Childs Nerv Syst (2008) 24:3–6
DOI 10.1007/s00381-007-0411-9

REVIEW PAPER

Is the brain biopsy obligatory or not for the diagnosis of Schilder's disease? Review of the literature

Yuksel Yilmaz · Canan Kocaman · Hakan Karabagli · Memet Ozek

Received: 25 February 2007 / Revised: 24 May 2007 / Published online: 25 August 2007

Abstract
Background Schilder's myelinoclastic diffuse sclerosis (Schilder's disease) is a rare demyelinating disorder. Clinical features and neuroimaging findings of this disease might mimic an intra-cranial mass lesion including an abscess or a tumour.
Case report Clinical and radiological findings of two children with the diagnosis of Shilder's disease are reported, and the role of brain biopsy as a diagnostic tool is discussed.

Keywords Schilder's disease · Diffuse myelinoclastic sclerosis · Cerebral mass · Steroid

Introduction

Schilder's disease is a rare, sporadic, acute or sub-acute demyelinating disorder affecting mostly children [1]. The disease was first described by Schilder in 1912. The original case, a 14-year-old girl, had progressive mental deterioration and increased intra-cranial pressure: Neuropathological diagnosis was reported as 'encephalitis periaxialis diffusa' [2]. Although there are several case reports, the diagnostic criteria are not clear yet, as well as the pathogenesis. The diagnosis of some reported patients are contraversial [3]. The diagnostic criteria described by Poser et al. [4] are as follows: 1, sub-acute or chronic myelinoclastic disorder resulting in formation of one or more roughly symmetric bilateral plaques measuring at least 2× 3 cm in two of three dimensions involving the centrum semiovale; 2, no other lesions demonstrable by clinical, paraclinical or imaging methods; 3, no peripheral nervous system lesion; 4, normal adrenal function; 5, normal very-long-chain fatty acids and 6, histopathology identical to multiple sclerosis. Garell et al. [3] proposed that only 21 patients of all reported cases until 1998 match these criteria.

Based on these criteria, the histopathological evidence is obligatory for the diagnosis. On the other hand, in half of the reported patients, the diagnosis was made without brain biopsy [5–7]. In this report, the clinical, laboratory and serial magnetic resonance imaging (MRI) findings of two children with the diagnosis of Schilder's disease is presented as well as the literature overview since 1998, and the role of the histopathological examination is discussed.

Case report

Case 1 An 8-year-old girl was admitted to our hospital with a history of left hemiparesia and gait disturbance that had occurred 4 weeks ago. Her past medical history was unremarkable, and there was no preceding viral illness or recent vaccination. Vital signs and the physical examination was normal; the patient was afebrile. Neurological examination showed mild left hemiparesis, gait disturbance and

Y. Yilmaz · C. Kocaman
Department of Pediatrics, Division of Pediatric Neurology,
Marmara University, School of Medicine,
Istanbul, Turkey

H. Karabagli · M. Ozek
Department of Neurosurgery, Division of Pediatric Neurosurgery,
Marmara University, School of Medicine,
Istanbul, Turkey

Y. Yilmaz (✉)
Selami Ali Mh Gazi Cd. No: 76, Usküdar,
Istanbul, Turkey
e-mail: yukselymd@e-kolay.net

intentional tremor on the left side. She was unable to tandem walk. Routine blood tests including sedimentation rate, C-reactive protein, complete blood count and biochemistry were normal. Cerebrospinal fluid examination (CSF) was normal (opening pressure and protein and glucose levels were within normal limits). Bacterial cultures and serological tests of CSF including herpes simplex virus (HSV) 1 and HSV2, Echovirus, measles, mumps, varicella, cocksakie, rubella, cytomegalovirus, respiratory syncytial virus and tick-borne encephalitis were negative. No cells were detected by cytocentrifugation. Myelin basic protein and the immunoglobulin G index were normal, and the oligoclonal band was not detected. The cranial MRI demonstrated focal signal change on the right parietal white matter extension to the cerebral cortex. Low-signal intensity on T1-weighted images was observed on the right parietal region. Gadolinium half-rim enhancement was detected (Fig. 1a and b). Based on the radiological findings, the diagnosis of Schilder's disease was considered, and intravenous steroid (20 mg/kg) was given throughout 7 days. On the third day of steroid treatment, significant clinical improvement was seen. Steroid therapy was continued orally (2 mg/kg per day) for 1 month. Cranial MRI was repeated after 4 weeks of the diagnosis and revealed significant regression on the signal change as well as the size of the lesion and the degree of contrast enhancement The dose of steroid was tapered and stopped at the end of the third month. Cranial MRI performed at the end of the treatment showed minimal signal intensity and no contrast enhancement on the involved area (Fig. 2c). The patient was followed for 2 years without any complaint and neurological sequela.

