CLINICAL RESEARCH

Interferon γ in acute and subacute encephalitis

P LEBON, B BOUTIN, O DULAC, G PONSOT, M ARTHUIS

Abstract

Intrathecal synthesis of interferon γ was shown in 14 out of 16 samples of cerebrospinal fluid collected in the first days of disease in adults, children, and newborn infants with herpes encephalitis. This synthesis was concomitant with that of interferon α and was switched off when the specific antibodies in the central nervous system increased. No endogenous interferon γ was detected in 11 serum samples or 13 samples of cerebrospinal fluid collected early in the course of the disease from patients with measles encephalitis and rubella encephalitis, or in serum and cerebrospinal fluid samples from seven patients with subacute sclerosing panencephalitis. In serum collected after the 10th day after the onset of neurological symptoms interferon γ was present at low concentrations in only three out of 11 serum specimens from patients with measles encephalitis or rubella encephalitis.

Interferon γ was present in patients with acute herpes encephalitis and there was active virus replication, but it was not present in postinfectious encephalitis. Possibly the local production of specific antibodies masks the viral antigens and switches off the induction of interferons.

Introduction

Different pathogenic processes are found in primary and postinfectious encephalitis: firstly, in the primary disease the virus replicates in the central nervous system, whereas in postinfectious disease viral antigens are not generally detected in the brain cells[1]; and, secondly, one factor in the non-specific host defence, interferon α, has been shown to be present in herpes encephalitis but not in measles encephalitis or rubella encephalitis.[2,3] No data have been reported on the incidence of interferon γ in acute and chronic viral infections of the central nervous system. As interferon γ has a key role in the immune response and in particular enhances or induces the expression of class II histocompatibility antigens in astrocytes[4,5] and endothelial cells[6] we investigated its presence in cerebrospinal fluid and serum from patients with viral infection of the central nervous system.

Institut National de la Santé et de la Recherche Médicale, Unité 43, Hôpital St-Vincent-de-Paul, 75674 Paris Cedex 14

P LEBON, MD, virologist
B BOUTIN, MD, consultant paediatrician

Clinique de Pédiatrie, Université Paris V, Service de Neuropédiatrie, Hôpital St-Vincent-de-Paul

O DULAC, MD, consultant paediatrician
G PONSOT, MD, professor of paediatrics
M ARTHUIS, MD, professor of paediatrics

Correspondence to: Dr Lebon.

Patients and methods

From 1981 to 1985 we collected samples of cerebrospinal fluid and serum from 40 patients. The patients comprised 17 with herpes encephalitis (three adults and eight children with mild disease and six newborn babies, in whom the disease was lethal); seven children with measles encephalitis; nine children with rubella encephalitis; and seven children with subacute sclerosing panencephalitis. For each patient the serum and cerebrospinal fluid samples were collected on the same day and stored at −30°C.

The diagnoses of herpes encephalitis and subacute sclerosing panencephalitis were based on increased intrathecal synthesis of specific antibodies evaluated with methods previously described.[3] In five of the six newborn infants herpes encephalitis was diagnosed by isolation of virus from brain tissue collected after necropsy. Postinfectious encephalitis was diagnosed when specific IgM antibodies were detected in serum by two different methods[6,7] and by the absence of persistent synthesis of IgG in cerebrospinal fluid samples collected late in the course of the illness. All samples, both serum and cerebrospinal fluid, were tested simultaneously in the same assays for endogenous interferon α and interferon γ.

Interferon α was measured in a biological assay as previously described, with Madin-Darby bovine kidney cells and vesicular stomatitis virus as the challenge virus.[2,8] Interferon γ was measured by a solid phase radioimmunoassay (Centocor Corporation) that allowed its detection despite the presence of interferon α in the samples. This test, described by Chang *et al*,[9] can detect as little as 0·5 IU/ml; the monoclonal antibodies used in the assay were specific for the epitopes of biological activity of human interferon γ.[10] For values at the limit of 0·5 IU/ml the specificity of the test was controlled by adding serum containing polyclonal antirecombinant interferon γ to the specimens before performing a new radioimmunoassay. Under these conditions the added serum reduced the specific binding of the monoclonal antibody labelled with iodine-125 by over 90%.

