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Laboratory Diagnosis of Radicular and Pseudoradicular Syndromes in Cerebrospinal Fluid (CSF): Reliability of Methods in Consideration of Pathogenetic Aspects

Report on Section "CSF Diagnosis" of 4th Klagenfurter Neurology Workshop Conference on Radicular and Pseudoradicular Syndromes[1], Klagenfurt, Austria, August 28–29, 1992

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Dedicated to Prof. Dr. K. Felgenhauer on the occasion of his 60th birthday

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Summary: Laboratory tests may be used to confirm the clinical differentiation of pseudoradicular syndromes and radicular syndromes. In the presence of pseudoradicular syndromes, CSF and blood samples yield no positive results with either non-specific or specific methods. Radicular syndromes give rise to positive findings; using non-specific methods they can be subdivided into inflammatory and non-inflammatory forms, with and without blood-nerve barrier impairment. Non-specific quantities of CSF routine diagnosis are total protein, albumin, leukocyte counts and differential cell count, *L*-lactate, intrathecal -IgG, -IgA, -IgM and immunoglobulin-class oligoclonal bands. Oligoclonal bands enable the highly sensitive differentiation of non-inflammatory from subacute-chronically inflammatory forms of radicular syndromes. Most of the specific quantities are the subject of current research, e. g. bacterial antigens, *D*-lactate, cultivation tests, polymerase chain reaction tests and pathogen-specific oligoclonal bands. Pathomechanisms affecting the permeability of the blood-nerve barrier to increasing concentrations of protein and to leukocyte subsets possibly explain the CSF findings in radicular and pseudoradicular syndromes.

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Definition and Pathogenesis of Radicular and Pseudoradicular Syndromes

Radicular and pseudoradicular syndromes frequently become symptomatic as sensations and pain localized in dermatomes.

Clinically, radicular syndromes usually include sensitivity and motor deficits of characteristic distribution (1). They are of different causality. Thus, trauma of the spine and compression of nerve roots or spinal cord by disc herniation may produce similar clinical symptoms, resembling those sometimes found in patients with inflammatory diseases of the peripheral nervous system, caused e. g. by viral infections (2, 3), especially by tick-borne polyneuritis (1, 4). Various neuropathies of inflammatory and non-inflammatory genesis may also show radicular symptoms. As the blood-nerve-barrier appears to be involved in inflammatory diseases, humoral and cellular quantities of blood-nerve barrier function are important components of laboratory diagnosis.

With pseudoradicular syndromes, pain and sensations are not restricted to dermatoma and, by definition, there are no lesions of nerve roots, leading to sensitivity or motor deficits (5). Pseudoradicular syndromes may be caused by torsional or compression injuries of the disc anulus fibrosus (6), or by spondylopathic pain in intervertebral joints, leading to tendinosis and myogelosis with rupture of muscle fibres (cf. l. c. (7)). The latter may also be of rheumatic genesis e. g. with collagenosis or immune vasculitis (cf. l. c. (7)).

The significance and reliability of laboratory methods in the differential diagnosis of radicular and pseudoradicular syndromes were discussed at the CSF laboratory section of the 4th Klagenfurter Neurology Workshop Conference on radicular and pseudoradicular syndromes, recently published in German in Berichte der ÖGKC. In view of the important aspects of the laboratory diagnosis and pathogenesis of radicular and pseudoradicular syndromes reported at this conference, a summary report is presented here in English.

Laboratory Diagnosis of Radicular and Pseudoradicular Syndromes

Pseudoradicular syndromes generally do not give rise to positive results for CSF analysis: but slightly elevated protein contents were found in some cases of lumbar disc protrusions (tab. 1), obviously caused by protrusion of the degenerated disc into the spinal space. A disc protrusion can lead to back pain by irritation of nerve endings in the compromised anulus fibrosus (6). In blood serum, occasionally elevated creatine kinase (creatine kinase-MB < 6%) activities from affected skeletal muscles were detected, as well as rheumatic factors (8).

Radicular syndromes are indicated by non-specific quantities in CSF; they can be verified by specific quantities (8).