Case 2 A previously healthy 9-year-old girl had a history of vomiting, weakness in her left side and altered gait for 2 weeks. Her previous history was unremarkable as well as the family history. She had no previous history of infection and vaccination. On admission, physical and neurological examination was normal expect for moderate left hemiparesis. Complete blood count, erythrocyte sedimentation rate, C-reactive protein, routine blood biochemistry and very-long-chain fatty acid analysis were negative. CSF analysis showed no abnormalities: Opening pressure and protein and glucose levels were within normal limits, and no cell was detected. Cranial MRI demonstrated focal signal change on the left frontoparietal white matter and inferomedial adjacent of the right lateral ventricle, which had hypo-intensity on the central region of all sequences. Gadolinium half-rim enhancement was detected (Fig. 2a–c). The diagnosis of Schilder's disease was considered based on the clinical and neuroradiological findings, and intravenous pulse steroid therapy was given for 5 consecutive days (20 mg/kg). On the fifth day of the treatment, hemiparesis resolved completely. Orally steroid therapy (2 mg/kg) was continued for 1 month and tapered slowly. Cranial MRI repeated after 5 weeks of admission revealed significant regression on the signal change and the size of the lesion, and no contrast enhancement was detected. The small lesion on the right peri-ventricular area disappeared. Focal

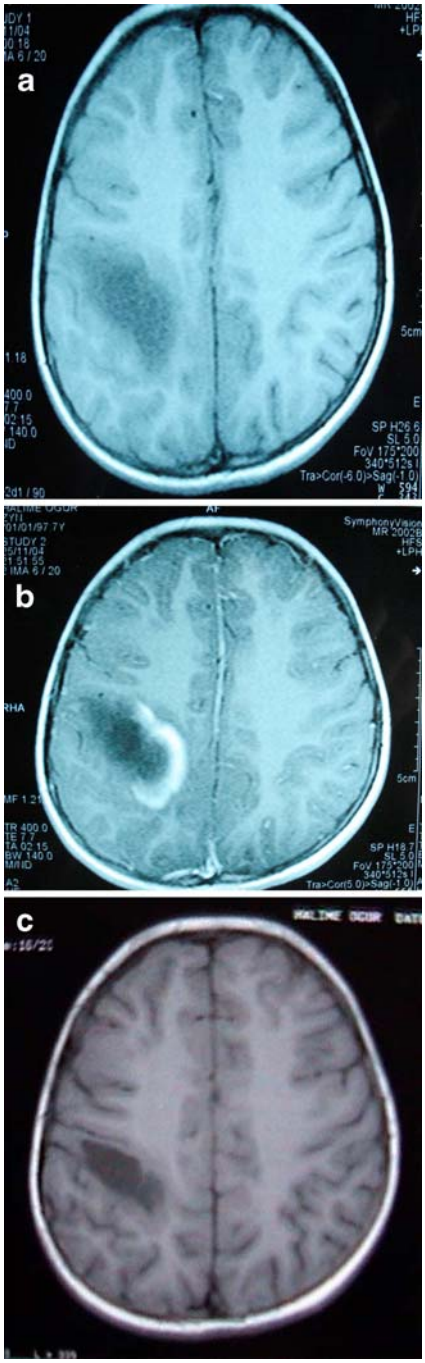

Fig. 1 Case 1: Spin-echo T1- weighted axial image (**a**) shows hypo-intense large lesion on the right parietal white matter and a contrast-enhanced T1-weighted axial image (**b**) demonstrates hypo-intensity and peripheral half-rim enhancement. **c** Case 1: Spin-echo T1-weighted axial image with intravenous gadolinium–DTPA; 3 months after, the treatment shows no contrast enhancement focal hypo-intensity on the right parietal region

