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Case Report

Hemimegalencephaly with Facial Congenital Infiltrating Lipomatosis in a Child

Adrián SANTANA-RAMIREZ [1], ****Felipe FARIAS-SERRATOS*** [2], ***José SANCHEZ-CORONA*** [3], ***Gema CASTAÑEDA-CISNEROS*** [3], ***Nadia M. FARIAS-SERRATOS*** [4]

1. *Dept. of Neurosurgery, Hospital Civil Juan I. Menchaca, Guadalajara, Jalisco, México*
2. *Dept. of Research, Hospital Regional de Alta Especialidad del Bajío, León, Guanajuato, México*
3. *Mexican Institute of Social Security (IMSS), Jalisco, Centro de Investigación Biomédica de Occidente (CIBO), México*
4. *Dept. of Surgical Oncology, Hospital Regional de Alta Especialidad, Cd. Salud Chiapas, México*

***Corresponding Author:** Email: felipe_serratos@yahoo.com

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Abstract

We report an unusual case of hemimegalencephaly (HMG) associated with ipsilateral congenital-infiltrating lipomatosis of the face in a five–month-old boy. Hemimegalencephaly is a rare but unique malformation characterized by enlargement of all or parts of a cerebral hemisphere. The affected hemisphere may have focal or diffuse neuronal migration defects, with areas of polymicrogyria, pachygyria and heterotopia. Our aim was to investigate morphologic abnormalities occurring on the affected hemisphere by Magnetic Resonance Imaging (MRI), but some MRI findings were also noted outside of the affected hemicerebrum. There are a few case reports that have described various other abnormalities accompanying this condition, such as enlargement of ipsilateral brainstem, cerebellum and left lateral ventricle. MRI may be the most useful method demonstrating features of hemimegalencephaly with infiltrating lipomatosis of the face. However, studies using electroencephalogram (EEG) and brain single photon emission computerized tomography (SPECT) can show distinct variants of discharges and brain-perfusion anomalies.

Keywords: Epilepsy, Brain malformation, Magnetic Resonance Imaging

Introduction

Hemimegalencephaly can be an isolated malformation or it can be associated with neurocutaneous syndromes involving the brainstem and cerebellum such as neurofibromatosis (1), tuberoses sclerosis, Proteus syndrome, Kippel-Trenaunay-Weber syndrome and linear sebaceous nevus syndrome (2, 3). The association of hemimegalencephaly with an ipsilateral congenital infiltrating lipomatosis of face was described by Slavin et al. (4); congenital-infiltrating lipomatosis of the face is characterized by a fatty mass on the cheek that infiltrates the adjacent structures, causing facial hypertrophy. This association has been documented in previous cases (5-7).

We describe a case of congenital-infiltrating lipomatosis of the face associated with hemimegalencephaly and compare this with the hemimegalencephaly associated with other neurocutaneous mixed syndromes.

Case Presentation

A five-month-old boy presented at the Hospital Civil Juan I. Menchaca, Guadalajara, Jalisco, México, 2012, with repeated partial seizures with

right focal and multifocal tonic-clonic limb movements, and a characteristic facial abnormality was studied. He was product of a full-term pregnancy of non-consanguineous parents; the prenatal history was normal and the baby cried immediately after birth. Height at birth was 51cm and weight was 2800 g. His seizures began on the eighth day after birth and were not controlled with fenitoin (5 mg/kg). At physical examination showed left cheek enlargement caused by a mass, which had been noted at birth. This mass had well-defined borders covered by skin of normal color and texture occupied the entire part of left cheek. The oral cavity showed ipsilateral macroglossia and macrodontia and early eruption of deciduous teeth on the left side causing gross facial deformity (Fig. 1). Because of the facial deformity, biopsy was performed of inner left cheek.

Physical examination revealed normal height and weight according with age, bilateral inguinal hernia and not another corporal asymmetry was found. Dermatological examination was normal. The neurological examination showed developmental delayed, (e.g. head control was not achieved). Right spastic hemiparesis (4/5) was noted. The ophthalmologic examination yielded normal results.

For the analysis of the case, we performed laboratory studies as blood and urine test, growth hormone, thyroid profiles; screening tests for inherited error of metabolism, karyotype, and serological test for *Toxoplasma*, *Rubeolla*, Cytomegalovirus, herpes and syphilis (TORCHS); histological examination of the biopsy, EEG mapping, brain 3D computed tomography (CT), Cerebral MRI, and SPECT.

