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Comparison of brain perfusion SPECT and MRI findings in children with neuronal ceroid-lipofuscinosis and in their families

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Purpose: Neuronal ceroid-lipofuscinoses (NCL) are among the progressive encephalopathies of childhood that are inherited in an autosomal recessive manner. In this study we specifically aimed to investigate any white-matter changes in the carriers (parents) and the healthy siblings of individuals with neuronal ceroid lipofuscinosis disease and whether we may be able to predict the occurrence of any neurological symptoms in healthy children in the future thus enabling early management. ***Materials and Methods:*** Since the NCLs are genetically determined diseases, we investigated fifteen individuals in three families that had diseased children of the juvenile type, with brain perfusion SPECT and MRI. Brain perfusion SPECT was performed after administering 222–555 MBq (6–15 mCi) Tc-99m HMPAO intravenously in a dimmed and quiet room. Imaging was performed at least one hour after injection, with a three headed gamma camera equipped with high resolution collimators. A Metz filter (FWHM: 11 mm) was used for processing. Cranial MRI was performed with an imager operating at 1.5 Tesla. Spin-echo T1- and T2-weighted and FLAIR slices were obtained for each individual. ***Results:*** In all of the five diseased children we observed pathologic findings both on MRI and Tc-99m HMPAO SPECT. The findings on MRI were mainly features of cerebral and cerebellar atrophy and the observations on Tc-99m HMPAO SPECT were regional perfusion abnormalities. We observed some structural abnormalities on MRI in four of the parents and two of the four healthy siblings. We also noted perfusion abnormalities on Tc-99m HMPAO SPECT in two of the parents and two of the healthy siblings. ***Conclusion:*** Because the disease is inherited in an autosomal recessive manner, the parents and the healthy siblings were not supposed to exhibit any demonstrable brain lesions, but the brain perfusion SPECT and MRI examinations clearly revealed multiple lesions in some of the parents and healthy siblings. Detailed neurological examinations of these individuals were normal except for one apparently healthy sibling (EY). Follow-up imaging of these families is being undertaken and further studies are essential in understanding the pathogenesis and genetics of neuronal ceroid-lipofuscinoses.

Key words: neuronal ceroid-lipofuscinosis, brain perfusion SPECT, MRI

INTRODUCTION

THE NEURONAL CEROID-LIPOFUSCINOSES (NCL), a group of lysosomal storage disorders of the central nervous system, are considered among the neurodegenerative diseases of childhood. The disease is inherited in an autosomal recessive manner and the NCLs are classified into four major forms on the basis of age of onset, clinical findings, neurophysiologic observations, and pathologic studies: as infantile, late infantile, juvenile and adult forms. The clinical manifestations are epilepsy, mental retardation, ataxia, myoclonia, and visual failure. The disease is known to occur worldwide.[1–3] Relatively few reports on functional neuro-imaging findings on NCL patients exist. The most commonly reported findings on

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Table 1 Brain perfusion SPECT, MRI and clinical findings in Y family

Family 1 (Y family)

Individual, age, gender	Brain perfusion SPECT findings	MRI findings	Clinical findings
Father (AY) 33 M	Normal	Multiple milimetric lesions in bilateral centrum semiovale, anterior/posterior parietal, white matter, and left lentiform nucleus	Normal
Mother (KY) 33 F	Hypoperfusion in bilateral inferior frontal lobes especially on the left	Multiple milimetric lesions in bilateral centrum semiovale especially left	Normal
Diseased child (SY) 15 F (Fig. 1A, 1E)	Severe cerebral hypoperfusion especially in bilateral inferior frontal and occipital cortices and in right parietal cortex	Marked cerebral and cerebellar atrophy, thin corpus callosum, few lesions in right internal capsule and parietal white matter	Blindness, rigidity, fainting, speech disorder
Healthy child (EY) 12 M (Fig. 1C, 1F)	Severe hypoperfusion in the right temporal and mild hypoperfusion in the right frontal cortices	8 mm solitary lesion in left posterior parietal white matter	Anxiety, imaginary visions when falling asleep
Healthy child (NY) 3 F	Hypoperfusion in right temporoparietal cortex	Normal	Normal

Table 2 Brain perfusion SPECT, MRI and clinical findings in A family

Family 2 (A family)