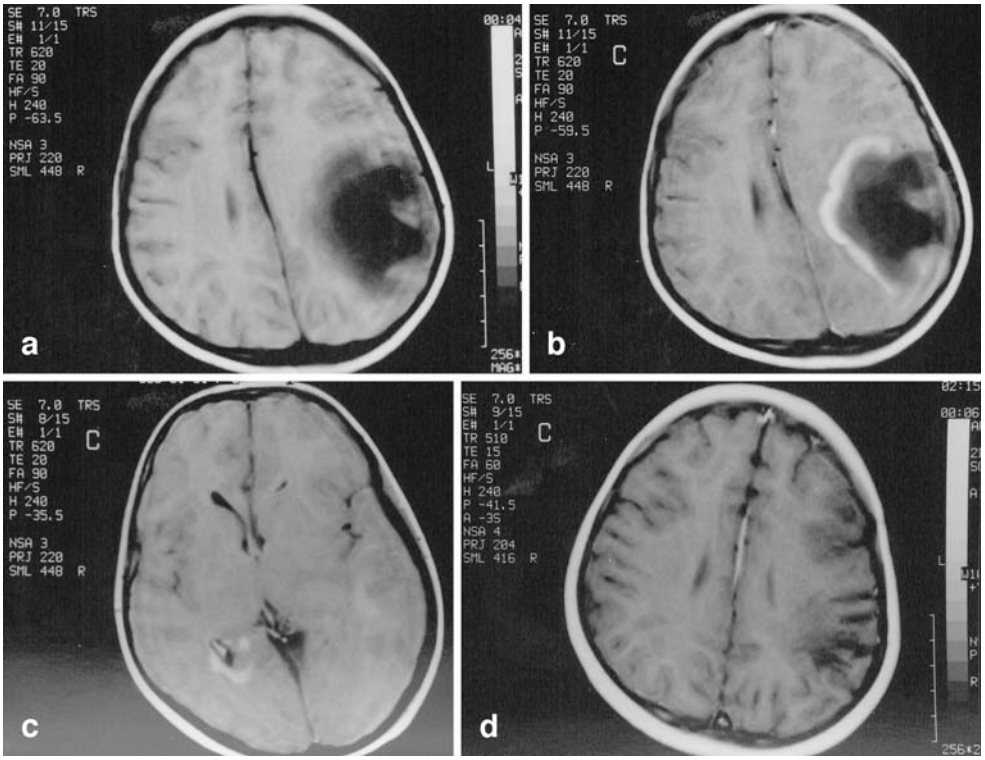

Fig. 2 **a**, **b** Case 2: Spin-echo T1-weighted axial image pre-contrast and after intravenous gadolinium–DTPA: A large left parietal mass with a hypo-intense center and incomplete ring enhancement along the medial border. Mass effect and midline shift to the right are minimal when compared to the size of the lesion. **c** Case 2: Spin-echo T1-weighted axial image; a smaller second lesion with contrast enhancement abutting the right lateral ventricular border with no apparent central hypo-intensity. **d** Case 2: Spin-echo T1-weighted axial image with intravenous gadolinium–DTPA; 3 months after the treatment: significant shrinkage of the large lobar lesion. No contrast enhancement is present

atrophic changes were detected on the cranial MRI repeated after 3 months (Fig. 2d). The patient has been followed for 6 years without any recurrence and neurological sequela.

Discussion

Schilder's diffuse sclerosis is a rare myelin disorder, which might mimic intra-cranial abscess or neoplasm [8]. The diagnostic criteria, treatment modalities and the pathogenesis remain unclear [5]. The typical lesion is large, with sharply outlined focus of myelin destruction usually localising in the cerebral hemisphere [9]. Incomplete rim enhancement and peri-lesional oedema are associated findings on MRI. Histological findings including well-demarcated demyelination, peri-vascular infiltration of lymphocytes and macrophages and microglial proliferation indicated immuno-mediated myelin destruction and inflammation [10]. The patients might present with signs and symptoms that are comparable with the features of an intracranial mass lesion [11].

