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Fulminant central nervous system demyelination associated with interferon-α therapy and hepatitis C virus infection

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Hepatitis C virus (HCV) infection is common in the general population and may coincide with disease in the central and peripheral nervous system. Interferon-α (IFN-α) is used as treatment for HCV infection. The therapeutic benefit is assumed to result from activation of natural killer cells and CD8+ T cells. Despite its beneficial effects, it has been associated with a number of autoimmune disorders, such as chronic inflammatory demyelinating polyneuropathy and multiple sclerosis. Several clinical reports including magnetic resonance imaging exist, but neuropathological confirmation of MS associated with IFN-α therapy and HCV infection is lacking. We report a case of a female patient with chronic HCV infection who developed 'acute MS'-like demyelinating disease after IFN-α administration, with extensive lesions throughout brain and thoracic spinal cord. The patient died after a disease duration of 6 months. Brain autopsy revealed Baló-like demyelinating plaques with positive HCV sequences within florid lesions. The development of fulminant demyelinating disease after administration of IFN-α suggests that autoimmune mechanisms such as T cell mediated tissue damage might be initiated or aggravated by IFN-α therapy. Additionally, the presence of HCV RNA within the demyelinated lesion indicates a possible role in triggering or propagating disease. *Multiple Sclerosis* 2007; **13**: 1100–1106. http://msj.sagepub.com

Key words: CD8+ T cells; concentric sclerosis (Baló); hepatitis C virus; interferon-α; multiple sclerosis (MS)

Introduction

Hepatitis C virus (HCV) is a member of the family of *Flaviviridae,* which possesses a single-stranded positive-sense RNA (ss+RNA) genome. At present, 170 million people worldwide are estimated to be infected by the virus, which leads to chronic liver disease, cirrhosis, and hepatocellular carcinoma. Although HCV is a primary hepatotropic virus, there is some evidence that it can affect the central nervous system either by direct infection or by immune-mediated processes. A possible pathogenetic role of HCV in neuropathology is supported by the detection of HCV RNA in peripheral nerve, muscle, brain tissue, and CSF of patients with nervous system disorders (Table 1). Additionally, replication of HCV at extrahepatic sites was shown in blood macrophages/monocytes and brain tissue by detection of HCV negative-strand RNA sequences [1,2].

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Table 1 References to hepatitis C virus infection and IFN-α therapy associated with disorders in the central and peripheral nervous system

Hepatitis C				
Neurological disease associated with HCV infection	HCV infection	Detection of HCV RNA		
		Not done	Negative	Positive in respective tissue or CSF**
Peripheral neuropathy*	Chronic	[30–32]		[33]
Myelitis*	Chronic	[34,35]	[36]	[37]
Progressive encephalomyelitis	Chronic			[38]
Neuropsychologic symptoms/cognitive impairment*	Chronic			[1,2,24,39,40]
Acute encephalitis, acute disseminated encephalitis (ADEM)	Acute	[41]	[42]	[38]

* Non-exhaustive listing of references.
** Without microdissection of tissue; thus contamination by blood cannot be excluded.

Interferon-α	
Neurological syndrome associated with IFN-α treatment	IFN-α treated disease
Multiple sclerosis	HCV-infection [10] Chronic myelogenous leukemia [11]
Peripheral neuropathy	HCV-infection [43] melanoma [44]

Interferon-α (IFN-α) is a leukocyte-derived cytokine that is used for the therapy of chronic HCV infection. Immunomodulatory properties including activation of natural killer cells (NK) and cytotoxic T cells, upregulation of class I and II major histocompatibility complex, and terminal differentiation of dendritic cells are assumed to be responsible for the antiviral effect [3,4]. Both, HCV infection and IFN-α treatment have been associated with the occurrence of a number of nervous system disorders like peripheral neuropathy and demyelination in CNS (Table 1). Despite of repeated clinical reports including magnetic resonance imaging, histopathological descriptions of MS associated with IFN-α therapy are lacking. We report a patient with chronic HCV infection who developed 'acute MS'-like demyelinating disease in association with IFN-α therapy with detectable HCV RNA within active demyelinating lesions.

