Progressive Facial Hemiatrophy: Central Nervous System Involvement and Relationship with Scleroderma en Coup de Sabre

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ABSTRACT. ***Objective.*** To investigate the relationship of progressive facial hemiatrophy (PFH) and scleroderma en coup de sabre by establishing the presence and type of central nervous system (CNS) involvement in both diseases and the possible coexistence of PFH with scleroderma in other body sites.

Methods. We divided 19 cases of PFH into 2 groups: group 1 in which atrophies were preceded by cutaneous indurations (n = 10) and group 2 with no precedent indurations (n = 9). The third group consisted of 7 cases of scleroderma en coup de sabre with no PFH features. Clinical and laboratory investigations included indirect immunofluorescence for antinuclear antibodies, and routine neurological examination involved electroencephalography, magnetic resonance imaging (MRI) before and after contrast application to evaluate the integrity of blood-brain barrier, angio-MRI to evaluate intracranial blood vessel anomalies, and 99mTc-HM-PAO-SPECT to evaluate regional cerebral blood flow (CBF).

Results. We found similar anomalies in all 3 groups. MRI did not show abnormality in 2 out of 9 PFH cases preceded by indurations, in 5 out of 9 cases not preceded by indurations, and in all 7 cases of scleroderma en coup de sabre, including 5 patients, in whom the CBF was found to be diminished. In single cases of groups 1 and 2, SPECT was normal despite some MRI abnormalities. Angio-MRI was not contributory since the same abnormalities of Willis circle were found in normal controls. In single cases of both PFH groups, MRI with contrast disclosed some damage of the blood–brain barrier.

Conclusion. Our results suggest frequent CNS involvement in PFH cases, regardless of the time of presentation of cutaneous indurations, with or without coexistent plaques of localized scleroderma in other locations. This indicates a close relationship between PFH and scleroderma en coup de sabre. The detection of abnormal SPECT by normal MRI in some cases of PFH and scleroderma en coup de sabre is of practical importance. This indicates the usefulness of SPECT in studying both PFH and scleroderma en coup de sabre. (J Rheumatol 2003;30:1997–2004)

Key Indexing Terms:
CUTANEOUS SCLERODERMA NERVOUS SYSTEM FACIAL HEMIATROPHY
SCLERODERMA EN COUP DE SABRE CEREBRAL BLOOD FLOW

Progressive facial hemiatrophy (PFH) of Parry-Romberg is characterized by self-limited hemiatrophy of the skin, the subcutaneous tissues, and sometimes the underlying muscles and bones of the face. The pathogenesis of the disease remains unknown despite an association with epilepsy or other neurological abnormalities in about 10% of cases, since it is not clear whether the involvement of the central nervous system (CNS) is primary (epileptic seizures and dizziness, sometimes preceding appearance of PFH[1]) or secondary. The neurological abnormalities are slight or subclinical in most cases; severe CNS involvement was found only in patients in whom the changes were present from birth or appeared after trauma.

PFH was described by Romberg[2] as trophoneurosis, and was believed to be related to the sympathetic nervous system[3]. Recently this hypothesis found some confirmation because ablation of the superior cervical ganglion in rabbits reproduced the principal clinical manifestations of PFH: hemifacial atrophy, alopecia, enophtalmus, and bone atrophy on side of sympathectomy[4]. The distribution of cutaneous atrophy along the 3 divisions of trigeminal nerve might be due, in part, to the close connection of this nerve with sympathetic nervous fibers. Cases of PFH associated with trigeminal neuralgia and cramps[5] have been reported.

Clinical presentation and distribution of PFH shows a striking similarity to involutionary linear scleroderma (LS)

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after regression of sclerosis. [Of note, we are using the term linear scleroderma to describe the scleroderma variant characterized by linear distribution on the face and extremities that frequently leads to deep atrophies and deformities, especially on the face (scleroderma en coup de sabre)].The first case of PFH reported by Romberg[2] had all typical features of facial LS. Both conditions may show overlap or transition, with progressive shrinkage of the skin and subcutaneous tissues. The histopathological study of the orbital fat revealed perivascular lymphocytic infiltrates, atrophy, and slight fibrosis[6]. The subcutaneous atrophy and flattening of the dermis has also been established by MRI study[7].

The ultrastructural study of vessels in PFH revealed vascular changes like those seen in scleroderma[8]. Similar vascular cerebral abnormalities may also occur in systemic sclerosis without involvement of facial skin, due to generalized, often subclinical microangiopathy[9,10]. The relationship of PFH and scleroderma is further strengthened by cases of PFH coexistence with morphea (localized scleroderma) or LS at various body sites.

