The role of positron emission tomography/CT in hypoxic ischaemic encephalopathy in children

Zehra Pinar Koc,¹ Tansel Ansal Balci,¹ Saadet Akarsu,² Kemal Unal³

¹Department of Nuclear Medicine, Firat University Hospital, Elazig, Turkey

²Department of Pediatric Haematology, Firat University Hospital, Elazig, Turkey

³Department of Nuclear Medicine, Training Hospital, Elazig, Turkey

Correspondence to

Dr Zehra Pinar Koc,
zehrapinarkoc@gmail.com

SUMMARY

The role of positron emission tomography/CT (PET/CT) in diagnosis and follow-up of newborns with hypoxic ischaemic encephalopathy has been documented before; however, this is the first presentation of elder children with both diagnostic and follow-up PET/CT results as far as we know.

BACKGROUND

Hypoxic ischaemic encephalopathy can cause permanent damage to the brainstem of the growing child. The damage at the end of the disease process is usually unpredictable by means of morphological imaging methods. Functional imaging methods, especially positron emission tomography (PET) imaging, can provide prognostic information which is important for management of the patients.¹ Different therapeutic interventions have been carried out in special groups.²

PET imaging patterns of possible clinical presentations of hypoxic ischaemic encephalopathy (HIE) are particularly well understood in infants. Cerebral palsy (CP) is the most common presentation of HIE after the disease process which has a wide spectrum of clinical features. Previous studies about infantile HIE have shown that PET imaging patterns might help with the prediction of which type of CP will appear after the HIE period.³ Also, PET imaging can provide information regarding cerebral blood flow, receptor concentration or metabolism of brain tissue. All these different investigations provide information about different potential mechanisms of CP types. Specifically, fluorodeoxyglucose PET shows glucose metabolism of brain tissues and shows metabolic alterations during ischaemia (perinatal ischaemia). Specific hypometabolism patterns might predict which type of CP would occur in the infants.

One of our patients was an exceptional case who was 5 years old and aetiology of HIE was probably adult respiratory distress syndrome (ARDS). She was also exceptional with her outcome; full recovery. Although the patient was at a different age group at the time of diagnosis, and aetiology of HIE was different, PET imaging pattern at the time of diagnosis and follow-up was the same as with previous HIE reports.

CASE PRESENTATION

Case 1

A 5-year-old girl with diagnosis of (CALLA+) B-cell acute lymphoblastic leukaemia (B-ALL) is presented in this report. Chemotherapy protocol of Children's Oncology Group AALL0331 standard risk B-precursor acute lymphoblastic leukaemia was

started to the patient without cranial radiation therapy. Remission was observed in the treatment course. Eighteen months later, in the maintenance status febrile neutropenia and additionally ARDS ($\text{PaO}_2/\text{FiO}_2 < 100$) and HIE occurred. The patient was followed up in the intensive care unit because she needed ventilation support. Neurological examination revealed no response to verbal and tactile stimulation; additionally, unconsciousness and myoclonic seizures were observed. Spasticity of all the extremities was also observed and the diagnosis of HIE was confirmed according to clinical, physical examination findings and EEG^{4,5} which confirms HIE with severe bioelectrical impairment in both the hemispheres. She received Valproate treatment because of seizure activity in left centrofrontal region for 6 months.

PET/CT imaging was performed to obtain prognostic information and revealed diffuse hypometabolism of cerebral cortex and bilateral hypermetabolism of subcortical nuclei (figure 1A). Control PET/CT scan in the sixth month revealed normalisation of cortical uptake but hypometabolism of subcortical nucleus compared with age-matched normal study (figure 1B,C). The chemotherapy of the patient is completed and she is in remission without treatment and without any neurological sequel in 6-month follow-up.