Material and methods

Clinical history

In 1990, a 25-year old female patient presented with first-time-manifestation of schizophrenic psychosis. At the same time, vasculitic purpura of both lower extremities was noted. In 1995, ongoing aggressive HCV infection which has led to cirrhosis was confirmed by liver biopsy. In 2001, IFN-α therapy (3×3 million U/week) was initiated. After a dose reduction in 2002 (2×3 million U/week), IFN-α therapy had to be stopped in February 2003 due to leukopenia.

In May 2003, the patient presented with spastic paraparesis and hypoalgesia of the lower extremities, atactic gait, and mild urinary incontinence. Additionally, hypothyreoidism as well as high serum levels of immune complexes and vascular purpura affecting the lower limbs were found. Histological examination of a cutaneous biopsy showed chronic leukocytoclastic vasculitis with mild IgM and C3 deposits. Lumbar puncture revealed two γ-globulin fractions but no oligoclonal bands. MRI examination of cervical and thoracic spinal cord detected no pathological alterations.

In October 2003 right-sided hemiparesis of the upper arm, sensomotoric aphasia, delirium, and epileptic seizures occured. Respective lesions were found in cranial CT. These lesions were hyperintense in MRI-FLAIR sequences and apart from a faint enhancement of one lesion, contrast enhancement was virtually absent (Figure 1). CSF analysis revealed mild lymphocytic pleocytosis. Tests for HIV, CMV, EBV and Toxoplasmosis were negative. To verify possible brain abscess, parainfectious demyelinating disease (ADEM), multiple sclerosis, or vasculitis, the patient underwent stereotactic brain biopsy. Histology showed areas of active demyelination and intensive perivascular inflammatory infiltrates. Despite treatment with high-dose methylprednisolone neurological symptoms worsened, the

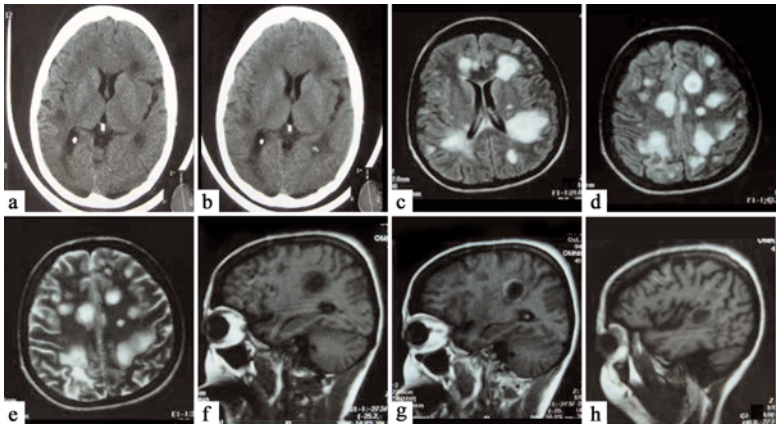

Figure 1 CT (a, b) and MRI examination with axial FLAIR (c, d, e) and contrast enhanced sagittal T1-weighted images (f, g, h). Widespread hypodense (CT, a, b) non-space-occupying bilateral lesions in the fronto-temporal and parieto-occipital lobes involve the deep and the subcortical white matter, with high signal intensity (FLAIR, c, d, e). Except one lesion (g), contrast enhancement was virtually absent (f, g, h).

patient became unconscious and finally died in November 2003 due to sepsis.

Neuropathology

Formalin fixed and paraffin embedded brain tissue was stained with hematoxylin/eosin (HE) and Luxol fast blue/PAS to assess inflammation and demyelination, respectively. Immunohistochemistry was performed with well characterized antibodies according to previously described protocols [5].