The patient's parents have given their informed consent for the case report to be published as well as for the pictures and images.

The laboratory studies (blood, urine test), growth hormone, thyroid profiles; screening tests for inherited error of metabolism, karyotype, and serological test for TORCHS; were all normal or negative. The EEG mapping showed bilateral discharges and over the malformed hemisphere we detected continuous burst suppression and the spiking revealed asymmetry. The 3D CT soft reconstruction showed prominent facial asymmetry. This asymmetrical enlargement on the left cheek caused deformity and significant disfigurement (Fig. 1).

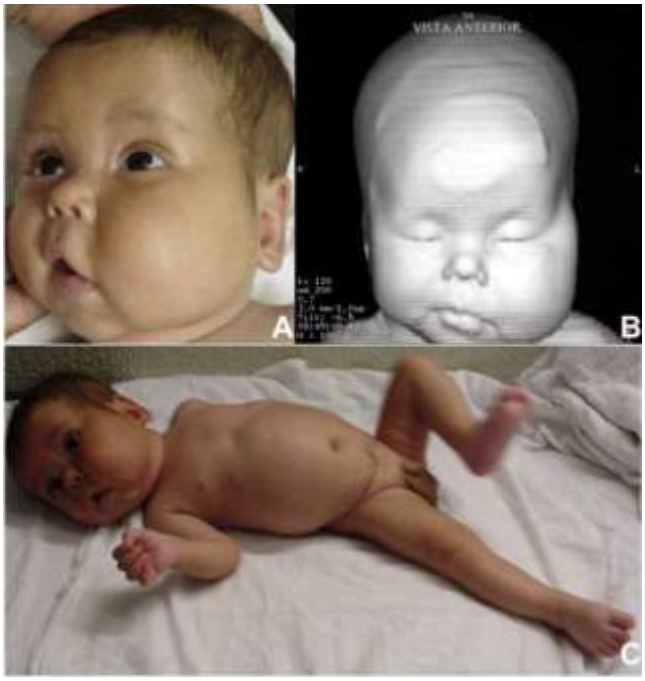

Fig. 1: A. Showing asymmetrical enlargement of the left cheek of the patient causes gross facial deformity with significant disfigurement of the face, **B.** The 3D CT soft reconstruction shows prominent facial asymmetry, **C**. Note the symmetry of body as well as bilateral surgical scar of inguinal hernia and absence of skin lesions

Facial CT in the coronal view confirmed a fatty mass located in the cheek, which infiltrated the adjacent structures causing the facial hypertrophy. There was not bone destruction. MRI T2 weighted also demonstrated an infiltrating lipomatosis of face. The left cheek mass was consistent with the fat signal and showed a good correlation with CT image. The MRI T2 weighted axial view revealed several intracranial abnormalities such as Hemimegalencephaly with colpocephaly (Fig. 2 and 3).

A SPECT was performed with Tc- 99m perfusion and showed decreased perfusion in the left side; the asymmetry was most pronounced in the occipital lobe (Fig. 4).

Histological examination of mass biopsy revealed the presence of no encapsulated normal adipose tissue (Fig. 5).

The patient was treated with phenobarbital combined with valproic acid and he has had a very good response to management regarding seizures for 2 years, contrary to most of hemimegalencephaly cases that are refractory to medical management.