We studied patients with facial hemiatrophy who are most often referred to dermatologists or rheumatologists due to scarce neurological symptoms and complaints, and not infrequent overlap with cutaneous scleroderma. In many such cases the differentiation between PFH and LS may be very difficult or impossible[11,12]. We wanted to determine the presence of CNS abnormalities with the use of various techniques, some of which have not previously been used for PFH [cerebral blood flow (CBF) studied by SPECT method, angio-magnetic resonance imaging (MRI), and volumetric examinations]. In addition, we wanted to investigate the relationship between PFH and scleroderma by establishing whether CNS involvement and course of the disease differ in cases of PFH preceded or not preceded by cutaneous sclerosis; whether coexistence of plaque morphea and LS elsewhere in the body is more frequent in cases preceded by sclerosis; and whether CNS involvement in PFH is characteristic of the disease and whether it differs from that in scleroderma en coup de sabre.

MATERIAL AND METHODS

Patients. The study was performed in 19 cases of PFH divided into 2 groups: group 1: 10 patients with hemiatrophy preceded by cutaneous sclerosis, 5 of whom had plaque morphea or LS on the trunk and/or extremities; group 2: 9 patients, hemiatrophy not preceded by cutaneous sclerosis, 4 of whom had morphea or LS on the trunk and/or extremities; and the control group 3: 7 patients with scleroderma en coup de sabre, 2 of whom had morphea or LS on the trunk and/or the arm.

In the first and second groups, the disease onset was mostly in childhood: the mean age of onset was 10.7 yrs in the whole group (excluding 2 with adult onset disease, the mean age of onset was 7.4 yrs). In the third group, the mean onset of scleroderma en coup de sabre was 16.4 yrs (excluding the 2 adults, the mean age of onset was 8.8 yrs). The mean followup for groups 1 and 2 was 9.4 yrs, for scleroderma en coup de sabre, 6.4 yrs. The study covered a period from 6 months to several years after disease onset.

Clinical evaluation. Detailed clinical and neurological examinations were conducted, as well as EEG, MRI, angio-MRI of the intracranial vessels, and CBF using the SPECT method.

MRI was performed in all patients before and after injection of a standard dose of 0.1 mmol/kg Magnevist (Schering, Berlin, Germany) using the 1.5 Tesla unit. Axial, sagittal, and coronal slices were obtained. T1 weighted, proton density and T2 weighted spin echo sequences were used.

Twenty individuals were selected and randomized for sex and age as controls.

MRI volumetry was performed using a graphic workstation (Magicview, Siemens, Erlangen, Germany). Cross sectional areas of selected structures (hemispheres, hippocampus, Gasser regions) were measured. Manual tracing of the structure was done by a radiologist who was blinded to the clinical information. Normal right-left volumetric differences were obtained in the 30 controls.

Angio-MRI was performed using 3-dimensional time of flight (TOF) MRI angiography. The slab was centered on the Willis circle. A maximum intensity projection (MIP) algorithm was used to reconstruct angiogram-like images.

CBF was studied after intravenous injection of 740 MBq *99mTc-HM-PAO (Ceretec, Amersham, UK).* Imaging started 20 min after injection. A simple head SPECT camera system (DIACAM, Siemens) equipped with low-energy high resolution parallel collimator was used for the tomographic acquisition. Slices 10 mm thick were obtained to measure the density count. Using the cerebral atlas, regions of interest were delineated manually. Regions were mirrored from one hemisphere to the other. All regional uptake values were compared and an asymmetry of radioactivity was estimated. Sixty-five examinations in healthy individuals were used as controls. Left/right asymmetry in this group was 1.05 ± 0,05. In no instance did the asymmetry exceed 10%. This result is in accordance with other authors[13]. On this basis, an asymmetry of activity > 10% was regarded as pathological.

RESULTS

The summarized results in all groups are presented in Table 1. EEG found abnormalities in 5 out of 10 cases in group 1, and in 3 out of 8 in group 2. MRI was abnormal in 7 out of 9 cases studied in group 1, and in 4 out of 9 in group 2. The abnormalities were mostly ipsilateral, showing variable patterns: enlargement of spaces around the hippocampus, asymmetry of the hippocampus, enlargement of lateral ventricles, and signal derangement in the white matter (Figures 1, 2, and 3). No changes were seen in the Gasser ganglia regions nor in the trigeminus. MRI with contrast showed signal potentiation in 1 out of 9 cases in group 1, and in 3 out of 9 in group 2 (Figure 4). Angio-MRI disclosed various anomalies of the Willis circle vessels in both groups; however, such anomalies were also seen in about 36% of controls.