Based on these Poser's criteria established 21 years ago, histological examination must be done for the accurate diagnosis. Brain biopsy is usually performed to rule out other causes such as an infections, malignancy or metabolic condition. However, with the advent and wide use of more informative neuroradiological investigations, paediatric neurologists and neurosurgeons can obtain detailed and

Table 1 Literature overview: results of the patients diagnosed as Schilder's disease since 1998

Authors (year)	Number	Sex	Biopsy	Treatment	Response to treatment	Recurrence
Pretorius et al. (5)	3	2F,1M	N/A	IVIG, steroid	1 complete recovery 2 hemiparesis	−
Leuzzi et al (1999)	2	M	A	Steroid, azathioprine	1 complete recovery 1 paretic nystagmus	+ (2 cases)
Fitzgerald et al (2000)	1	M	A	Streroid	1 hemiparesis	+
Afifi et al (2001)	1	F	A	Steroid	1 visual defect	−
Fernandez et al (6)	5	4F,1M	N/A	Steroid	5 minor sequela	+(3 cases)
Poppe et al (2001)	1	M	A	Steroid	1 tetraparesis, pseudobulbar palsy	+
Farideh et al (2002)	1	F	A	Steroid	1 complete recovery	−
Obara et al (2003)	1	M	A	Steroid	1 complete recovery	−
Kurul et al (7)	1	F	N/A	Steroid	1 complete recovery	+
Garrido et al (2004)	2	M,F	A	Steroid	2 complete recovery	+

F Female *M* male, *N/A* non-available, *A* available

reliable data about the lesion. In addition, the early response to the steroid treatment might be followed by MRI non-invasively. To make the accurate diagnosis of Schilder's disease, the most important point is exclusion of other possibilities, particularly an abscess or a tumour.

We did not perform brain biopsy in these children. A brain abscess was in the differential diagnosis; however, the patients were afebrile, blood and CSF analysis did not demonstrate any evidence indicating a bacterial infection, and complete ring enhancement that is typical for brain abscess was not seen on MRI [17]. A glial tumour thought to be a likely diagnosis because of clinical presentation and radiological findings (single large lesion involving the right parietal white matter with oedema and half-rim enhancement). Distinguishing clearly a tumour and tumefactive demyelinating lesion based on the MRI findings could be very difficult; however, both patients had excellent and early response to the steroid treatment clinically and radiologically.

Brain biopsy is an invasive procedure in children and must be performed under general anaesthesia. Stereotactic brain biopsy-related morbidity rate is ranging from 0.7 to 9% and mortality rate between 0 and 1.2% in the recent literature [12–15]. On the other hand, the histopathological findings might not be specific. Ferreira et al. [15] reported a series of 170 patients with stereotactic brain biopsy; in 19 patients (11%), histopathologic changes were reported as non-specific inflammatory lesions.

Garell et al. [3] reported three patients and a literature overview investigating all reported patients until 1998 and proposed that only 21 patients out of more than 100 reported cases had 'true' Schilder's disease. Table 1 shows reported patients since 1998. The histological examination was performed in 9 of reported 18 patients since 1998, whereas in half of the patients, the diagnosis was made without brain biopsy. In these patients, the radiological findings were sufficient to diagnose the disease, and all patients were treated by steroid successfully [5–7].

Immuno-mediated disorders involving the central nervous system have a wide spectrum. Definitive diagnosis might be difficult despite the radiological findings and even biological markers indicating demyelination [16]. Schilder's disease is accepted as an immuno-mediated disorder; however, the pathogenesis on treatment modalities are open to discuss.

Corticostreoids probably arrest active demyelination, while cystic degeneration with axonal damage remains unchanged [5]. The current literature does not provide clear guidelines regarding the dosage or duration of corticosteroids therapy in Schilder's disease. We used intra-venous pulse steroid 20 mg/kg daily for both two cases and obtained good clinical response. Steroid treatment was continued until the repeated MRI observed no inflammatory change.