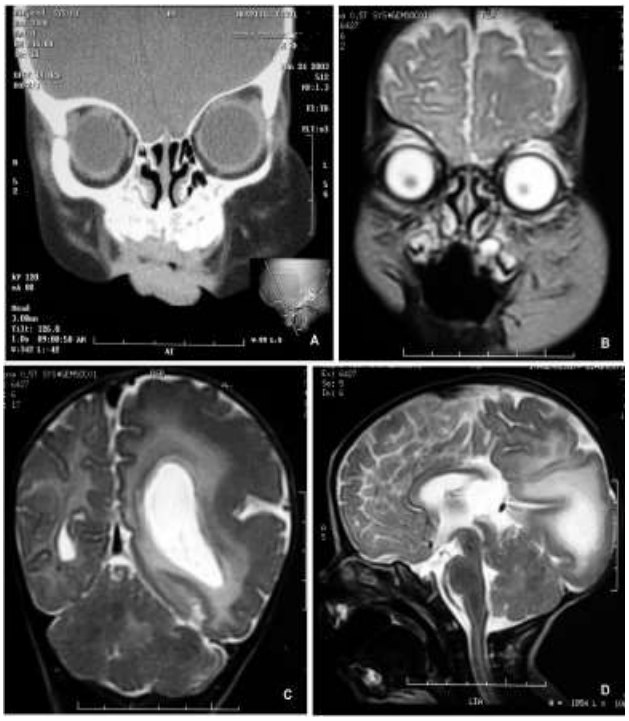

Fig. 2: A. Facial CT on coronal view shows a fatty mass located in the cheek that infiltrated the adjacent structures causing facial hypertrophy. There is no bone destruction. **B.** MRI T2 WI also demonstrated infiltrating lipomatosis of the face. The left cheek mass was consistent with a fat signal having a good correlation with the CT image. Note the infiltration of the adjacent soft-tissue structures such as the muscle planes. **C.** MRI T2 WI on coronal view shows hemimegalencephaly with generalized hyperintensity of the periventricular white matter suggestive of gliosis and other myelin abnormalities. Also, note the hypertrophy of cerebellum and vermis. **D.** MRI T2 WI on sagittal view shows hypertrophy of the cerebellum and vermis, agenesis of the corpus callosum tail, and diffuse pachygyria mainly in the parietal, temporal and occipital regions

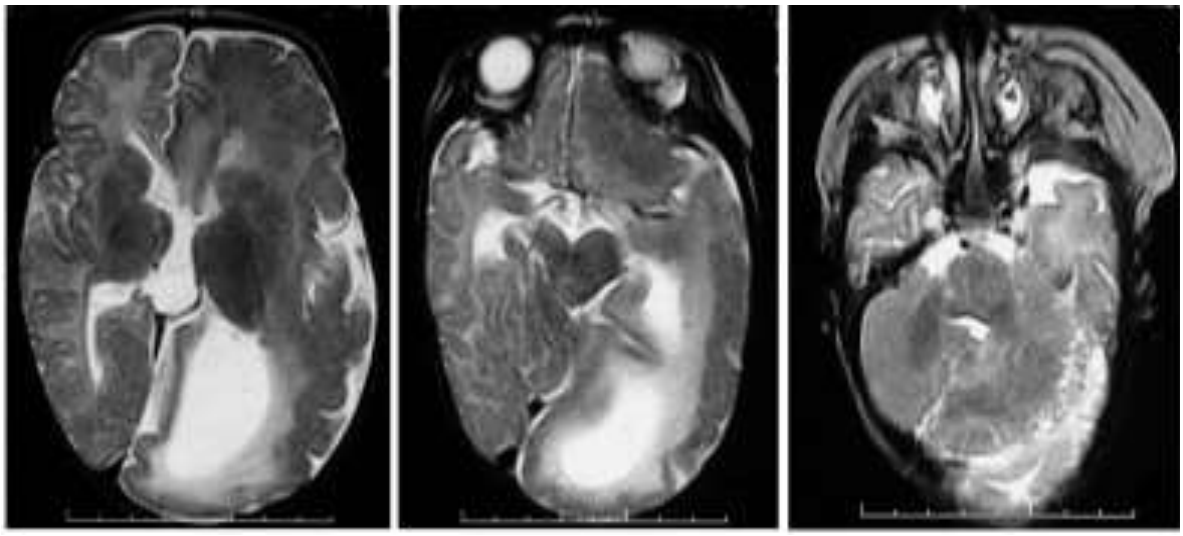

Fig. 3: MRI T2 WI axial view revealed several intracranial abnormalities such as hemimegalencephaly with colpocephaly. There was a unilateral hypertrophy of the left cerebral hemisphere, left brain stem, and left cerebellum with thickening of the gyri (pachygyria) and asymmetrical enlargement of the left lateral ventricle. There was also heterotopic grey matter in the basal ganglia of the affected cerebral hemisphere and agenesis of the corpus callosum tail