SPECT showed focal or multifocal abnormalities in 8 out of 10 patients of the first group (Figures 1 and 2), in 5 out of 9 in the second group (Figure 3), and in 5 out of 7 patients with scleroderma en coup de sabre (Figure 5). The changes were mostly in frontal and temporal areas. The blood flow, contralateral or ipsilateral, was decreased with no direct relationship to areas of cutaneous and brain involvement. The results were concordant with EEG findings in 5 out of 10 cases in the first group, in 5 out of 9 cases in the second group, and in 2 out of 6 cases of scleroderma en coup de sabre. EEG was less sensitive than MRI in 2 out of 10 cases

Table 1. Summary of abnormal findings.

	Group 1	Group 2	Group 3
MRI	7/9*	4/9	0/7
MRI with contrast	1/9 (Figure 1 and 2)	3/8[1/] (Figure 4)	0/7
Angio-MRI	5/9	2/9	4/7
SPECT	8/10 (Figure 2)	5/9 (Figure 3)	5/7 (Figure 5)
Neurological findings (epilepsy, transient, seizures)	1/10	3/9	4/7
EEG			
Concordant with other techniques	5/10	3/9	4/6**
Less sensitive than MRI	2/10	4/9	0/6
Less sensitive than SPECT	3/10	2/9	1/6
Trauma as preceding or triggering factor	6/10	2/9	4/7

* MRI not done for 1 patient due to claustrophobia. ** EEG not done in one patient.

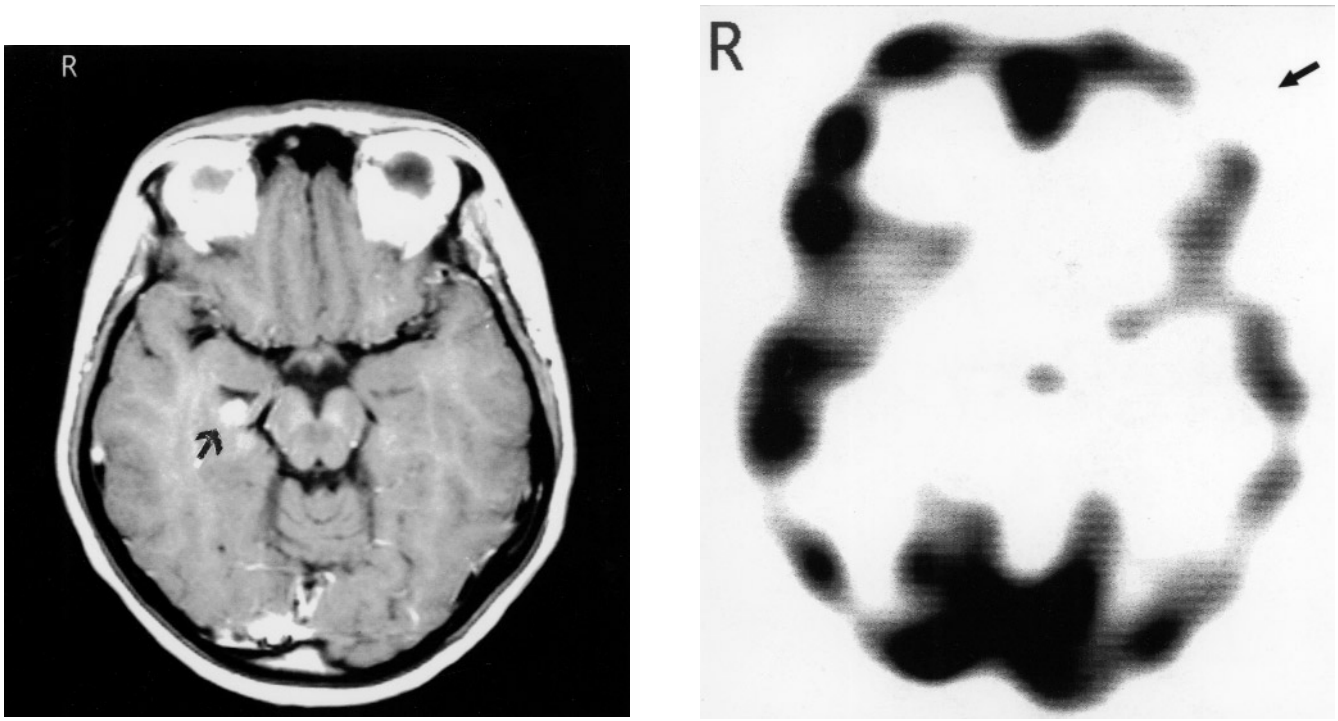
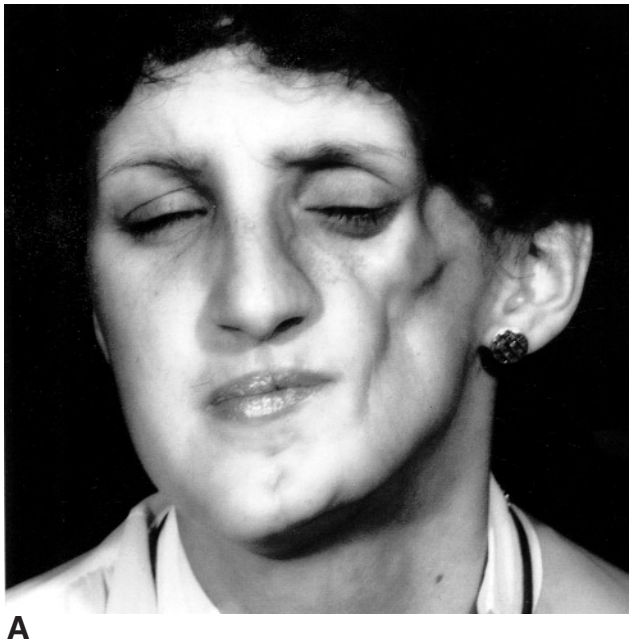