Results

Table I shows the results of the assays on the samples from patients with herpes encephalitis. Interferon γ was detected in the first serum sample from one newborn infant but not in nine first samples from the other patients. (The assay was not done on serum from all the patients.) Interferon γ was present in the cerebrospinal fluid of adults, children, and newborn

TABLE I—*Concentrations of interferon α and interferon γ in herpes encephalitis*

Case No	Age	Day after onset of neurological symptoms that samples were collected	Interferon α (IU/ml)		Interferon γ (IU/ml)		Titre of antibody to herpes simplex virus*	
			Serum	CSF	Serum	CSF	Serum	CSF
1	58 years	6	<10	120	<0·5	1	20	<1
		19	<10	<2		<0·5	160	32
2	41 years	5	<10	50	<0·5	40	80	1
		45				<0·5	640	128
3	47 years	8	<2	60	<0·5	1	80	2
		36	<8	<2	<0·5		160	32
4	6 months	3	16	100	<1	2	10	<1
		90	<4	<2	<0·5	<0·5	320	4
5	2 years 5 months	6	10	100	<1	2	10	<1
		29	<10	<8		<0·5	320	8
6	1 year	4	<25	100	<1	2	20	<1
		120	<8	<2		0·5	640	25
7	11 years	10		10		24		4
		17	<10	<2	<1	<0·5	320	16
8	6 months	9	<2	4	<0·5	<0·5	640	32
		21	<2	<2	<0·5	<0·5	320	32
9	2 years	2	8	4		<1	20	<1
		31	<10	<1			1280	32
10	1 year 2 months	7	8	50		39	10	<1
		17		<7		<0·5	960	50
11	5 years	7	4	60		26	<6	<1
		20		<2		<0·5	600	30
12	21 days	2	250	120		14	20	<1
		12		<2		2	160	6
		35	<2	<2		<1	320	16
13	21 days	8	80	50	<1	4	160	60
14	14 days	1	16	130	<1	3	40	<1
		16	<2	<4	<1	<1	80	8
15	15 days	2				11	20	16
16	25 days	2	20	100		5	160	2
17	10 days	1	300		5		10	

CSF=Cerebrospinal fluid.
*Titres expressed as reciprocal of serum and cerebrospinal fluid dilutions that neutralise 50% of the viral cytopathic effect.
Assays were not done on samples in all patients.

TABLE II—*Number of patients showing synthesis of interferon γ* before and after 10th day after onset of neurological symptoms*

	Viral agent			
	Measles (postinfectious encephalitis) (n=7)	Rubella (postinfectious encephalitis) (n=9)	Herpes simplex (n=17)	Measles (subacute sclerosing panencephalitis) (n=7)
	On or before 10th day after onset of symptoms			
Serum	0/7	0/5	1/10	
Cerebrospinal fluid	0/6	0/7	14/16	
	After 10th day after onset of symptoms			
Serum	1/4	2/7	0/5	0/7
Cerebrospinal fluid	1/7	0/5	1/20†	0/7

*Titre of 0·5 IU/ml or more.
†Additional samples were tested; these are not shown in table I.

infants. It was synthesised exclusively in 14 out of the 16 samples of cerebrospinal fluid that were collected early in the course of the illness and became undetectable (<0·5 IU/ml) in 19 out of the 20 specimens collected later from the 17 cases of herpes encephalitis (table II). The concentrations of interferon γ in the cerebrospinal fluid were generally as high in the newborn infants as in the children. Interferon γ was always associated with the presence of interferon α in the cerebrospinal fluid, but no linear relation could be established between their concentrations. The disappearance of the interferons from the central nervous system was concomitant with an increase in intrathecal synthesis of specific antibodies. Table II also shows the results of the incidence of synthesis of interferon γ in all 40 patients before and after the 10th day after the onset of neurological symptoms.

Discussion

The presence of interferon γ in cerebrospinal fluid was related to the acute type of encephalitis and also to the time of sampling. It was detected early in the course of herpes encephalitis but not during the course of postinfectious encephalitis.

The absence of interferon γ in measles encephalitis and rubella encephalitis could be related to the absence of viral antigens in the central nervous system as has been shown in some lethal cases by Johnson *et al.*[1] In specimens collected from these patients later in the course of their illness the low concentrations of interferon γ found in only three out of 11 serum samples and one out of 12 samples of cerebrospinal fluid may have been due to an immune response against autoantigens rather than viral antigens. Other techniques such as molecular hybridisation in situ and immunocytochemistry applied to histological materials are needed to evaluate the role of interferon γ in postinfectious encephalitis.

