Original article

Brain Perfusion SPECT in Juvenile Neuronal Ceroid Lipofuscinosis

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Abstract

The juvenile neuronal ceroid-lipofuscinosis (JNCL) is a recessively inherited progressive encephalopathy. We studied 21 JNCL patients with a duration of illness of 1 to 17 years by ^{99m}Tc-HM-PAO single photon emission computed tomography (SPECT) and correlated the findings with clinical parameters. All patients had at least one hypoperfused brain area, the median number of such areas was 5 per patient. Parietally, occipitally, and in the cerebellar lobes hypoperfusion was usually mild whereas it was temporally more severe. Right parietal hypoperfusion correlated to neurological dysfunction.

Key words

Juvenile neuronal ceroid lipofuscinosis – Single photon emission computed tomography

Introduction

The juvenile neuronal ceroid-lipofuscinosis (JNCL) is a progressive encephalopathy characterized by visual failure, epilepsy, dysarthria, extrapyramidal symptoms, ataxia, and dementia. The onset takes place by 4 to 7 years and the disease leads to death usually before 30 years of age. The pathogenesis of this form, with substantial phenotypic variation (10, 15) is yet unknown. The defective gene on chromosome 16 (4) has recently been identified but its function is not known (17).

Relatively few reports on functional neuroimaging findings on JNCL patients exist. The most commonly reported findings on CT and MRI are symmetric supratentorial and infratentorial brain atrophy and white matter abnormalities on MRI (1, 12, 14). On ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) thalamic hypometabolism, as well as cortical hypometabolism in the more posterior parts of the brain have been observed (3, 13).

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Abnormalities of the brain metabolism are closely linked to abnormalities in perfusion, which can be assessed by using single photon computed tomography (SPECT) and the lipophilic blood flow tracer ^{99m}Tc-labelled hexamethylpropyleneamine oxime (HMPAO). This technique allows the assessment of the distribution of brain perfusion tomographically. Here, we characterize the encephalopathy of JNCL by correlating the SPECT and clinical findings of 21 patients.

Material and methods

We studied 21 JNCL patients (15 male, 6 female) aged 8 to 28 years (mean 13.9 years) with a duration of illness of 1 to 17 years (mean 6.9 years). The diagnosis was confirmed in all cases by a typical clinical course, vacuolated lymphocytes on a peripheral blood smear, and typical electron microscopic histopathological appearance in rectal biopsy specimen (15). Visually analyzed perfusion findings of 6 patients without semiquantitation or clinical correlation have been previously reported (7).

All patients had been treated with antioxidants (16). Seven patients were on anticonvulsive medication.

For correlation of clinical status with the perfusion findings motor performance, balance, co-ordination, speech, epilepsy and activities of daily life (ADL) were scored into five scores as described earlier (16).

SPECT imaging was done with the same equipment and procedure as described in part 1. A dose of 222–537 MBq ^{99m}Tc-HMPAO depending on the patient's weight was used.

The perfusion tomograms were analyzed semiquantitatively with the cerebellum as reference: 46 regions of interest (ROI) were drawn on 7 adjacent transversal tomographic slices. The mean count densities were used for the semiquantitative calculations. *Lassen*'s linearity correction algorithm was used (19). For determining abnormal ROI values, 20 controls were used for determining the normal range of the semiquantitated supratentorial regional blood flow. The ROI values were expressed as Z-scores (8, 9) and individual Z-score values greater than 2 were considered abnormal. The most abnormal Z-value in each cerebral lobe was subsequently used for correlating perfusion findings with clinical parameters.

Because JNCL patients have cerebellar pathology, which also affects the cerebellar perfusion (thus, affecting also the semiquantitation results), the semiquantitative assess-

ment was additionally verified by a visual assessment done blindly by two viewers. The perfusion in cerebellar hemispheres, frontal, temporal, parietal, and occipital cortex was visually scored into normal, moderate, and marked hypoperfusion. In cases of discrepancy, the less abnormal assessment was included in the analysis. The semiquantitative and visual assessments of the supratentorial brain regions correlated well (*Spearman* r ranging from 0.66 frontally to 0.89–0.93 in other areas).