Detection of hepatitis C virus in paraffin embedded liver and brain biopsies

The tissue was prepared according to a previously published protocol [6]. Briefly, primers were chosen from the 5'UTR to perform a nested PCR. The resulting lengths of amplification products were 140 bp and 162 bp, respectively. RNA was extracted with phenol/chloroform and converted to cDNA with reverse transcriptase (Amersham, Braunschweig, Germany). The cDNA-sequencing was performed in an automatic sequencer (LI-COR, Lincoln, NE). In brain sections, microdissection was applied to pick up brain tissue and avoid contamination by serum. For this purpose, sections were viewed under a microscope and demyelinated white matter with some lymphocytes and macrophages but without vessels was dissected using a laser microbeam (P.A.L.M., Wolfrathshausen, Germany) as reported perviously [7]. We did not perform *in situ* hybridization, since in our experience this method did not prove to be reliable for HCV RNA detection, as artefacts make interpretation of results difficult.

Results

Histopathological findings

Neuropathological examination of frontal, temporal, parietal, and occipital lobes of the brain and spinal cord showed large confluent areas of selective demyelination with relative preservation of axons, consistent with characteristic histopathological findings of multiple sclerosis. In brain, demyelination was characterized by a mosaic pattern consisting of alternating patches of demyelination and intact myelin, with perivascularly preserved myelin (Figure 2a–d). The outer edges of the lesions showed ongoing demyelinating activity, defined by degradation products positive for all myelin proteins within the cytoplasm of macrophages (Figures 2e and 3a). In the left parietal lobe a fresh hemorrhage was observed with numerous erythrophages and some siderophages (Figure 2f, g). None of the lesions showed deposition of immune complexes positive for IgM, IgG or C3b on degenerating myelin or phagocytosed myelin fragments or reactivity for the activated complement complex C9neo (data not shown). At the edge of the expanding lesions, signs of hypoxia-like tissue injury were apparent, with expression of hypoxia-inducible factor 1α (HIF-1α), D-110-epitope and heat shock protein 70 (hsp70) in macrophages, astrocytes and oligodendrocytes (Figure 3b, c).

In general, perivascular infiltrates and inflammation deep in the CNS parenchyma were dominated by CD8-positive and granzyme B-positive cytotoxic T cells and macrophages (Figure 3d–f) which were most abundant in the actively demyelinating lesion areas. In addition, low numbers of OPD4-positive T (helper)-cells and some scattered perivascular plasmocytes were found. MHC class I molecules (α-chain, $\beta_2$microglobulin-light chain of