In herpes encephalitis interferon γ was synthesised in the central nervous system as concentrations were always higher in the cerebrospinal fluid than in serum. Interferon γ was produced early in cerebrospinal fluid, simultaneously with interferon α; 10 days after the onset of the neurological disorder neither interferon could be detected. At this stage specific antibodies that are synthesised locally could also be one of the factors in the disappearance of both interferons from cerebrospinal fluid; indeed, specific antibodies

have been shown to neutralise the capacity of viruses or viral antigens to induce interferon α.[11] Although in newborn infants with herpes encephalitis the peripheral blood mononuclear cells have been shown to produce lower amounts of interferon than those from adults in vitro,[12] our infants had concentrations of interferon γ in cerebrospinal fluid equivalent to those in the adult and child patients. The presence of interferon γ in cerebrospinal fluid has already been reported in tuberculous meningitis,[13] but no interferon α was detected.[14] Interferon γ was shown to be produced in vitro by T lymphocytes in the presence of herpes virus antigens and accessory cells[15]; its synthesis therefore needs interleukins 1 and 2, which are probably also secreted in the central nervous system during the course of herpes encephalitis. In addition to its property of inducing histocompatibility antigens in different cells,[16] interferon γ enhanced the production of antibodies by B cells.[17] It may consequently participate in the sequence of events leading to the synthesis of virus antibodies to herpes in the central nervous system. In this study we could not make a precise correlation between the evolution of the disease and the concentrations of interferon γ in the cerebrospinal fluid as antiviral treatment was introduced at different stages of the disease. High concentrations of interferon γ and interferon α, as seen in cases 10 and 11, however, were not an aggravating factor of the disease as these patients recovered with only minor sequelae after antiviral treatment.

Despite the presence of viral antigens in the brain tissue patients with subacute sclerosing panencephalitis had no interferon γ detectable in the cerebrospinal fluid or serum; the important local production of specific antibodies in this disease probably masks the viral antigens and switches off the induction of both interferon γ and interferon α.[8]

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Acylcoenzyme A dehydrogenase deficiency in heart tissue from infants who died unexpectedly with fatty change in the liver

FIONA ALLISON, M J BENNETT, S VARIEND, P C ENGEL

Abstract

Heart muscle from infants who died unexpectedly and who showed fatty changes in the liver at necropsy was analysed for long chain and medium chain acylcoenzyme A dehydrogenase activities by using the natural electron acceptor. In two of the seven cases investigated a deficiency in acylcoenzyme A dehydrogenase activity was found. In one case the deficiency was in medium chain acylcoenzyme A dehydrogenase activity and in the other long chain acylcoenzyme A dehydrogenase activity.

These findings emphasise the importance of investigating fatty acid oxidation in infants who have died unexpectedly.

Children's Hospital, Sheffield S10 2TH
FIONA ALLISON, BSC, basic grade biochemist
M J BENNETT, PHD, MRCPATH, principal biochemist
S VARIEND, MD, MRCPATH, consultant pathologist

Department of Biochemistry, University of Sheffield, Sheffield S10 2TN
P C ENGEL, MA, DPHIL, reader in biochemistry

Correspondence to: Mrs Fiona Allison, Department of Chemical Pathology, Children's Hospital, Western Bank, Sheffield S10 2TH.

Introduction

It has recently been shown that some cases of unexpected death in infancy and which previously would have been classified as the sudden infant death syndrome are attributable to various inherited defects of fatty acid beta oxidation.[1,2] Three fatty acylcoenzyme A dehydrogenases are concerned in the mitochondrial degradation of straight chain fatty acids: these are long chain, medium chain, and short chain acylcoenzyme A dehydrogenases.[3] When fatty acylcoenzyme A's are oxidised by the acylcoenzyme A dehydrogenases the electrons generated reduce electron transfer flavoprotein, which in turn is reoxidised by electron transfer flavoprotein dehydrogenase, and are then passed along the mitochondrial respiratory chain to oxygen, the terminal electron acceptor. Defects of either long chain or medium chain acylcoenzyme A dehydrogenase often result in periodic episodes of hypoglycaemia accompanied by a hypoketotic dicarboxylic aciduria.[4]

Defects of electron transfer flavoprotein and electron transfer