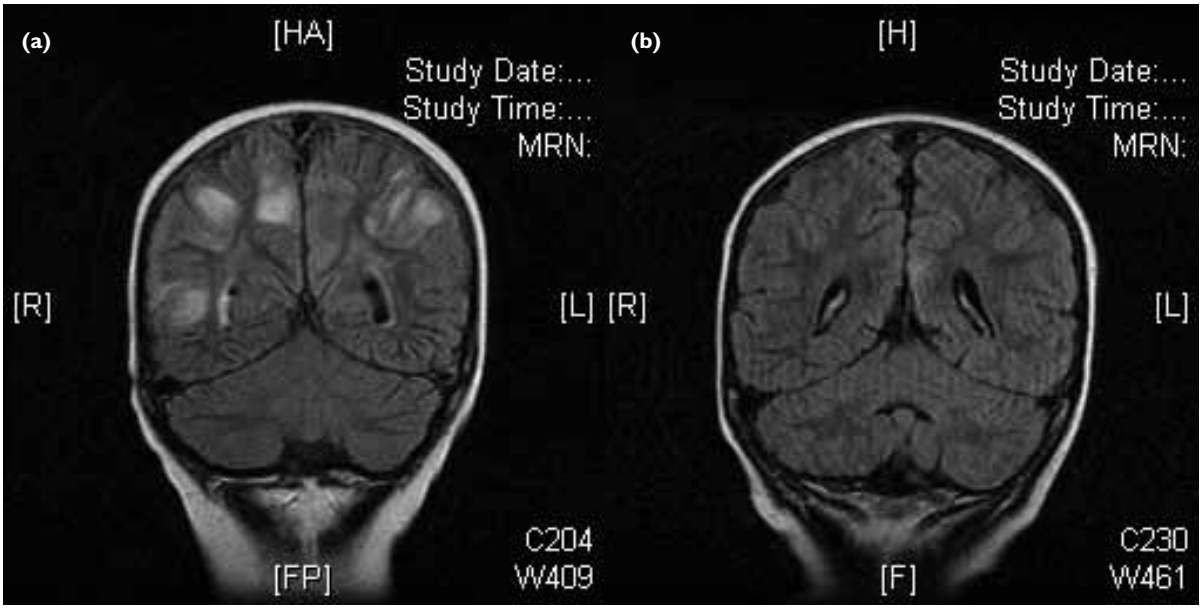


**FIG. Magnetic resonance images of the brain in patient No. 2**
(a) At presentation: coronal T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence showing bilateral cortical and subcortical white matter oedema at parieto-occipital lobes, and (b) at follow-up: coronal T2-weighted FLAIR sequence showing complete resolution of the white matter oedema

| EEG findings at presentation | MRI findings at presentation | MRI findings within 4 weeks | Long-term sequelae |
|---|---|---|---|
| Post-ictal changes and some intermittent slow waves | Bilateral symmetrical cortical and subcortical white matter oedema at parietal and occipital lobes | Complete resolution | Died of relapsed brain tumour |
| Left posterior sharp slow waves | Bilateral symmetrical cortical and subcortical white matter oedema at bilateral parietal and occipital lobes | Complete resolution | None |
| No epileptiform discharge | Extensive bilateral symmetrical cortical and subcortical white matter oedema in both cerebral hemispheres | Residual abnormal T2-weighted hyperintense subcortical white matter lesions at bilateral occipital lobes | Died of refractory leukaemia |
| NA | Bilateral symmetrical white matter oedema at frontal lobe | Complete resolution | Epilepsy<br>(MRI brain 7 years later: right mesial temporal sclerosis) |
| Posterior sharp slow waves | Bilateral symmetrical white matter oedema at parietal and occipitotemporal lobes | Small focal infarcts at right occipital lobe | None |

Patients 2 and 5 remained neurologically stable after a mean follow-up of 6 years.

## Discussion

Reversible posterior leukoencephalopathy syndrome was first described by Hinchey et al[1] in 1996 in 15 patients, of whom seven were on immunosuppressive therapy. Over the years, RPLS has been known by other names including: posterior reversible encephalopathy syndrome, reversible occipital-parietal encephalopathy,[7] posterior leukoencephalopathy syndrome, hyperperfusion encephalopathy, reversible encephalopathy, occipital-parietal encephalopathy, and reversible posterior cerebral oedema syndrome.[8] Reversible posterior leukoencephalopathy syndrome is characterised by subacute or acute onset of headache, altered consciousness and behaviour, and visual disturbance (ranging from blurred vision to total cortical blindness); seizures are common and usually herald onset of the syndrome.[1,5,9] In our case review, three of the five cases had such classical symptoms, which were similar to previous descriptions in the paediatric literature.[6] Focal neurological deficits are uncommon[1,8] as agreed in our cases. Typical radiological features are bilateral symmetrical predominant white matter oedema affecting parietal and occipital lobes, frontal lobes, inferior temporo-occipital junctions and the cerebellum, and resemble brain watershed zones.[1,9] The cortex is involved to varying degrees. Partial, asymmetric, or mixed patterns may be encountered, which can be a diagnostic challenge. Magnetic resonance diffusion-weighted imaging is used to offer a prognosis, as focal areas of restricted diffusion indicate infarction and hence signifying an adverse outcome.[10] The majority of the patients show complete or near-complete resolution of clinical and radiological abnormalities within days to weeks.[1,4] In a case series involving 36 adults, 66% of the patients showed complete resolution of the imaging abnormalities, occurring as early as 5 days after the onset.[4] Only three of our patients showed complete radiological resolution in their follow-up MRIs 4 weeks later, while two showed residual abnormalities without any obvious neurological deficit.