Individual, age, gender	Brain perfusion SPECT findings	MRI findings	Clinical findings
Father (NA) 40 M	Normal	Multiple milimetric lesions in bilateral frontal and parietal white matter and right lentiform nucleus	Normal
Mother (AA) 31 F (Fig. 2A, 2C)	Hypoperfusion in right caudate nucleus, bilateral frontal, right temporal and left occipitotemporal cortices	Multiple milimetric lesions in bilateral frontal and posterior parietal white matter and lesion in corpus callosum	Normal
Healthy child (AA) 14 F	Normal	4 mm solitary lesion in right anterior parietal white matter	Normal
Diseased child (AA) 12 F	Hypoperfusion in bilateral occipital cortices and hypoperfusion in left posterior parietal cortex	Cerebral and cerebellar atrophy, lesion in left posterior parietal white matter, thin splenium of corpus callosum	Blindness, fainting, epileptic seizures, speech disorder
Diseased child (IA) 10 F	Hypoperfusion in bilateral inferior frontal cortices	Few lesions in bilateral corona radiata and left thalamus	Blindness, mental retardation

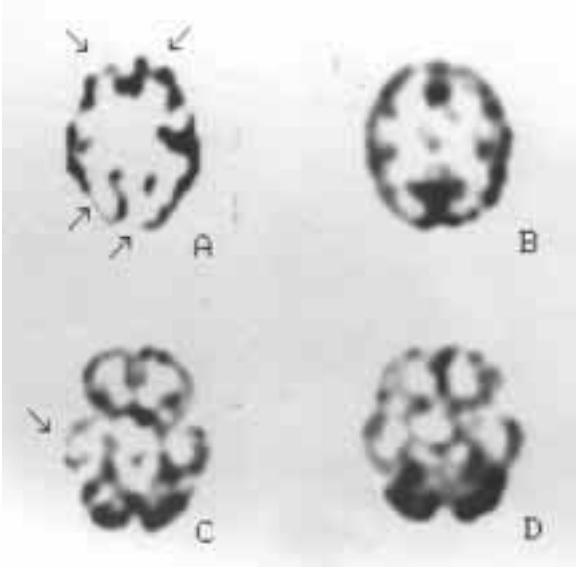
CT and MRI examinations are cerebral and cerebellar atrophy and white matter abnormalities. Commonly observed brain perfusion SPECT findings are variable degrees of cerebellar hypoperfusion and focal perfusion abnormalities in the temporal, frontal and parietal regions.[1,3,4]

Since the NCLs are genetically determined diseases, we investigated fifteen individuals in three families that

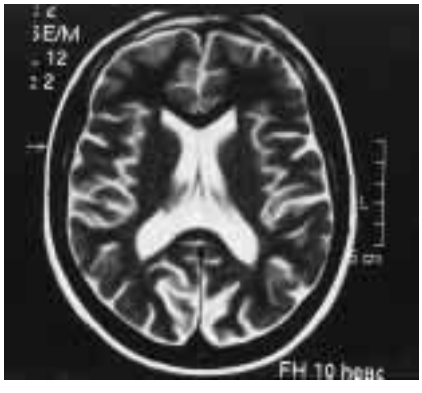
Table 3 Brain perfusion SPECT, MRI and clinical findings in G family

Family 3 (G family)

Individual, age, gender	Brain perfusion SPECT findings	MRI findings	Clinical findings
Father (HG) 43 M	Normal	Normal	Normal
Mother (RG) 39 F	Normal	Normal	Normal
Diseased child (FG) 15 F	Hypoperfusion in all cerebral and cerebellar cortices most prominent in the occipital cortex	Marked cerebral and cerebellar atrophy, thin corpus callosum	Blindness, epileptic seizures, speech disorder
Diseased child (EG) 12 M (Fig. 3)	Hypoperfusion in all cerebral and cerebellar cortices most prominent in the occipital cortex	Marked cerebral and cerebellar atrophy, thin corpus callosum	Blindness, epileptic seizures, irritability, speech disorder
Healthy child (IG) 3 F	Normal	Normal	Normal



A–D



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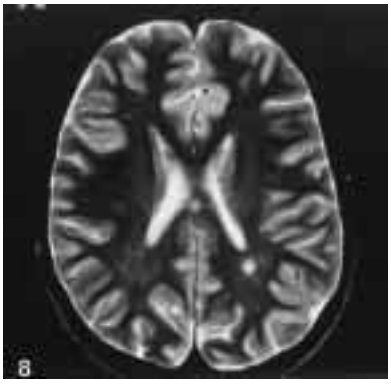