Non-specific Laboratory Quantities of Radicular Syndromes

A: *Quantities of the blood-nerve barrier.* As in the case of the blood-brain barrier (9, 10), increased total protein (and albumin) contents in CSF and decreased blood/CSF protein (albumin) gradients are signs of blood-nerve barrier disturbance in the CSF (see tab. 1). To explain the pathogenetic aspects, blood-nerve barrier is defined here briefly:

Blood-nerve barrier is present in the perineurium of every nerve consisting of concentric sleeves of flattened polygonal cells (11), and in endothelial cells from the vasa nervorum (12), both linked by "tight junctions", similar to the blood-brain barrier (cf. l. c. (10)). In the area of nerve roots, however, the perineurium barrier and endothelial barrier are partially permeable to albumin, immunoglobulins and their complexes, to medicaments and other compounds as well as to leukocytes or pathogens (11, 12). Therefore, the CSF space becomes accessible to systemic influences in the area of nerve roots. This may explain the pathomechanisms of neuropathies associated with metabolic or immune system-diseases or intoxications (see tab. 1 and l. c. (13, 14)).

Moreover, constituents of the endoneurinal space of nerves may enter retrogradely the CSF in the root area, so that they are detected in CSF samples. Thus, blood-nerve barrier breakdown with protein-rich vasogenic oedema of the endoneurinal space, as found e. g. in inflamed or mechanically damaged nerve roots, results in the elevation of protein in lumbar CSF. Examples of these pathomechanisms with inflammatory neuropathies and non-inflammatory neuropathies or compression neuropathies are presented in table 1. Note that the steepness of serum/CSF protein gradients correlates with the magnitude of the nerve damage produced by different forms of disc herniation with foraminal or spinal stenosis (causing nerve compression). To discriminate between blood-nerve barrier and blood-brain barrier functions barrier quantities in cisternal and lumbar CSF samples from the same patient have to be analysed simultaneously. However, it is inconvenient and inappropriate to perform cisternal and lumbar punctures simultaneously on patients for daily routine analysis.

As patients with viral meningitis may show radicular symptoms (7), the extent of blood-nerve barrier disturb-

Tab. 1 Leukocyte counts using a *Fuchs-Rosenthal* chamber (9) and total protein (biuret method (10)) in cerebrospinal fluid (CSF) samples from controls and various patients with respect to the differential diagnosis of radicular and pseudoradicular syndromes. Diagnosis was ascertained clinically and verified by imaging or laboratory techniques.

Patient Group (number of cases)	CSF	Leukocyte counts		Total protein		Serum protein / CSF protein	
		Median 10^6/l	Upper range 10^6/l	Median mg/l	Range mg/l	$\bar{x}$	Range
Controls of lumbar CSF (72)	L	1	5	310	170–450	217	140–404
Controls of cisternal CSF (43)	C	1	3	220	120–280	313	225–550
Traumatic and compression neuropathies							
Contusio spinalis (21)	L	2	51	420[A]	220–1000	162[A]	75–327
Lumbar disc protrusion (156)	L	1	7	440[A]	180–535	164[A]	65–343
Lumbar disc herniation medial (36)	L	1	6	385[A]	140–860	194[A]	78–514
latero-medial (65)	L	1	6	460[A]	230–1160	158[A]	65–322
lateral (331)	L	1	9	470[A]	150–2200	147[A]	30–460
Massive disc herniation lumbar (28)	L	1	14	625[A]	300–1440	108[A]	57–250
Cervical disc herniation (37)	C	0	5	280[A]	170–530	254[A]	123–433
Cervical syndrome (22)	C	1	10	250[B]	140–515	272[B]	120–450
Inflammatory diseases of the nervous system							
Meningitis							
bacterial (25)	L	635[A]	30773	2150[A]	390–24640	31[A]	3–241
viral (30)	L	40[A]	608	480[A]	250–3550	143[A]	20–236
Meningeosis neoplastica (15)	L	2	1571	670[A]	300–10720	101[A]	6–240
Tick-borne polyneuritis (30)	L	77[A]	553	960[A]	330–4250	70[A]	16–239
Garin-Bujadoux-Bannwarth							
Facial paresis peripheral (33)	L	2[B]	207	410[A]	180–910	162[A]	81–394
Mono-, di-, tetra-plegia (38)	L	1	18	490[A]	250–6150	140[A]	9–288
Inflammatory neuropathy							
Neuritis (12)	L	4[A]	42	810[A]	320–1690	74[A]	40–228
Landry-Guillain-Barrè Syndrome (31)	L	5[A]	270	1030[A]	330–13070	68[A]	6–188
Multiple sclerosis (175)	L	6[A]	32	440[A]	210–1325	158[A]	25–336
relapsing (36)	L	7[A]	39	420[A]	290–830	161[A]	86–248
Optic neuritis (25)	L	2[B]	13	330	220–590	221	119–332
Neuropathy associated with systemic disease							
Diabetic neuropathy (14)	L	2	4	710[A]	350–1670	94[A]	42–197
Polyneuropathy due to alcoholism (9)	L	1	6	490[A]	300–1490	156[A]	46–197
Polyneuropathy of unknown causality (64)	L	1	18	455[A]	220–3190	153[A]	23–272
Neuro-muscular diseases (19)	L	1	6	430[A]	210–660	158[A]	100–314