Figure 1. A 18-year-old girl with slight PFH on the right side and morphea on the trunk. A. MRI examination after contrast application shows a pathological focus in the right hippocampus. Enlargement of the subarachnoid space around the hippocampus and its hypoplasia (volumetrically proven) was also found. B. CBF-SPECT study shows decreased regional blood flow in the left frontal-temporal region. Angio-MRI showed lack of anterior communicating artery, and EEG showed slow waves in the region of the left hemisphere. Neurological examination was normal.

in the first group, and 2 out of 9 cases in the second group, and less sensitive than SPECT in 3 of 10 cases in the first group, 2 of 9 cases in the second group, and 2 of 6 cases in the scleroderma en coup de sabre group.

Neurological symptoms and complaints were rather scarce in all groups. Epilepsy was diagnosed in 2 patients and transient seizures in one patient in the first group; one case of epilepsy was recognized in the third group, and some abnormalities (headaches, vertigo, vision disturbances, nystagmus) in 4 cases in the second group. Paradoxical pupillary reactivity and Horner signs were a frequent finding in both groups.

MRI was normal in all 7 patients with scleroderma en coup de sabre. Slight neurological symptoms were found in 4 patients in this group: headache and dizziness, and in one adult patient, ipsilateral paresis of n. facialis.



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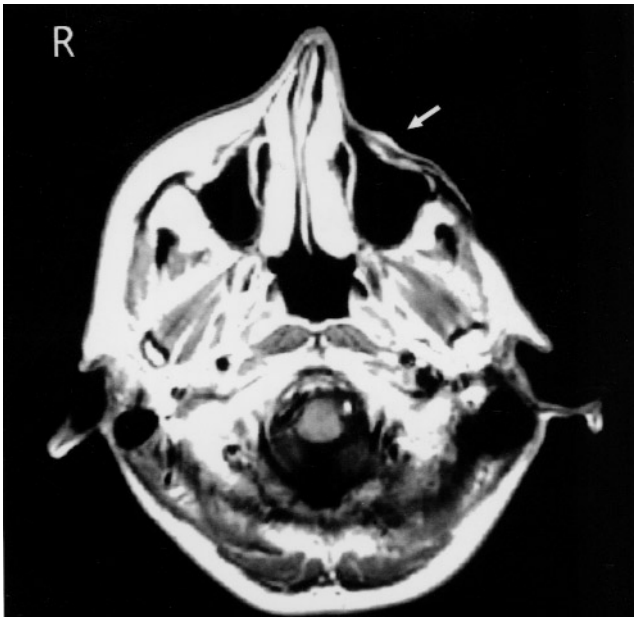