F

Fig. 1 Brain perfusion SPECT and MRI images of the diseased child of Y family (SY), of a healthy child of Y family (EY) and normal perfusion SPECT of a normal child. A: Brain perfusion SPECT shows severe cerebral hypoperfusion especially in bilateral frontal (*top arrows*) and occipital cortices (*down arrows*) and in the right parietal cortex (SY). B: Normal brain perfusion SPECT for comparison. C: Brain perfusion SPECT shows severe hypoperfusion in the right temporal (*arrow*) and mild hypoperfusion in the right frontal cortices (EY). D: Normal brain perfusion SPECT for comparison. E: T2-weighted axial MRI slice reveals cerebral atrophy and ventricular dilatation (SY). F: T2-weighted axial MRI slice shows a 8 mm solitary lesion in the left posterior parietal white matter (EY).

had diseased children of the juvenile type with brain perfusion SPECT and MRI and noted any pathologic findings. In this study we specifically aimed to investigate any white-matter changes in the carriers (parents) and the healthy siblings of individuals with neuronal ceroid

lipofuscinosis disease and whether we may be able to predict the occurrence of any neurological symptoms in healthy children in the future thus enabling early management. We compared pathologic findings to see whether any correlation existed between structural abnormalities observed on MRI and significant hypoperfusion detected on brain perfusion SPECT.

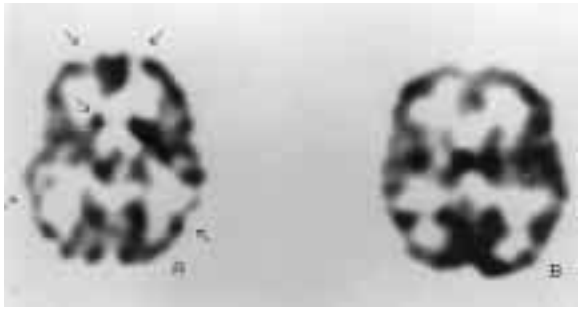
MATERIALS AND METHODS

Fifteen individuals in three families with five diseased children were investigated with technetium-99m hexamethylpropylene amine oxime (Tc-99m HMPAO SPECT) and MRI. There were ten females and five males aged from 3 to 43 years. Detailed neurological examination was performed in all the individuals and none of the parents had the asymptomatic disease of the adult form, but an otherwise apparently healthy sibling (EY) had anxiety and imaginary visions when falling asleep.

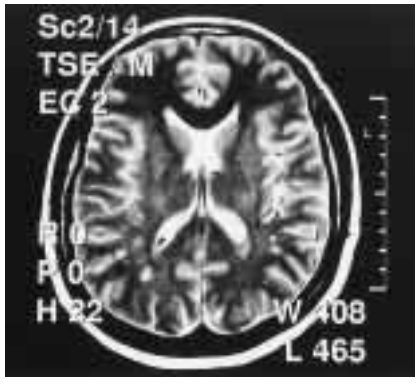
The diagnoses of all the diseased children were ascertained by muscle and nerve biopsies. In addition one of the children was examined by conjunctival biopsy (SY) and one other child by skin biopsy (AA). The study had been approved by our hospital's ethics committee and all subjects gave their written informed consent before the investigations. Tc-99m HMPAO SPECT was performed within a week of MRI.

Tc-99m HMPAO was prepared from a commercial kit (Ceretec, Amersham International plc, U.K.) by adding 1110 MBq (30 mCi) of freshly eluted Tc-99m pertechnetate to 5 m*l* of saline solution. The solution was administered to the patient no more than 30 minutes after preparation. Brain perfusion SPECT was performed after administering 222–555 MBq (6–15 mCi) Tc-99m HMPAO intravenously in a dimmed and quiet room. The child dose was calculated according to the body weight. Chloralhydrate was given for sedation to children 10 minutes after Tc-99m HMPAO injection. Imaging was performed at least one hour after injection, with a three-headed gamma camera equipped with high resolution collimators (Neurocam, GE, Horsholm, Denmark). One hundred and twenty-eight images of 35 seconds duration in a 64×64 matrix were obtained over 360 degrees. Two pixel thick slices in coronal and sagittal planes were obtained after reconstruction of two pixel slices in the transaxial plane parallel to the orbitomeatal line. Attenuation correction was performed. A Metz filter (FWHM: 11 mm) was used for processing. Images were independently evaluated by two observers blinded to MRI or clinical findings.