The true incidence of RPLS is unknown, but it affects age-groups ranging from 2 to 78 years.[4,9] It is commonly associated with hypertensive encephalopathy, eclampsia, renal failure, and the use of immunosuppressive therapy.[1,5] In our paediatric oncology patients, we only focused on RPLS induced by chemotherapy. So far, Morris et al[11] have described the largest paediatric series in cancer children and included 11 children.

The pathophysiology of RPLS still remains unclear. Sudden elevations in blood pressure exceeding the auto-regulatory capacity of the brain and direct or indirect cytotoxic effects of immunosuppressive agents on the vascular endothelium have both been implicated. Both lead to a breakdown of the blood-brain barrier with transudation of fluid and haemorrhage. The preferential involvement of the parietal and occipital lobes is believed to be related to the relative sparse sympathetic innervation of the posterior circulation.[1] Whatever the aetiology, whether multi-factorial or not, the key feature seems to be vascular endothelial damage. Predilection of the white matter rather than grey matter has been hypothesised due to the tightly packed cortex as compared to white matter, which results in water accumulation.

Another more recently proposed pathophysiology involves cortical spreading depression (CSD) which is a phenomenon similar to that occurring in migraines. Sánchez-Carpintero et al[12] performed single-photon emission computed tomography scans on three children who developed RPLS while receiving treatment for osteosarcoma, and demonstrated hypoperfusion of the parietal-occipital regions of the brain. Although CSD is a phenomenon which is as yet not completely understood, it is known that hypomagnesaemia is strongly associated with its development.

A review of paediatric oncology literature showed an increasing awareness of RPLS as a complication of cancer treatment.[5-7,12-14] No single chemotherapeutic agent or therapeutic regimen has been identified as causal and consistently associated. Implicated drugs include cisplatin,[15] cyclosporine,[16] or gemcitabine[17] as well as combinations of doxorubicin, L-asparaginase, cyclophosphamide, vincristine, corticosteroids, ifosfamide, etoposide and cytarabine.[5,13,14] One of our patients (patient 1) received cisplatin and etoposide. Three patients received a combination of dexamethasone, vincristine, L-asparaginase and doxorubicin. It will be difficult to identify which agent is the culprit. An important observation was that four of our patients received high doses of steroids during the re-induction and induction phase for ALL. High-dose steroids may trigger RPLS directly or indirectly by contributing to steroid-induced hypertension.

Once RPLS has been diagnosed, it is essential to provide supportive (including intensive care unit) care and aggressive treatment of seizures, hypertension, and electrolyte imbalances. Hypertension is a common feature in most reported cases complicating cytotoxic chemotherapy.[13,15,18] In contrast to malignant hypertension-induced encephalopathy, patients with RPLS usually present with only moderately high blood pressure, representing a significant increase above baseline values. In our series, the mean systolic blood pressure at presentation was 158 mm Hg (range, 148-165 mm Hg). Antihypertensive

agents could be successfully tailed off over a period of 10 to 14 days. Anti-epileptic agents should also be started as soon as possible to control the acute event. Currently, there is no evidence that the continuation of anti-epileptic drug therapy prevents the development of late seizures after brain injury.[19] In all our patients without any recurrence of seizure, anti-epileptic drugs were tapered off over a period of 10 days to 3 months.

Whether the associated offending cytotoxic drugs should be withdrawn from the chemotherapy regimen is still debated. Lucchini et al[19] reported RPLS developed in 12 children with cancers. All of them continued their scheduled therapeutic regimen after the complete resolution of the acute neurological event, and none reported recurrence of the symptom. In patient 1, cisplatin was subsequently replaced by carboplatin for the remaining chemotherapy cycles. In the remaining four cases, chemotherapy was continued as scheduled after the acute event resolved. All patients ran the uneventful courses. Changing the chemotherapeutic agent or decreasing the dosage of certain chemotherapeutic agents may alter treatment outcomes of the underlying disease. However, the risk of RPLS recurrence during re-challenging with the same chemotherapeutic agents is surely an area to be explored. Furthermore, the potential role of prophylactic anti-epileptic or anti-hypertensive agents in the prevention of RPLS during further chemotherapy is another major unresolved issue.

Most reported RPLS cases in the past were fully reversible in a matter of days to weeks, with timely control of blood pressure. However, prolonged seizures, high blood pressure, or both may result in permanent neurological disability and cerebral infarction. Kwon et al[9] reported one of 12 patients with small haemosiderin deposits on follow-up MRI had neurological sequelae. The mesial temporal sclerosis presenting as epilepsy detected 7 years after the event (patient 4) could also have been due to the consequences of prolonged seizures from RPLS. Lucchini et al[19] reported late epilepsy in 33.3% of their sample.

In general, vasogenic oedema is considered to account for the pathophysiology and symptoms of RPLS, but the presence of cytotoxic oedema is the main prognostic factor for the condition as it signifies irreversible brain injury. Diffusion-weighted imaging becomes important in making such diagnosis by detecting abnormal hyperintense signal changes in involved areas, as shown by Ay et al.[20] In two of our cases, follow-up MRIs 1 month later showed persistent signal changes in the involved areas on diffusion-weighted imaging but clinically the child did not endure any neurological deficit.

## Conclusion

In conclusion, RPLS is an underappreciated complication in cancer children receiving cytotoxic therapy. Brain MRI is the most appropriate radiological modality to document the central nervous system features and it should be performed as soon as possible. The syndrome is potentially reversible with prompt treatment and therefore early recognition during cancer therapy of children is essential to prevent irreversible brain damage and long-term neurological sequelae. Late complications may be noted years after the initial insult. Long-term follow-up of involved patients is advocated and should entail regular clinical and radiological surveillance.

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