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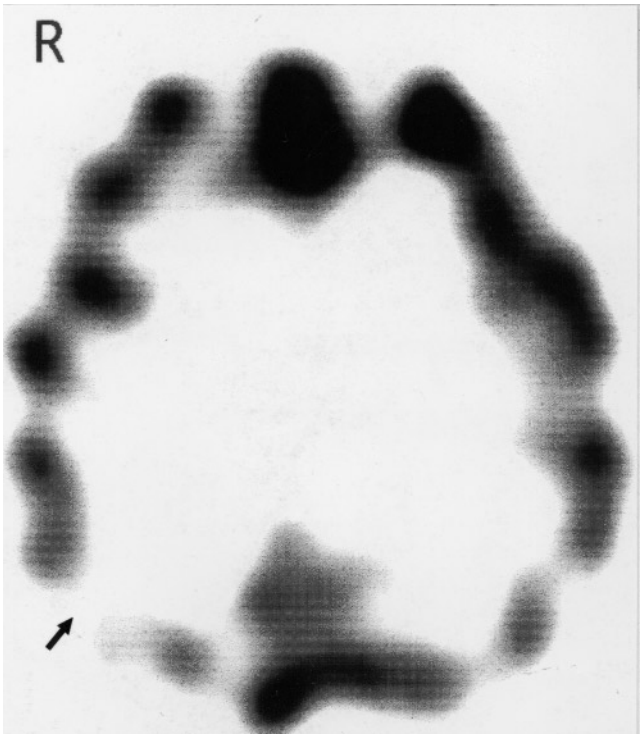

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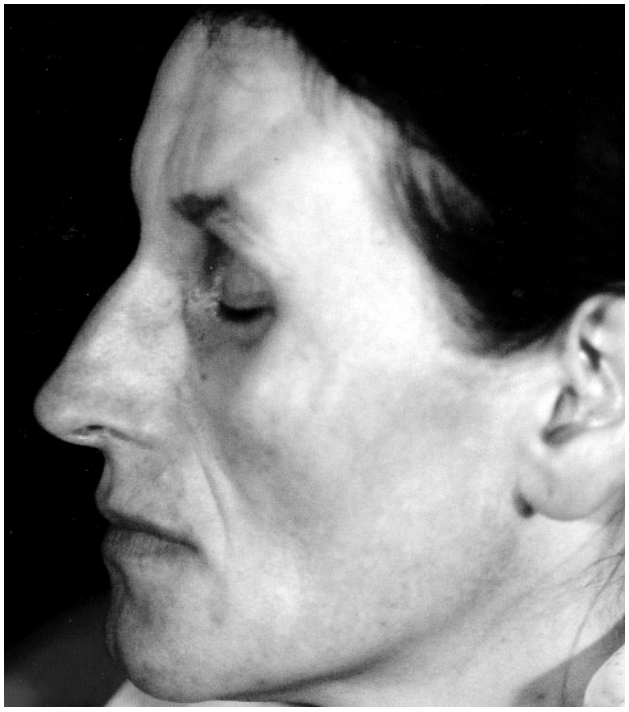
Figure 2. A. A 42-year-old woman with PFH on the left side. B. MRI examination shows deep atrophy of the cutaneous tissue and bone. In addition, in the MRI there were hyperintense foci localized in the brain stem. C. CBF-SPECT study shows decreased blood flow in the right temporal region. The EEG was normal.

DISCUSSION

Using several techniques we detected discrete abnormalities in the CNS in almost all patients with PFH and scleroderma en coup de sabre.

We found minimal differences between the anomalies found in PFH both preceded and not preceded by cutaneous indurations. The neurological examination did not show any abnormality in 10 out of 19 PFH patients, and in 5 out of 7 patients with scleroderma en coup de sabre, including 3 patients with history of epilepsy. MRI provides important information on the involvement of CNS and on localization of the brain lesions. Various abnormalities disclosed by MRI were also reported in PFH by others: white matter lesions and vascular malformations[6,14], cortex thickening, gyral effacement, and cystic infarcts with foci of encephalomalacia[15], blurring of the white-gray interface, intracranial calcification, and chronic localized meningo-encephalitis with vascular involvement[8,16]. Some authors found even concurrence between the MRI stage and clinical stage of the disease, suggesting that MRI staging could be of some prognostic significance[7]. It should, however, be stressed that MRI did not show any abnormalities in our cases of scleroderma en coup de sabre, which enhances the significance of other techniques, especially SPECT.