Cranial MRI was performed with an imager operating at 1.5 Tesla (Philips Gyroscan ACS-NT). Spin-echo axial T1-weighted (SE 500/20), axial and coronal dual turbo spin-echo T2-weighted (TSE 2000/110) and sagittal FLAIR (Fluid Attenuated Inversion Recovery) (TSE 11000/140/2725) slices were obtained for each individual. The MR images were evaluated by one radiologist without knowledge of brain Tc-99m HMPAO SPECT or clinical findings.



A, B



C

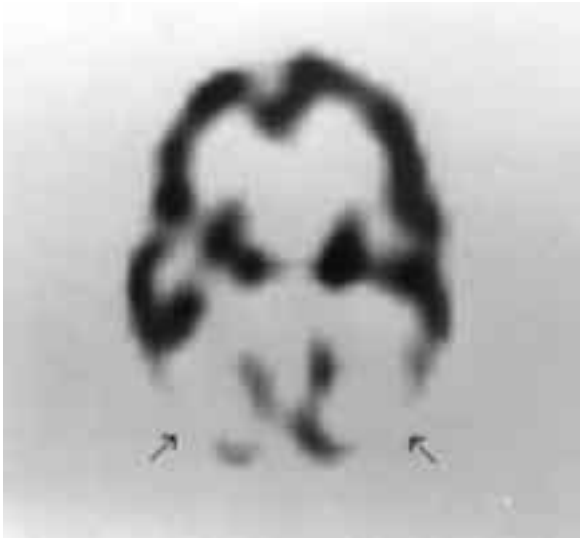
Fig. 2 Brain perfusion SPECT and MRI images of the mother of A family (AA) and normal perfusion SPECT of a normal adult. A: Brain perfusion SPECT shows hypoperfusion in right caudate nucleus (*middle arrow*), bilateral frontal (*top arrows*), right temporal and left occipitotemporal cortices (*arrows*) (AA). B: Normal brain perfusion SPECT for comparison. C: T2-weighted axial MRI slice reveals milimetric multiple bilateral lesions especially in the right in posterior parietal white matter (AA).

RESULTS

We investigated five diseased (four females, one male, age range: 10–15, mean duration of the disease was 6.2 ± 1.8 years) and 10 normals of which four were three healthy sisters and one brother (age range: 3–14 years), and six were parents of diseased children (age range: 31–43 years). The MRI, Tc-99m HMPAO SPECT and clinical findings of all the family members are summarized in Tables 1–3. All the individuals underwent a thorough neurological examination by the same neurologist.

In all the diseased individuals the brain SPECT and MRI examinations yielded pathologic results. Tc-99m HMPAO SPECT examination was normal in six of the normal individuals (6/10) whereas the MRI examination was normal in four of the normals (4/10).

Figures 1 and 3 demonstrate brain perfusion SPECT



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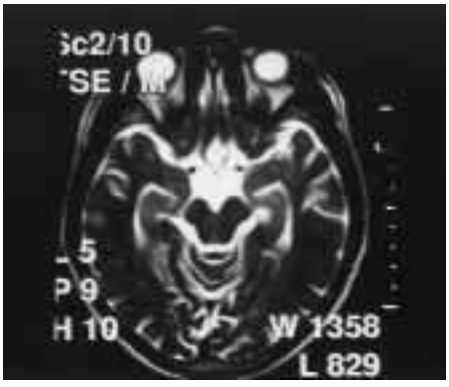

B

Fig. 3 Brain perfusion SPECT and MRI images of a diseased child of G family (EG). A: Brain perfusion SPECT shows hypoperfusion in all cerebral and cerebellar cortices most prominent in the occipital cortex (*arrows*) (EG). B: T2-weighted axial MRI slice demonstrates marked cerebral and cerebellar atrophy.

and MRI images of the diseased children in Y and G families (SY and EG, respectively). The neuroimaging findings in SY are more severe than EG, probably because the disease duration in SY is longer than in EG.