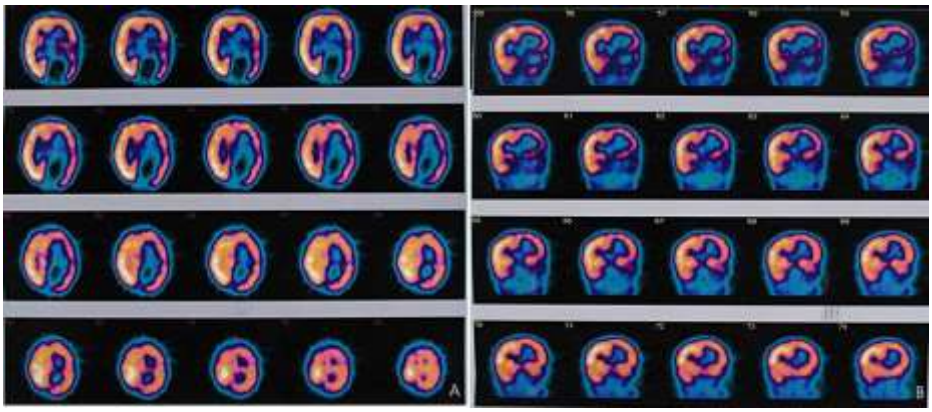

Fig. 4: Brain SPECT showed images with decreased perfusion in the left side; the asymmetry was most pronounced in the occipital lobe: **A** axial and **B** coronal views

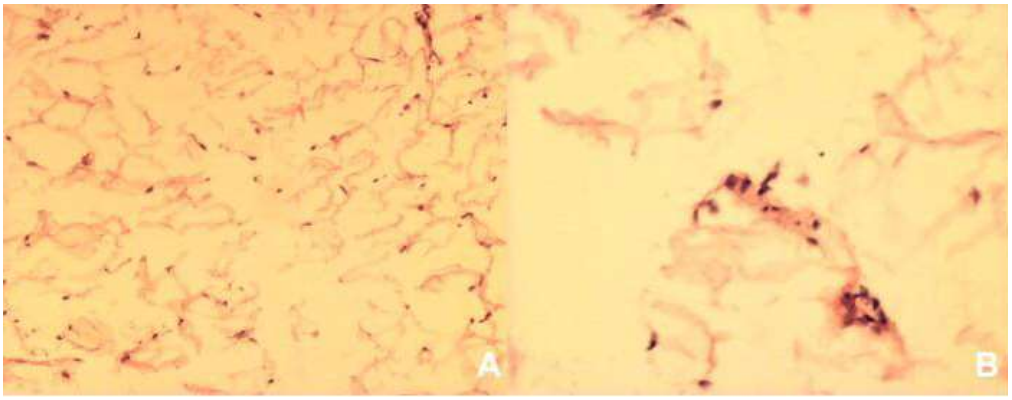

Fig. 5: Histological examination of biopsy revealed non-capsulated fatty tissue formed by mature adipocytes. **A.** Low power view (H & E, 10x), **B.** Medium magnification (H & E, 40x)

Discussion

The hemimegalencephaly clinical syndrome consists of medically intractable epilepsy, developmental delay, hemiparesis and hemianopsia. The extreme asymmetry in the involvement of brain is intriguing because it does not correspond to any know embryologic stage during normal human brain development (5, 6). It remains unclear whether hemimegalencephaly represents a unique pathologic entity or whether it is a heterogeneous condition with a phenotypic spectrum (7, 8) hemimegalencephaly may occur as an isolated anomaly or in association with various other neurocutaneous syndromes (Table 1), such as, neurofibromatosis type 1 and tuberous sclerosis (9,10) epidermal nevus syndrome (11-13) hypomelanosis of Ito (incontinentia pigmentia achromians), Proteus syndrome, Klippel- Trenau-nay-Webwer syndrome (14), encephalocraniocutaneus lipomatosis (15), Stratton-Parker syndrome (16).

Encephalocraniocutaneous lipomatosis is a rare congenital neurocutaneous lipomatosis characterized by lipomatous craneofacial hamartomas, and ipsilateral brain anomalies such as hemimegalencephaly, enlarged lateral ventricles, cerebellopontine angle tumors (17), agenesis of the corpus callosum, hemiatrophy of the brain, and central nervous system (CNS) lipomas. Ocular anomalies are the distinguishing factor of encephalocraniocutaneous lipomatosis; the most common ocular manifestation is epibulbar choristoma (15, 17).