Abbrevations used: C: cisternal CSF; L: lumbar CSF; S: blood serum. Significance between median value of controls and median value of patients was calculated by the *Mann-Whitney* U-test (51): [A]) $p < 0.001$; [B]) $p < 0.05$. The values given for controls agree with reference values (9, 10).

ances appeared to be useful in discriminating between viral and bacterial genesis of radicular syndromes (15), but it was useless in the differential diagnosis of radicular syndromes (16). Diseases in the peripheral nerve (e. g. peripheral facial paresis, optic neuritis) exterior to the CSF space rarely show signs of blood-nerve barrier disturbance (tab. 1).

B: *Leukocytosis and its differentiation* into granulocytosis (with acute inflammation), lymphocytosis (with subacute inflammation), or monocytosis, as well as mixed pleocytosis in CSF indicate the cellular stage of inflammation in the nervous system (cf. l. c. (9, 10)). With radicular syndromes caused by inflammations (e. g. inflammatory neuropathy), all stages were found, depending on the disease process (1, 15, 17). No typical pattern of cellular differentiation was associated with inflammatory radicular syndromes.

Lymphocyte subsets were therefore investigated in CSF and venous blood by flow cytometry (18, 19), to detect a blood-CSF barrier: a blood/CSF ratio of ≈ 2,000 to 1 was found for total lymphocytes and activated T or helper/inducer T cells in controls (tab. 2); higher ratios were observed in the order cytotoxic/suppressor T cells > $CD3^+16^+56^+$ cells (a subset of cytotoxic T cells) > NK cells > B lymphocytes. The ratio was lower for $CD8^+4^+$ cells (premature T lymphocytes (cf. l. c. (20))

Tab. 2 Lymphocyte subsets determined by flow cytometry (18, 19) in cerebrospinal fluid (CSF) and venous blood samples from controls and patients with inflammatory diseases of the nervous system.

Lymphocyte Subset and Diseases [n]	Cerebrospinal fluid cell count [10^3/l]*	Peripheral blood cell count [10^6/l]*	Blood / CSF
T-Lymphocytes $CD3^+$)			
Controls (cf. l. c. (18, 19)) [22]	818	1516	1900 : 1
Inflammation of nervous system			
acute, bacterial [6]	10946	79	70 : 1
subacute [9]	56712	966	20 : 1
Inflammatory neuropathy [5]	1088	1413	1300 : 1
Activated T-lymphocytes ($CD3^+$ $HLA\text{-}DR^+$)			
Controls (cf. l. c. (18, 19)) [22]	83	180	2200 : 1
Inflammation of nervous system			
acute, bacterial [6]	1676	112	70 : 1
subacute [9]	5578	180	30 : 1
Inflammatory neuropathy [5]	44	129	2900 : 1
Helper-/inducer T-lymphocytes ($CD3^+4^+$)			
Controls (cf. l. c. (18, 19)) [22]	600	1071	1800 : 1
Inflammation of nervous system			
acute, bacterial [6]	7647	473	60 : 1
subacute [9]	42128	677	20 : 1
Inflammatory neuropathy [5]	651	926	1400 : 1
Cytotoxic/suppressor T-lymphocytes ($CD3^+8^+$)			
Controls (cf. l. c. (18, 19)) [22]	153	507	3300 : 1
Inflammation of nervous system			
acute, bacterial [6]	3212	326	100 : 1
subacute [9]	9514	372	40 : 1
Inflammatory neuropathy [5]	312	452	1500 : 1
$CD3^+16^+56^+$ *T-lymphocytes*			
Controls (cf. l. c. (18, 19)) [22]	21	127	6100 : 1
Inflammation of nervous system			
acute, bacterial [6]	286	64	220 : 1
subacute [9]	594	68	120 : 1
Inflammatory neuropathy [5]	27	84	3100 : 1
$CD8^+4^+$-*Lymphocytes*			
Controls (cf. l. c. (18, 19)) [22]	32	27	840 : 1
Inflammation of nervous system			
acute, bacterial [6]	399	12	30 : 1
subacute [9]	680	17	24 : 1
Inflammatory neuropathy [5]	38	33	860 : 1
Natural killer (NK) cells ($CD16^+56^+3^-$)			
Controls (cf. l. c. (18, 19)) [22]	37	387	10500 : 1
Inflammation of nervous system			
acute, bacterial [6]	481	193	400 : 1
subacute [9]	2173	296	140 : 1
Inflammatory neuropathy [5]	160	623	3900 : 1
B-Lymphocytes ($CD19^+$)			
Controls (cf. l. c. (18, 19)) [22]	9	266	30000 : 1
Inflammation of nervous system			
acute, bacterial [6]	283	162	600 : 1
subacute [9]	1095	204	190 : 1
Inflammatory neuropathy [5]	59	248	4200 : 1