Case 2

A 2.5-year-old girl with diagnosis of CALLA (+) B-ALL received chemotherapy protocol of Children's Oncology Group AALL0331 standard risk B-precursor acute lymphoblastic leukaemia without cranial radiotherapy. At the standard interim maintenance stage (in the third month after the beginning of chemotherapy), febrile neutropenia and additional ARDS occurred. Metabolic/respiratory acidosis, bradycardia, hypotension and multiple organ insufficiency (increased aspartate aminotransferase, alanine aminotransferase, bilirubin, urea and creatinine levels and oliguria) and encephalopathy (unconsciousness, spasticity predominantly in the upper extremities and abnormal reflexes) were observed. Her cranial CT was near normal; however, in EEG, severe brain activity impairment was present which confirmed HIE with clinical and physical examination findings. PET/CT was performed in order to obtain prognostic information and PET/CT study of the patient revealed right predominant bilateral hypermetabolism of subcortical nuclei (figure 1D). The neurological findings regressed in 20 days. She is still receiving chemotherapy.

All patients' SUVmean and SUVmax levels with corresponding cerebellum levels are given in (table 1).

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Figure 1 (A) Transaxial positron emission tomography (PET) image of first patient during hypoxic ischaemic encephalopathy (HIE) period. (B) Transaxial PET image of first patient at follow-up. (C) Normal brain PET image of same age subject. (D) Transaxial PET image of second patient.

OUTCOME AND FOLLOW-UP

Outcome of the first patient was unexpectedly complete recovery, but second patient's follow-up imaging has not been performed yet and clinical status is stable with minimal neurological deficit on the right side.

DISCUSSION

The mechanism of damage in brain tissue, as a consequence of HIE, is well understood owing to studies in newborns. It has been postulated that cortical brain damage is mainly restricted to areas of great glucose consumption and primary myelination; thalamus, basal ganglia and spinal cord.⁶ This theory is also realised in our patients' PET images which is a reflection of glucose metabolism. Our patients' subcortical nuclei were firstly hypermetabolic and this increased metabolism fades at the end of the disease process. This metabolism pattern was also described in an infant with long-term follow-up.² Our patients were the first patients with follow-up PET images of elder age onset of HIE.

Flow studies with PET tracers have also demonstrated focal increase of regional cerebral blood flow (CBF) at focal seizure site in an infant with HIE.⁷ Another CBF analysis study has

shown increased blood flow to the basal ganglia in infants with HIE and has confirmed this finding with postmortem examination.⁸ Also, a previous study has shown that there was a negative correlation with childhood IQ and CBF.⁹ Newborn studies have also demonstrated that prognostic information regarding HIE might be achieved earlier by means of PET than morphological imaging methods.¹⁰ Our patients also had hypermetabolism of the basal ganglia during the HIE period and, probably, this is a consequence of increased blood flow to those areas indicating local damage. This finding has been attributed to worse outcome for a previous case and other newborn studies.^{2, 8} However, our patients' outcome was full recovery, which is exceptional, and this pattern was also observed in other patients. This pattern may predict better outcome in elder patients. This issue needs to be evaluated with prospective studies.

A PET study in elder patients with brain injury has indicated that, although the oxygen extraction fraction increases and CBF decreases during the disease process, cerebral glucose metabolism does not alter.¹¹ These patients were elder patients and probably have different pathogenesis compared with children with HIE. As we mentioned earlier, these are the first cases with non-infant HIE and children.

Kannan *et al*¹ have evaluated different clinical features of HIE in newborns and also PET applications in different clinical outcomes in their review and have concluded that PET imaging can provide additional important information in HIE of infants. These are stages of HIE; although severe and mid-forms do not improve, mild forms may improve, as reported in a previous study in transplantation patients.¹² Maybe in the future, PET imaging can be addressed to all patients with HIE patients of all age groups to discriminate between mild, mid and severe forms to

Table 1 Maximum SUV values of patients

	R Caudate/R Cingulate*
Case 1	7,4/4,7
Control case 1	12,5/16,2
Case 2	6,2/3,4

determine patients which might recover. Our cases show that PET imaging in a child with HIE is a possible new area to investigate.

Learning points

- Hypoxic ischaemic encephalopathy (HIE) might occur as a complication during chemotherapy of patients with haematological malign diseases.
- Positron emission tomography /CT can give prognostic information about patients with HIE, and also about non-infant patients.
- Although it is exceptional, full recovery can happen in follow-up of patients with HIE.

Competing interests None.

Patient consent Obtained.

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