Table 1: Syndromes with hemimegalencephaly and facial lipomatosis

Entity	Clinical Findings	Inheritance Pattern
Encephalocranio cutaneous Lipomatosis	Macrocephaly, lipodermoids involving the conjunctiva, sclera or eyelids, and lipomatous swellings over the cranium or face.	Uncertain
Oculocerebrocutaneous Syndrome or Delleman Syndrome	Nervous system cyst or hydrocephalus, psychomotor retardation and seizures; orbital cysts or microphthalmia, and focal skin defects, focal dermal hypoplasia, periorbital skin appendages, punched out skin lesions over the nasal alae.	Autosomal dominant
Sebaceous Nevus Syndrome and hemimegalencephaly.	Nevus sebaceous of the fece or scalp, hemihypertophy, ipsilateral defects of the brain, coloboma of iris, equinovarus, genu recurvatum, syndactyly, hemimegalencephaly, paquigyria, agenesis of the corpus callosum and Dandy-Walker malformation.	Autosomal dominant
Hemihypertrophy	Hemihypertrophy, hemihypesthesia, hemiareflexia, scoliosis, myelomeningocele.	Autosomal recessive multifactorial
Proteus Syndrome	Hemihypertrophy, overgrowth generalized or any tissue, macrocephaly, hyperostoses, epibulbar dermoids, kyphoscoliosis, lymphangioma, lipoma, epidermal nevi, hypertrophy of skin of soles, depigmentation or hyperpigmentation, hemangiomata, brain malformations.	Isolated cases

The minimal diagnostic criterion for oculocerebrocutaneous syndrome includes central nervous system cyst or hydrocephalus, orbital cysts or microphthalmia, and focal skin defects (18). Differentiating between the oculocerebrocutaneous syndrome and encephalocra-niocutaneous lipomatosis is difficult. The most reliable discriminating features are orbital cysts and agenesis of the corpus callosum, which are unknown in encephalocraniocutaneous lipomato-sis, and cerebral calcifications, which are unreported in oculocerebrocutaneous syndrome (13). Epidermal nevus syndrome consists of several cutaneous lesions, including sebaceous nevus of the face or scalp associated with defects of the brain, eye and connective tissue (19). It is a rare type of phacomatosis consisting of the triad of linear sebaceous nevus, seizures and mental retardation, and is associated with a high incidence of congenital CNS abnormalities such as hemimegalencephaly, unilateral ventricular dilatation and porencephaly. The characteristic features of sebaceous nevus confirm the diagnosis (11, 20, 21) but we found no skin lesions in our case.

Proteus syndrome is another rare syndrome with CNS anomalies and brain malformations including hemimegalencephaly; characteristically with generalized or localized hemihypertrophy and overgrowth of any tissue. In our case, the absence of body asymmetry, a marked feature of Proteus syndrome, makes the diagnosis unlikely (19).

Kliplel-Trenaunay-Weber syndrome is a rare, but well document congenital malformation characterized by the triad of port wine stain, varicose veins, and hypertrophy of bones overlying soft tissue; in some cases it is associated with hemimegalencephaly and limb hypertrophy (14). We found no skin lesions in our case.

The association of hemimegalencephaly with congenital-infiltrating lipomatosis of the face is rare and has been described in previous reports (Table 2). In congenital infiltrating lipomatosis of the face, mature lymphocytes invade adjacent tissue (4). The phenotypic features include soft-tissue and skeletal hypertrophy, premature dental eruption, and regional macrodontia (22). Donati et al. (6) describe the first case of hemimegalencephaly and ipsilateral congenital–infiltrating lipomatosis of the face associated with cytomegalovirus infections verified by immunohistological parotid gland studies. However, in our case, no biopsy of parotid gland was performed and serological tests were negative. Unal et al. (7) reported three cases, in case one hemimegalencephaly and congenital-infiltrating lipomatosis of face were associated with pachygyria and agenesis of callosum body but

without brain stem involvement, unlike our case; second case reported by Unal et al. had skin lesions and third case present an intracranial lipoma and congenital-infiltrating lipomatosis of face, without hemimegaloenchepaly. Aydingoz et al. (5) reported a similar case of hemimegalencephaly and ipsilateral congenital-infiltrating lipomatosis of face in a three month-old infant who had ipsilateral scalp lipoma but not cerebellar or brain stem anomalies. Our case had no extra or intracranial lipoma.