* Medians are given

(tab. 2). The preliminary findings indicate the existence of a blood-CSF barrier with different permeability rates to lymphocyte subsets, and this permeability appeared to be altered to different extents in inflammatory diseases of the nervous system (tab. 2). Thus, during acute inflammation, barrier permeability increased by a factor of ≈ 30 to all subsets, except for B lymphocytes (permeability increased by a factor of ≈ 50). During the

subacute stage of inflammation (e. g. six days after the first clinical signs) permeability further increased, especially to helper/inducer T cells (responsible for antigen recognition and B cell activation) and NK cells, but not to $CD8^+4^+$ T cells. With inflammatory neuropathies (e. g. multiple sclerosis, tick-borne polyneuritis), permeability was particularly increased to B lymphocytes (responsible for the humoral immune response), as well as to cytotoxic/suppressor T cells, $CD3^+16^+56^+$ T cells mediating non MHC restricted cytotoxicity (cf. l. c. (18)), and NK cells (tab. 2). Our preliminary data indicate that blood-nerve barrier (and blood-brain barrier) may be involved in the regulation of the cellular immune response in the nervous system by controlling permeability to lymphocyte subsets. Further experiments are needed e. g. to explain increased suppressor activity in Lyme disease. The latter involves retarded antibody formation (21, 22), which may be explained by normal IL-6 activity (23) to B and T lymphocytes in CSF, in contrast to higher IL-6 concentrations in bacterial and nonbacterial meningitis (24).

C: *Metabolites.* The increased *L*-lactate concentration in CSF is a sign of acute ischaemia in the nervous system (10). Cytotoxic and intramyelinic oedema may cause elevated concentrations of *L*-lactate in lumbar CSF with intact blood-nerve barrier in acute spinal ischaemia, but they were rarely found with acute compressed nerve roots (16); in contrast inflamed nerve roots resulted in elevated concentrations of *L*-lactate and protein. Glucose concentrations (compared with blood) were without any diagnostic relevance for different radicular syndromes (1), although they were found to be diminished distal from a spinal blockage and in the presence of the cauda-equina syndrome of progressive HIV-1 polyradiculoneuritis (17).

D: *Intrathecally produced immunoglobulins* (Ig) were determined by calculation or by detection of oligoclonal bands in CSF (15, 25–27). Verification of oligoclonal Ig bands by isoelectric focusing (IEF), using the Phast System™ with self-made gels and immunofixation, proved to be more sensitive and specific than IEF with non-specific silver staining (fig. 1) (25–27). Moreover, compared with calculation procedures, the method was also more sensitive and specific for the determination of intrathecal IgG production with an intact or defective blood-brain barrier (28, 29). Therefore, IEF with Ig-specific oligoclonal band detection also provides a non-specific routine quantity for differentiating between non-inflammatory and inflammatory forms of radicular syndromes, especially in multiple sclerosis, with intact or defective blood-nerve barrier.