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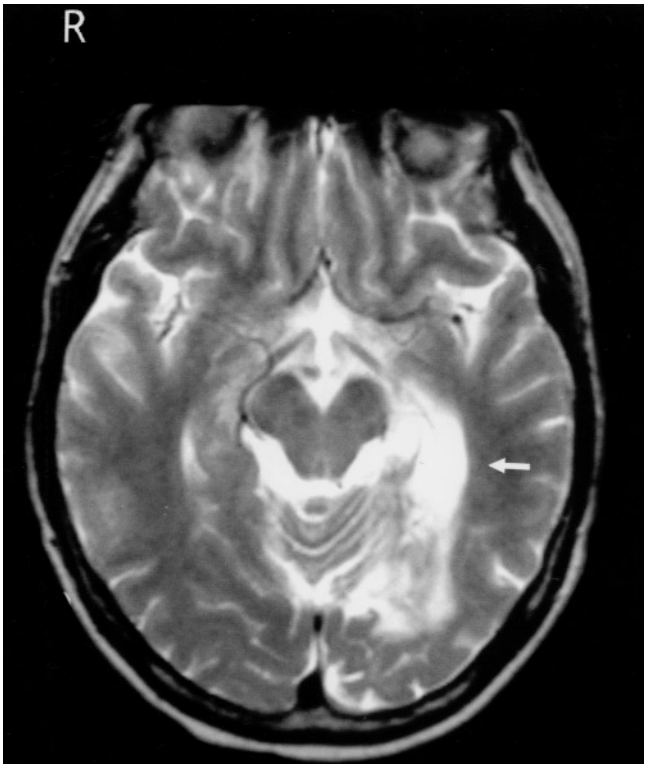

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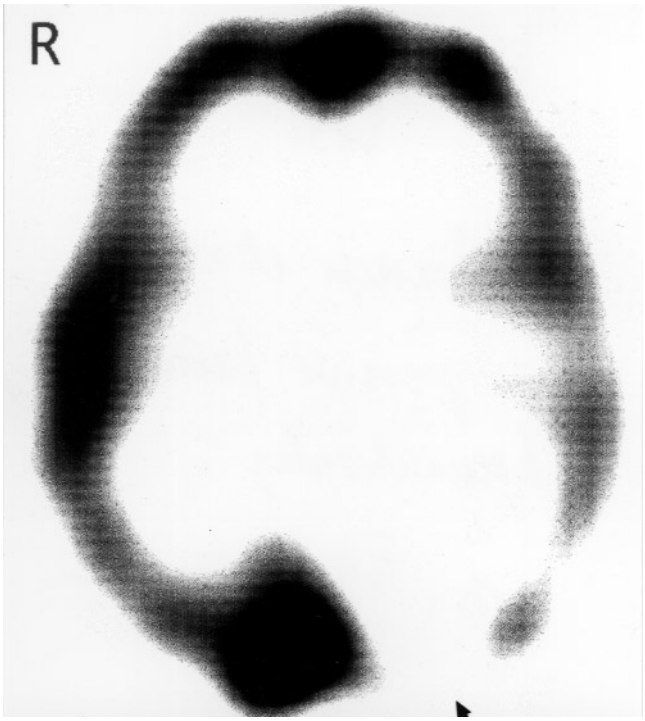

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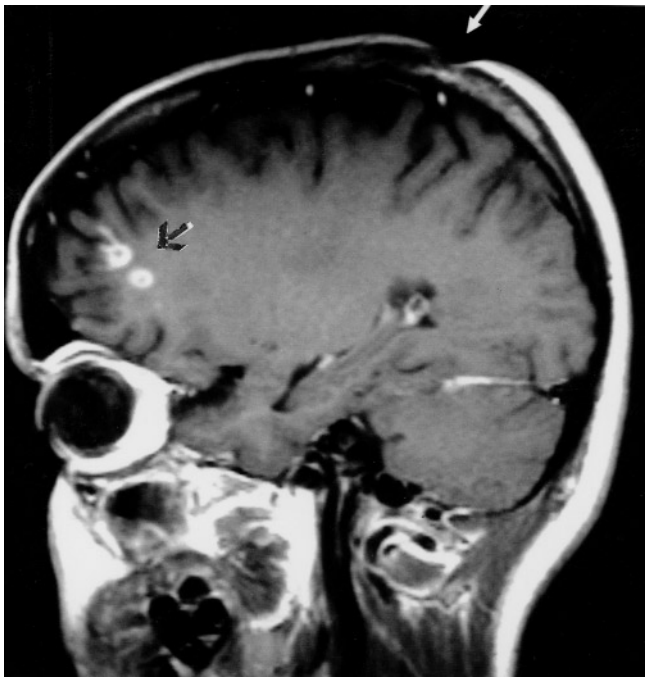
Figure 3. A. A 44-year-old woman with PFH on the left side and linear atrophy on the forehead. B. MRI examination shows a well-circumscribed area of high signal intensity on the T2 weighted image in the left temporal and occipital regions. C. CBF-SPECT study shows decreased blood flow in the left parieto-occipital region. In this patient, the EEG shows diffuse pathological changes with slow waves. Neurological examination disclosed hyperreflexia on the right, and Horner syndrome on the left side.