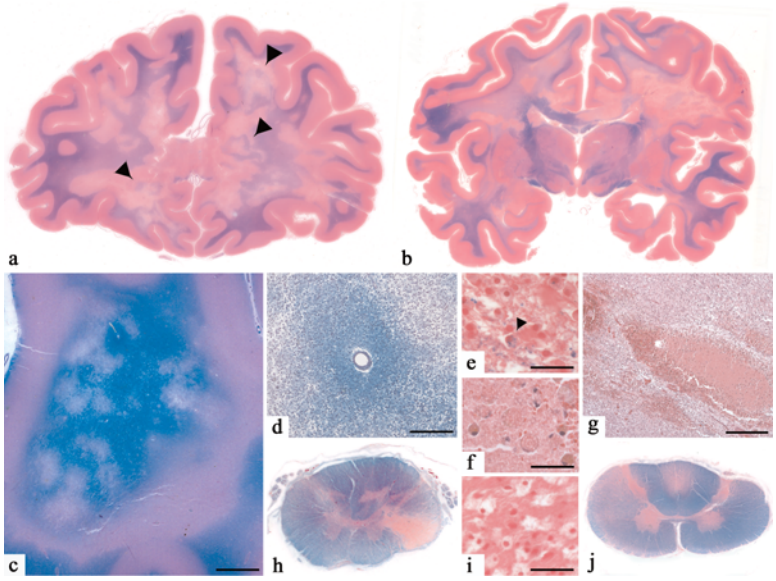

Figure 2 Histopathology in MS associated with IFN-α therapy and HCV infection. Widespread white matter lesions with alternating bands of demyelination and preserved myelin (a, b, arrows, Luxol fast blue) and mosaic pattern of demyelination (c) in the frontal lobe. Perivascularly preserved myelin (d) and ongoing demyelination activity with Luxol fast blue positive degradation products within the macrophages (e, arrow) characterize the lesions (c–e, Luxol/PAS staining). Fresh hemorrhage in the left parietal lobe with numerous erythrophages and some siderophages (f, g, H&E). Oldest MS-lesion in the thoracal spinal cord (h) contains macrophages with empty vacuoles (i). (h, i, Luxol fast blue). Degeneration of the gracile column in the cervical spinal cord (j, Luxol fast blue). Bars: **c**: 2 mm, **d**: 330 μm, **e, f, i**: 50 μm, **g**: 400 μm.

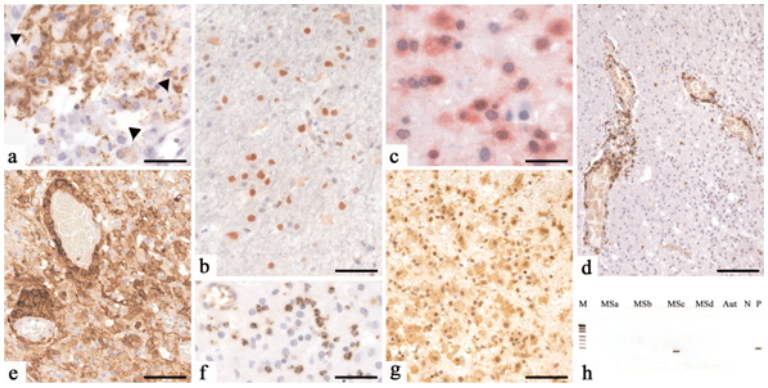

Figure 3 Immunohistochemistry (a–g) and PCR for HCV (h) in MS lesions. PLP (proteolipid protein) positive degradation products within macrophages indicate ongoing demyelination activity (a, arrow). Cells show signs of hypoxic stress with expression of HIF1α (b) and heat shock protein 70 (c) in macrophages, oligodendrocytes and astrocytes. CD8-positive T cells dominate in perivascular and parenchymal inflammatory infiltrates (d). Macrophages infiltrate the lesions and concentrate perivascularly (e, HLA-DR). Granzyme B, a marker for cytotoxic lymphocytes, is expressed in the majority of T cells (f). I-NOS positive macrophages and microglia can be identified in actively demyelinating zones and in the adjacent white matter (g). Detection of HCV-RNA in brain biopsy tissue (MS a–d: samples a–d from the MS-biopsy of the patient, Aut: autopsy brain tissue sample from MS-lesion, N: neg. control, P: pos. control). Bars: **a**: 50 μm, **b, e, g**: 67 μm, **c**: 26 μm, **d**: 100 μm, **f**: 42 μm.

MHC class I) were found upregulated mainly on macrophages and astrocytes. Macrophages in the actively demyelinating zones and microglia in the adjacent white matter were highly reactive for inducible nitric oxide synthase (I-NOS) (Figure 3g).

A solitary inactive plaque was found in the thoracic spinal cord, containing macrophages with empty vacuoles (neutral lipid stage of myelin degradation) (Figure 2h, i). Additionally degeneration of the cervical gracile fascicle was observed (Figure 2j).

PCR amplification of HCV sequences showed positive signals in both liver and brain, with an amplification band at 150 base pairs (Figure 3h). Sequencing of both amplicons from liver tissue and brain showed identical nucleotide sequences, indicating a single HCV genotype.

Discussion

In this case we find widespread actively demyelinating lesions in the white matter of brain and spinal cord, but not in cerebellum or brain stem. The clinical disease course with acute onset and rapid progression as well as histopathological features with alternating bands and patches of demyelination and intact myelin are compatible with Baló´s concentric sclerosis. Recent findings suggest hypoxic tissue preconditioning to be responsible for the formation of such particular type of demyelination [5,8]. Similar changes, characterized by upregulation of HIF-1α, D-110 and HSP70 were observed in our case. Detailed neuropathologic examination failed to demonstrate old, pre-existing MS lesions. The oldest plaque in the thoracic spinal cord had a lesion pathology in accordance with an age of several months, well corresponding the start of disease with spastic paraparesis 6 months before death.