Spearman's rank order correlation was used for calculating correlation coefficients between each SPECT and clinical variables and the significance were tested using the chi-square test.

The study had been approved by our hospital's ethics committee and informed consent was obtained from the patient and the patient's parents.

Results

All patients had at least one brain area where the perfusion was abnormal. The median number of hypoperfused areas was 5 per patient (range 1–8) in the visual analysis and 7 per patient (range 1–12) in the semiquantitative analysis. The more severely hypoperfused areas had on the average 72% of the perfusion measured from the normal controls. Milder forms of hypoperfusion were most commonly found at the parietal and occipital lobes and the cerebellum. The more severe changes were found mostly at the temporal lobes (Table 1). Although asymmetries in brain perfusion were common in single cases, there was no constant side to side difference in any brain area. Neither were there any constantly affected preferential areas in form of a "pattern" of hypoperfusion on a group level. Qualitatively, some patients had bilateral posterior temporal and parietal hypoperfusion (Fig. 1b). Illustrative images are shown in Figure 1.

The correlations between semiquantitative SPECT analysis and clinical variables are given in Table 2. The impairment of motor skills correlated best with right parietal abnormalities. Difficulties in maintaining balance was associated with a large total number of perfusion abnormalities, and thus correlated with perfusion abnormalities in most brain areas. Impairment of speech also coincided with the increase in total number of perfusion abnormalities. The worsening of the skills of co-ordination did not correlate with cerebellar pathology, but correlated with frontal and parietal abnormalities. The need for assistance as measured by ADL correlated with the total number of perfusion abnormalities as well as with temporal and parietal abnormalities. There was also a tendency, although not statistically significant ($r = 0.35$, $p = 0.11$), to a larger total number of abnormally perfused brain areas in patients with a long duration of disease.

In the visual assessment we found a good agreement with the semiquantitative analysis. The visual analysis resulted in a smaller total number of brain areas regarded as abnormal than the semiquantitative assessment. This was

Table 1 The number of abnormally hypoperfused areas of patients with JNCL in ^{99m}Tc-HMPAO SPECT in visual and semiquantitative evaluation.

Lobe	Type of assessment	Left side normal	moderate	marked	Right side normal	moderate	marked
Frontal lobes	visual:	19	2	0	17	4	0
	semiquantitative:	12	9	0	13	8	0
Temporal lobes	visual:	6	9	6	6	8	7
	semiquantitative:	5	7	9	6	8	7
Parietal lobes	visual:	13	8	0	11	10	0
	semiquantitative:	13	7	1	9	8	4
Occipital lobes	visual:	5	13	2	6	13	2
	semiquantitative:	5	9	7	6	11	5
Cerebellar hemispheres	visual:	6	13	2	6	13	2
	semiquantitative:	N. D.	N. D.	N. D.	N. D.	N. D.	N. D.

N. D. = not done

Table 2 The correlation of clinical characteristics and semiquantitatively analyzed ^{99m}Tc-HMPAO SPECT images in patients with JNCL.

	Total number of defects	Frontal r/l	Temporal r/l	Parietal r/l	Occipital r/l	Cerebellar r/l (visual assessment)
Duration of illness	ns	ns	ns	ns	ns	0.47, 0 = 0.033
		ns	ns	ns	ns	0.47, p = 0.033
Motor skills	ns	ns	ns	0.48, p = 0.27	ns	ns
		ns	ns	ns	ns	ns
Balance	0.58, p = 0.006	0.49, p = 0.023	0.49, p = 0.022	0.58, p = 0.006	0.48, p = 0.026	ns
		0.57, p = 0.007	ns	ns	0.47, p = 0.032	ns
Co-ordination	0.49, p = 0.025	ns	ns	0.53, p = 0.013	ns	ns
		0.47, p = 0.030	ns	ns	ns	ns
Speech	0.69, p = 0.0004	0.51, p = 0.018	0.54, p = 0.012	0.61, p = 0.003	0.58, p = 0.005	0.57, p = 0.007
		0.65, p = 0.001	0.57, p = 0.007	0.51, p = 0.017	0.55, p = 0.010	0.57, p = 0.007
Epilepsy	ns	ns	ns	ns	ns	ns
		ns	ns	ns	ns	ns
Activities of daily living	0.61, p = 0.004	ns	0.44, p = 0.047	0.50, p = 0.020	ns	ns
		ns	0.45, p = 0.041	0.48, p = 0.029	ns	ns