It is not clear whether PFH is an inflammatory process coexistent with malformation of cerebral arteries[6], a congenital cerebral defect producing both cerebral dysgenesis and hemiatrophy[17], a sympathetic nerve chain hyperactivity, or local meningo-encephalitis with vascular involvement[18,19]. Both the neurological symptoms and CNS abnormalities are diverse in individual cases. However, facial hemiatrophy present from birth is a different rare congenital hemiatrophy that is non-progressive and is associated with various anomalies[20-23], which should be differentiated from PFH.

The most important and still controversial problem appears to be the relationship of PFH with scleroderma, particularly the scleroderma en coup de sabre variant, which may coexist with or precede the hemiatrophy. PFH might even be regarded as an involutionary scleroderma with atrophies remaining after the cutaneous indurations have regressed, similar to cases of profound morphea or LS on the extremities. Very much like in PFH, the atrophies in deep morphea may not be preceded by induration[24]. The involvement of CNS disclosed in all our patients was similar in cases both preceded and not preceded by indurations and did



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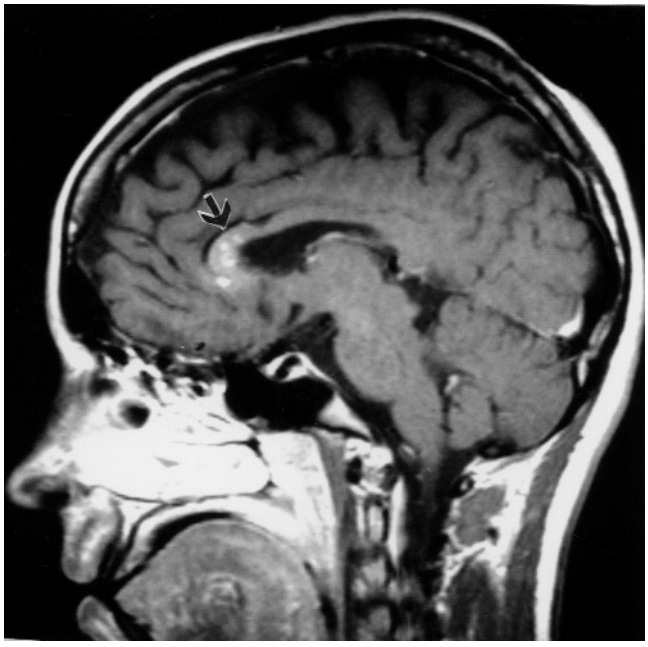

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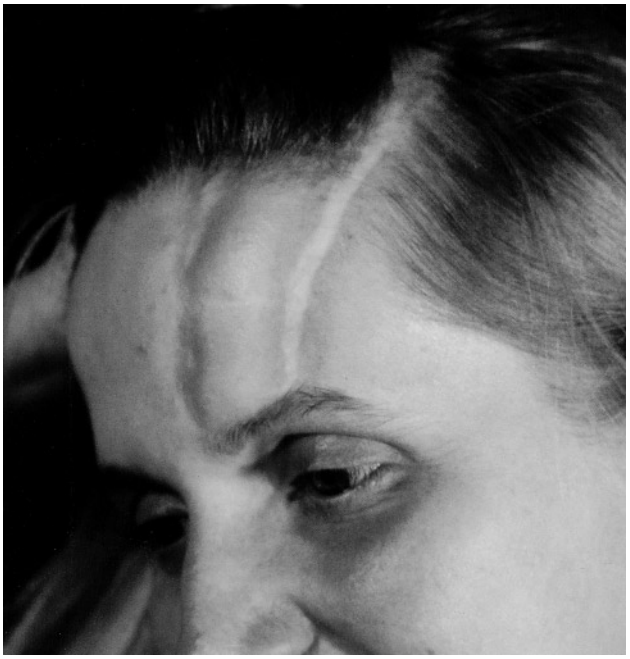
Figure 4. A 21-year old woman with PFH. MRI after contrast application shows multifocal hyperintensities in T1 weighted images in the frontal lobe (A) and in the corpus callosum (B).

not differ in patients in whom PFH coexisted with morphea or LS on the trunk and extremities. We have found such a coexistence in our previous study on a large series of 71 patients: in 37% of children and in 20% of adults with