After treatment with IFN-α our patient developed fulminant demyelinating disease. IFN-α is used as an effective therapy for chronic HCV infection which can lead to normalization of serum transaminase levels and reduction of HCV RNA in a high percentage of patients. However, IFN-α has been shown to initiate or exacerbate autoimmune disorders [9]. The leukocyte-derived cytokine has widespread immunomodulatory properties. Activation of NK-cells and cytotoxic T-cells as well as upregulation of class I and II of major histocompatibility complex and terminal differentiation of dendritic cells are some of the known effects [3,4]. Previous reports describe the appearance of MS after longterm treatment with IFN-α for chronic myelogenous leukemia and HCV infection [10,11]. These patients developed optic neuritis as well as sensory and motoric dysfunctions, with MRI-verified active lesions in the cerebral white matter and spinal cord. In all cases, symptoms subsided after interruption of IFN-α treatment, and in two cases a second attack was provoked after readministration of the cytokine. In our case, neurological symptoms occured with a time lag of 2 months after termination of IFN-α therapy. The low white blood cell count might have played a role in delayed manifestation of disease, as the onset of demyelination was concomitant with recovery of immunesystem. Although immunopathogenesis of MS is complex and heterogeneous, cytotoxic T cells seem to play an important role in induction of tissue damage [12,13]. Lymphocytic infiltrates in MS lesions are dominated by the CD8 positive T cell subset and clonal expansion is preferentially found in this T-cell subpopulation [14–18]. Moreover, acute axonal injury within the lesion correlates with the density of macrophages and CD8 positive T-cell infiltration [19–22]. In our case, IFN-α might have facilitated priming of autoreactive T cells, which then led to the induction of demyelination, following their expansion in the course of recovery from leukopenia.

Alternatively, onset of demyelination might be related to the exacerbation of HCV infection after termination of IFN-α therapy. PCR analysis in our case reveals positive HCV sequences in biopsy material from the active demyelinating lesion in the frontal lobe. Different studies describe detection of HCV sequences in brain tissue, CSF, muscle or peripheral nerve of patients with neurological disorders (Table 1). Trafficking of infected cells of monocyte/macrophage lineage through the blood-brain barrier and secondary spread of HCV to permissive resident microglial cells within the brain is discussed as a possible way of access [2]. Whether the presence of HCV in brain lesions is related to their pathogenesis or is a mere coincidence currently remains unresolved. Concentric layering of white matter lesions associated with the up-regulation of molecules involved in hypoxic preconditioning can occasionally be seen in classical virus induced brain diseases, such as herpes simplex virus- or cytomegalovirus-induced encephalitis [8,23]. Direct immune reactions against infected cells of the CNS or autoimmune reactions, triggered through molecular mimicry may play a role [1,2,24,25]. In addition, deposition of immunocomplexes on myelin sheaths is discussed as possible mechanism [26]. In our patient high serum titers of immune complexes as well as immune complex-mediated cutaneous vasculitis were detected. However, neither deposition of immunoglobulins such as IgG or IgM nor complement components or activated complement complex were detected by immunohistochemistry in the autopsy and biopsy material. In contrast, high numbers of cytotoxic T cells within the CNS parenchyma were evident, which might represent enhanced cellular reactivity triggered by the virus and amplified by the action of IFN-α.

In the last two decades IFN-α has been tested as a therapy for MS. In a series of studies, favourable results have been described [27]. Other investigations however could not confirm a clear therapeutic benefit. Compared to the placebo group, more IFN-α treated cases progressed from the relapsing to the progressive phase of the disease, and exacerbation of MS after administration of recombinant human IFN-α could be observed [28,29]. These conflicting results led to the decision to stop IFN-α treatment as therapy of MS. In addition to those cases, our observation confirms that it might be prudent to check for autoimmune disorders including MS before starting IFN-α therapy.

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