especially so in the frontal lobes, which were visually assessed mostly as normal or slightly abnormal, but were twice as often abnormal in the Z-score comparison. The cerebellar perfusion was regarded as abnormal in 15/21 (75%) patients and abnormalities correlated with long duration of illness.

Discussion

Due to ethical reasons our control group consisted of young adults and was on average 5.2 years older than the patient group. The patients were at least 8 years of age; in this age the distribution of brain perfusion is similar to that of adults. Thus, we think that such a comparison has not increased the likelihood of erroneously detecting hypoperfusion in patients, as also the semiquantitative and visual analyses were in agreement.

There was no specific perfusion distribution pattern for JNCL. Hypoperfusion in all parts of the brain, but mainly in the posterior regions without manifest frontal pathology were found in JNCL. Our results agree with those of the two previously published investigations on brain metabolism (3, 13). No cases of increased focal perfusion as seen in epilepsy were seen. Thus, although patients with JNCL frequently have

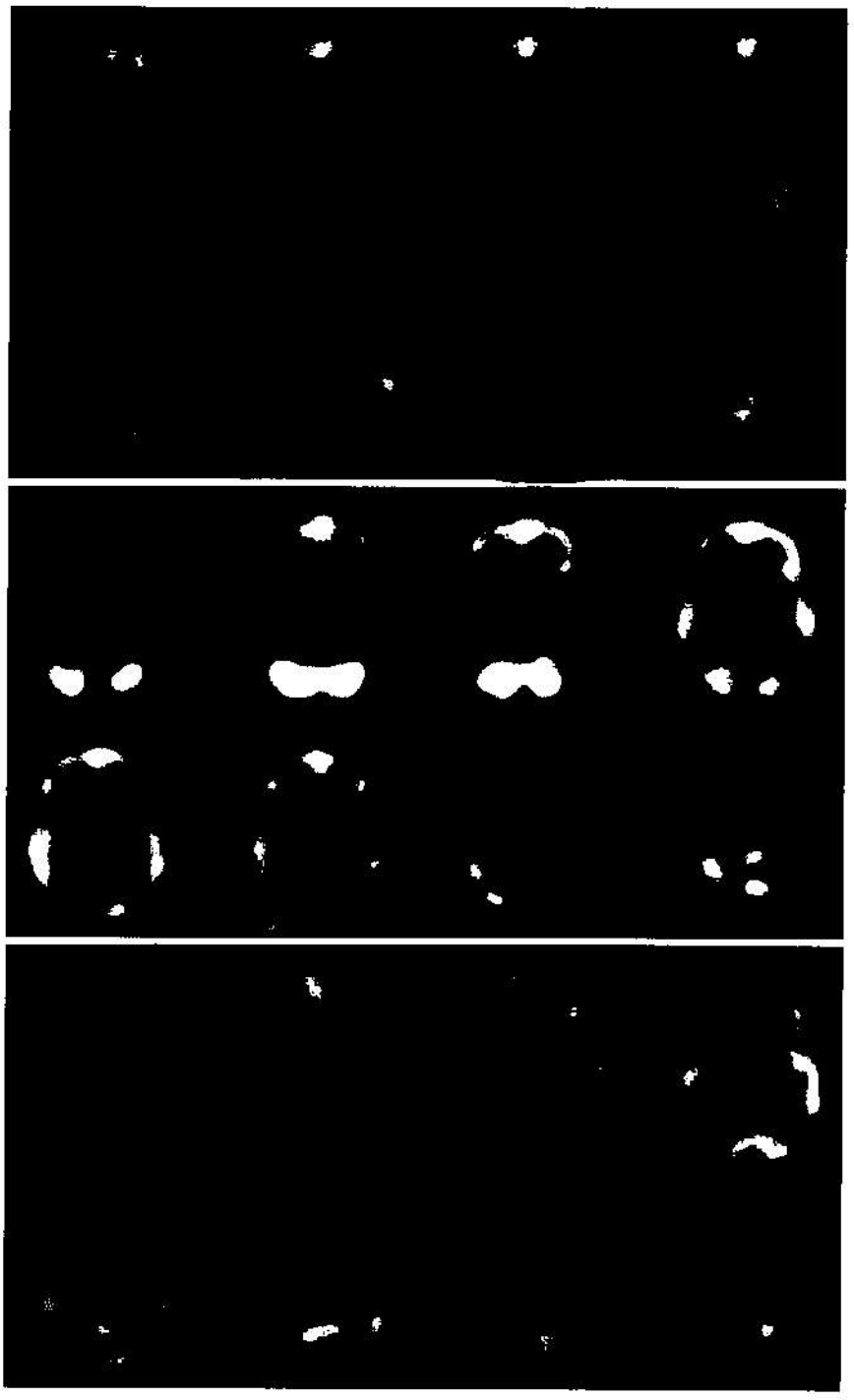

Fig. 1a to c *a)* ^{99m}Tc-HMPAO SPECT in a 10-year-old male with JNCL. The supratentorial cortical perfusion is normal, but cerebellar perfusion is moderately decreased. *b)* A 14-year female. Note the symmetrical temporal, posterior temporal and parieto-occipital hypoperfusion which resembles the SPECT finding of *Alzheimer's* disease. *c)* A 27-year-old male with clinical symptoms for 17 years. There is marked hypoperfusion in the infratentorial and occipital areas as well as moderate hypoperfusion temporally and frontally.

extrapyramidal symptoms and signs, a preferentially bilateral frontal hypoperfusion, as in many other extrapyramidal disorders (6, 18), was not observed in our patients. *Philippart* and colleagues found using PET and ^{18}F-fluorodeoxyglucose that the cortical association areas in the most severely incapacitated JNCL patients are symmetrically affected (13), in a similar manner as in adult onset dementias. Interestingly, three patients with low ADL-scores had similar bilateral temporal – parietal hypoperfusion as seen in *Alzheimer* disease (5, 11) (Fig. 1b).