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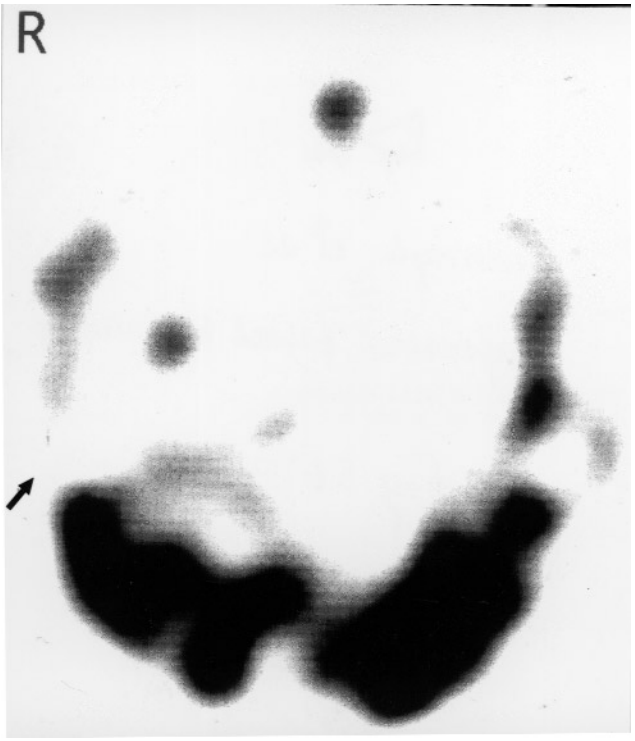

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Figure 5. A 37-year-old woman with scleroderma en coup de sabre on the left side. A. Two deep lines on the forehead. B. CBF-SPECT study shows decreased blood flow in the right temporal region. MRI examination was normal. Angio-MRI showed lack of both posterior communicating arteries. EEG and neurological examination were normal.

PFH[25]. In this study, morphea or LS coexisted on the trunk or extremities in 9 out of 19 patients with PFH (in 4/9 not preceded by indurations and 5/10 preceded by facial sclerosis). Two out of 7 patients with scleroderma en coup de sabre also had morphea elsewhere. These findings strongly favor a close relationship between PFH and scleroderma. Trauma appears to be a triggering factor in our cases of PFH preceded or not by indurations, as well as in scleroderma en coup de sabre. Thus we confirm our previous findings that trauma and the onset of PFH in early childhood are often associated with CNS involvement[26].

The neurological symptoms were somewhat more pronounced in cases not preceded by indurations but the differences were insignificant. The course of the disease was variable in all groups, and the CNS abnormalities were present in all.

The CNS involvement in localized scleroderma similar to that in PFH was reported by several authors: intracranial calcifications, white matter lesions in the frontal lobes[27,28], vascular and inflammatory lesions in brain parenchyma[29], and other findings. The histopathological study of brain tissue showed inflammatory, vascular, and sclerotic changes[27]. The case of scleroderma en coup de sabre reported by Chung[30] is of special interest since the excised cerebral lesion was found to be densely sclerotic with thickened blood vessel walls, surrounded by gliotic parenchyma, and scattered calcifications. The surgical resection of the involved brain area resulted in epilepsy regression.

Since cutaneous sclerosis may be found within hemiatrophy, and scleroderma changes elsewhere may coexist with PFH, it was even proposed to include PFH into the spectrum of LS[31].

Our study has revealed the involvement of CNS in all cases of scleroderma en coup de sabre, although in some cases the involvement was rather slight. There was disseminated focal decrease of the CBF in 5 out of 7 patients, while MRI did not detect any abnormality. Thus the functional disturbances revealed by SPECT are more relevant for diagnosis, prognosis, and followup of patients with deep and extended atrophies of scleroderma en coup de sabre. In all groups studied, only MRI and SPECT provided significant information. MRI with contrast might be useful exclusively in some advanced cases of PFH. Numerous abnormalities disclosed by angio-MRI were found in a similar percentage in the controls.

In conclusion our study has shown that CNS involvement is present in all cases of PFH, and is similar in PFH preceded or not preceded by sclerotic lesions, as well as in scleroderma en coup de sabre with no signs of PFH, thus confirming a close relationship between these conditions. Both PFH and scleroderma en coup de sabre appear to be heterogeneous neurocutaneous syndromes in the majority of cases in the broad spectrum of scleroderma. The use of MRI and SPECT, which reflects the CBF, made it possible to assess even slight CNS abnormalities. SPECT proved to be more useful in cases with less severe CNS involvement, especially in scleroderma en coup de sabre.

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