Figure 1 shows brain perfusion SPECT and MRI images of a healthy child in Y family (EY). This child had anxiety and imaginary visions when falling asleep. Both examinations revealed pathologic findings in this child, but there is a discordance, i.e. Tc-99m HMPAO SPECT shows severe hypoperfusion in the right temporal and mild hypoperfusion in the right frontal cortices whereas MRI shows a 8 mm solitary lesion in the left posterior parietal white matter.

Figure 2 shows brain perfusion SPECT and MRI images of the mother of A family (AA). Both neuroimaging findings reveal multiple pathologic observations in this parent.

DISCUSSION

Neuronal ceroid-lipofuscinoses are among the progressive encephalopathies of childhood. It is in fact the most common neuro-genetic storage disease in children. NCLs are characterized by neural and extraneural accumulation of autofluorescent and lipid-like storage material; the disease process leaves the brainstem and the spinal cord intact. The exact pathogenesis of NCL is still largely unknown despite the immense amount of research involved in this area.[5–7]

In the juvenile type the initial symptoms begin to be noticed at the age of 4–7 years. Failure of vision is usually the first complaint. Mental impairment, dysarthria, motor disability and epilepsy follow and death occurs by about the age of 20 years (range 13–40 years).[5]

Our study group included five juvenile type diseased children in three families. Although hyperintense white matter areas are observed in T2-weighted and FLAIR MRI images, they appear to be largely nonspecific findings, their presence is thought to be related to diffuse demyelination, gliosis, and possible axon preservation which are pathological processes probably responsible for manifestation of the symptoms of the disease.[1,3,4] Magnetic resonance imaging, especially when combined with a typical clinical pattern, makes the diagnosis of NCL highly likely. Radiological examinations of the brain may also prove important in following progression, as well as in investigating the pathophysiology of the disease.[3] Those areas of demyelination and gliosis are seen as hypoperfused regions on brain perfusion SPECT images. Brain perfusion SPECT reveals lesions prior to structural abnormalities seen on magnetic resonance or computed tomography, and such abnormalities are not always associated with significant hypoperfusion.[4] The early SPECT perfusion abnormalities may assist in the differential diagnosis of NCL and other neuro-degenerative diseases.[1] Posterior cortical territories might be more vulnerable than other cortical regions of the brain to chronic metabolic disturbances or to a chronic accumulation of a storage material[6]; this could explain the relative preponderance of parieto-occipital lesions in our patients; but we also observed the involvement of frontal areas. All the diseased children are blind and all of them except for one (IA) demonstrated hypoperfusion in the occipital cortex (possibly cortical blindness). After the diseased individuals become blind, metabolic activity decreases probably due to decreased functional activity, which may contribute to the hypoperfusion of the occipital cortices. Focal pathologic lesions in the white matter and cerebral and cerebellar atrophy are expected findings on MRI and brain perfusion SPECT for diseased individuals, but the structural abnormalities on MRI and significant hypoperfusion on Tc-99m HMPAO SPECT in some of the parents and healthy siblings in the three families were surprising observations. Considering the fact that the disease is inherited in an recessive

manner, the parents and the healthy siblings were not supposed to exhibit any demonstrable brain lesions. To the best of our knowledge, this is the first report in the literature dealing with lesions in carriers and healthy siblings of individuals with neuronal ceroid-lipofuscinosis disease. The lesions observed in the parents do not seem to be predictive of occurrence of the disease.

In the third family (G family) we were not able to detect any pathologic neuroimaging findings in the parents or the healthy child. In this family MRI and brain perfusion SPECT findings are in accordance with each other.

We wonder if the solitary lesions observed in the healthy 14-year-old female (AA) and 12-year-old male siblings (EY) (Fig. 1) would become multiple and diffuse as these children grow older and become adults. We also wonder if these individuals' children will have any clinical manifestations of the disease and whether we may be able to manage the disease process before the occurrence of symptoms.

The 12-year-old EY currently suffers from anxiety and imaginary visions when falling asleep and the location of the lesions observed on MRI and Tc-99m HMPAO SPECT does not seem to be responsible for this clinical presentation.

Follow-up imaging of these families is being undertaken for the verification of the above hypothesis and further studies are needed to see if any brain lesions in the parents or healthy siblings of the other diseased individuals exist. Further reports dealing with this issue may have considerable impact in understanding the pathogenesis and genetics of neuronal ceroid-lipofuscinoses. In this respect, postmortem studies of the parents and the healthy children could also highlight some essential factors in the pathogenesis of the disease.

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