Table 2: Comparative findings of different cases

Clinical signs		Case 1	Case 2	Case 3		case
Seizures	+	-	+	-	+	+
CILF (ipsilateral)	+	+	+	+	+	+
Developmental delay	+	-	+	-	+	+
EEG abnormal	+	NR	NR	-	+	+
Colpocephaly	+	+	+	-	+	+
Pachigiry	-	-	+	-	+	+
Hemimegalencephaly	+	+	+	-	+	+
Enlargement of Brainstem and cerebellum	-	-	+	-	-	+
Agenesis of corpus callosum	-	-	+	-	-	Partial
Intracranial lipomatosis	-	-	-	+	-	-
Skin affectations	-	+	-	-	+	-
Cranial asymmetry	+	+	+	-	+	+
Citomegalovirus infection	+	-	-	-	-	-

+ Present, - Absent, NR=Not reported

Previous reports indicate that hemimegalencephaly is often associated with early onset epilepsy, in which seizures are frequent and refractory to treatment. Several types of seizures may occur with focal and/or generalized semiology 2. The EEG can display distinct variants, such as continuous epileptiform discharges burst suppression and focal continuous spiking in the affected hemisphere (23, 24). Our case showed bilateral EEG alterations with epileptic discharges, which can be explained by commissural connection. There are few reports on the use of brain SPECT to study hemimegalencephaly. We believe that this technique is useful in excluding the seizure foci or other perfusion abnormalities in the contralateral side before epilepsy surgery (25). Our case showed hypoperfusion in the left hemisphere, mainly in the occipital lobe (Fig. 4).

MRI may be the most useful method for demonstrating the features of hemimegalencephaly with congenital-infiltrating lipomatosis of the face confinated to a single hemisphere and ipsilateral side, as demonstrated in our patient and in the cases reported previously. MRI may differentiate this pathology from the spectrum of hemimegalencephaly associated with other neurocutaneus syndromes. We believe that the evaluation of patients with hemimegalencephaly should not be limited to the brain and that this pathology could be an allelic variant of another neurocutaneus syndrome such as encephalocraniocutaneus lipomatosis.

Several histopathological studies have documented various cytoarchitectural and architectural anomalies in the injured hemisphere, including lack of aligning in cortical layers, abnormal cells, and the rare proliferation of white matter (1, 26, 27). Even though HMG pathogenesis is not fully understood, a subset of HMG cases is caused by somatic mutations within the PI3K-AKT3-mTOR pathway, which plays a role in regulating cell size and growth (28). Bearing in mind dysplastic and hypertrophic appearance of abnormal cells on HMG, previous articles have addressed the cell

proliferation state of HMG tissue. Staining for Ki-67 (MIB-1), a marker for cellular proliferation, expressed few dispersed proliferative cells in HMG tissues, while the identity of the Ki-67-positive cells remains to be determined (1, 28).

In our patient we detected various morphologic anomalies outside the involved hemisphere such as enlargement of ipsilateral brainstem, cerebellum and left lateral ventricle; in an examination of the largest number of hemimegalencephaly cases ever included, Sato et al., (29-31) have reported previously abnormalities outside the affected hemisphere in the same kind of patients, they conclude that this condition involves not only the cerebral hemisphere but also the cranial nerves, cerebral vessels, and cerebellum. Ipsilateral olfactory nerve enlargement, hemicerebellar hypertrophy, dilated cerebral vessels, and abnormal architecture of the cerebellar folia were observed for the same authors, but hemihypertrophy of the brain stem was rare.

Connor et al. (32) have reported nerve growth factor (NGF), produced and released by brain cells, and is involucrate in the regulation of choline acetyltransferase activity, (33) which is strongly expressed in regions of the central nervous system innervated by magnocellular cholinergic neurons of the basal forebrain including hippocampus, olfactory bulb, and neocortex. Antonelli et al. (34) have documented increased tissue levels of NGF and numerous high-affinity NGF-receptor-positive cells in hemimegalencephaly tissues compared with control brain tissues. Furthermore, not only neurons but also small blood vessels and nerve fibers displayed high-affinity NGF-receptor positivity. In this patient we consider these conditions can be supported by the findings of previous studies.

Ipsilateral enlargement may be due in part to increases in NGF and high affinity NGF receptor-positive cells, the interaction of which plays a very important role in neuronal growth, differentiation, and promotion of repair.

A few cases have described cerebellar and brain stem hypertrophy and alterations on the affected side in patients with hemimegalencephaly and facial congenital infiltrating lipomatosis as this case.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

The authors declare that there is no conflict of interests.

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