The large amount of abnormalities seen in SPECT already in early stages of JNCL was expected as the disease may be histologically detected already in utero (2). Hypoperfusion at the non-dominant parietal and infratentorial areas correlated best with all clinical findings in our patients. Lesions of the right parietal lobe cause various kinds of dyspraxias, visuoperceptual, and constructional inabilities, which might in part increase the difficulties which motor handicap imposes on ADL (10). The emergence of parietal lesions coincided also with an increasing number of abnormally perfused other brain areas. The pace of emergence of widespread abnormality, however, is highly individual. The most profound hypoperfusion was found at the temporal lobes and this finding correlated understandably with speech and ADL. However, the number of abnormal areas did not correlate with age ($r = 0.26$, $p = 0.25$), as the time of onset of clinical symptoms varies and the progression of this disease is not uniform.

In contrast to CT, which revealed symmetric atrophy as often in the supratentorial as in the infratentorial regions (14), SPECT revealed a number of asymmetric and focal abnormalities which may be due to neuronal disconnection, as MRI studies (1) have demonstrated abnormalities in white matter.

Based on our experience, it seems that the SPECT technique is useful in studying the pathophysiology of JNCL patients, although it lacks some of the resolution of PET and cannot be quantitated. The finding, that right parietal hypoperfusion and neurological dysfunction correlate, has encouraged us to include the patients in a rehabilitation program at an early stage. The SPECT pattern of JNCL is different from that seen in INCL giving further evidence of the different nature of these diseases.

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