Based on the features of the presented patients, we proposed that invasive brain biopsy is not always necessary for the diagnosis of Schilder's disease and that pulse steroid treatment is effective. Neurosurgical interventions might be performed by taking into consideration the clinical and radiological features of the patients as well as the early response to the steroid treatment.

References

1. Menkes JH (2006) Child neurology. In: Legido A, Tenembaum SN, Katsetos CD, Menkes JH (eds) Autoimmune and post-infectious disease. Lippincott Williams and Wilkins, Philadelphia, PA, pp 574–575
2. Schilder PF (1912) Zur Kenntnis der sogenannten diffusen Sklerose (über Encephalitis periaxialis diffusa). Z Gesamte Neurol Psychiatr 10 Orig:1–60
3. Garell PC, Menezes AH, Baumbach G, Moore SA, Nelson G, Mathews K, Afifi AK (1998) Presentation, management and follow up of Schilder's disease. Pediatr Neurosurg 29:86–91
4. Poser CM, Goutieres F, Carpentier MA, Aicardi J (1986) Schilder's myelinoclastic diffuse sclerosis. Pediatrics 77:107–112
5. Pretorius ML, Loock DB, Ravenscroft A, Schoeman JF (1998) Demyelinating disease of Schilder type in three young South African children: dramatic response to corticostreoids. J Child Neurol 13:197–201
6. Fernandez Jaen A, Martinez-Bermejo A, Gutierrez-Molina M, Lopez-Martin V, Tendero A et al (2001) Schilder's diffuse myelinoclastic sclerosis. Rev Neurol 33(1):16–21
7. Kurul S, Çakmakçı H, Dirik E, Kovanlıkaya A (2003) Schilder's disease: case study with serial neuroimaging. J Child Neurol 18:58–61
8. Kaye EM (1999) Disorders primarily affecting white matter. In: Swaiman KF, Ashwal S (eds) Pediatric neurology: principles & practice, vol. 2. Mosby, St. Louis, MO, pp 849–852
9. Mc Adam LC, Blaser SI, Banwell BL (2002) Pediatric tumefactive demyelination: case series and review of the literature. Pediatr Neurol 26:18–25
10. Sugita Y, Terasaki M, Shigemori M, Sakata K, Morimatsu M (2001) Acute focal demyelinating disease simulating brain tumors: histopathologic guidelines for an accurate diagnosis. Neuropathology 21:25–31
11. Galucci M, Caulo M, Cerone G, Masciocchi C (2001) Acquired inflammatory white matter diseases. Child's Nerv Syst 17:202–210
12. McGirt MJ, Woodworth GF, Coon AL, Frazier JM, Amundson E et al (2005) Independent predictors of morbidity after image-guided stereotactic brain biopsy: a risk assessment of 270 cases. J Neurosurg 102:897–901
13. Smith JS, Hinojosa AQ, Barbaro NM, McDermott MW (2005) Frame based stereotactic biopsy remains an important diagnostic tool with distinct advantages over frameless stereotactic biopsy. J Neuro-Oncol 73:173–179
14. Heper AO, Erden E, Savas A, Ceyhan K, Erden I et al (2005) An analysis of stereotactic biopsy of brain tumors and nonneoplastic lesions: a prospective clinicopathologic study. Surg Neurol 64:82–88
15. Ferreira MP, Ferreira NP, Filho AAP, Filho GAP, Franciscatto AC (2006) Stereotactic computed tomography guided brain biopsy: diagnostic yield based on a series of 170 patients. Surg Neurol 65:27–32
16. Angelini L, Bardare M, Martini A (2002) Immune mediated disorders of the central nervous system in children. In: Angelini L, Zibordi F, Bugiani M, Milani N (eds) Inflammatory immune mediated disorders of the central nervous system. Mariani Foundation Paediatric Neurology. Eastleigh, England, pp 32–35
17. Omuro AM, Leite CC, Mokhtari K, Delattre JY (2006) Pitfalls in the diagnosis of brain tumours. Lancet Neurol 5:937–948