E: *Nerve Constituents.* The presence of different myelin proteins (e. g. P_0, P_1, P_2) in CSF and blood samples is indicative of demyelinating processes due to autoimmune, inflammatory, or degenerative diseases, as well as to anoxia in the nervous system (cf. l. c. (30)). The incidence of creatine kinase-MB values higher than 20% of the total serum creatine kinase value was small (indicating creatine kinase-BB) (16). These quantities were not disease-specific.

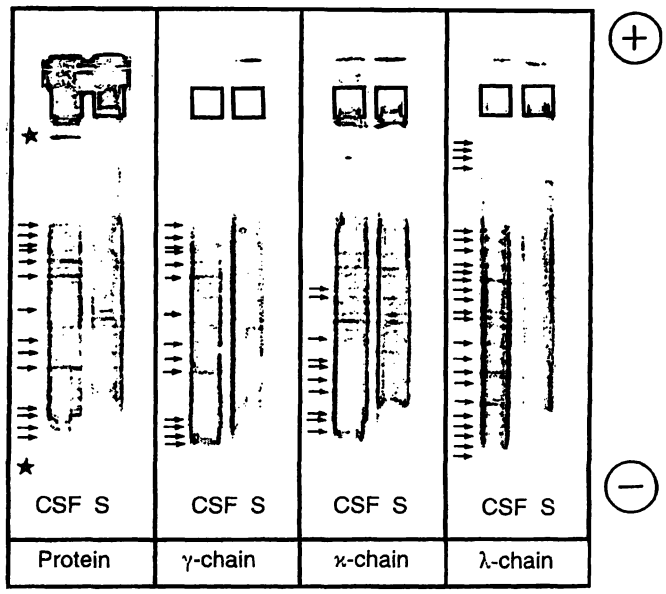

Fig. 1 IEF pattern of native cerebrospinal fluid (CSF) and serum (S) samples from a patient with tick-borne polyneuritis. Isoelectric focusing (IEF) was done as described (25–27) followed by silver staining after different precipitation methods:
"protein": non-specific precipitation with trichloroacetic acid;
immunoglobulins of "γ-chain" type: immunofixation with monospecific antiserum against human IgG (γ-chain);
immunoglobulins of "κ-chain" type: immunofixation with monospecific antiserum against human immunoglobulin kappa-chains (free and bound);
immunoglobulin of "λ-chain" type: immunofixation with monospecific antiserum against human immunoglobulin lambda-chains (free and bound).
Samples were diluted to 20 mg/l IgG (protein, κ-chain, λ-chain) or to 8 mg/l (γ-chain) with saline and 4 µl per lane were applied 4 mm before the anode (□) using a selfmade applicator and selfmade polyacrylamide gels in the pH range 3–10.
Note: The sum of additional bands in CSF (some are marked by arrows) after fixation with antisera against free and bound light chains of kappa chain type and lambda chain type was higher than after fixation with antiserum against IgG (γ-chain) alone or non-specific fixation with trichloroacetic acid yielding two additional bands (marked by *).

Conclusion

Non-specific CSF quantities are helpful in discriminating between pseudoradicular syndromes and radicular ones. Nearly all pseudoradicular syndromes caused by disc protrusion or cervical syndromes as well as neuromuscular diseases, exhibited normal leukocyte and protein values (tab. 1). By combining leukocyte counts and the values for non-specific quantities of blood-nerve bar-

rier function, some radicular syndromes can be distinguished: disc herniation (with nearly normal leukocyte counts and blood-nerve barrier quantities) from other blood-nerve barrier disturbances with or without elevated leukocyte counts; but neuropathies associated with systemic diseases cannot be excluded (tab. 1). Radicular syndromes with high pleocytosis and blood-nerve barrier defects were found in a few cases of bacterial inflammations with *L*-lactate concentration $\geqslant 3.5$ mmol/l (9, 10), whereas viral inflammations showed low pleocytosis combined with normal or slightly elevated protein and *L*-lactate values (tab. 1). Tick-borne polyneuritis can show similar findings (4, 32, 33). Most inflammatory neuropathies showed normal or slightly elevated leukocyte counts (and *L*-lactate concentrations) together with normal or high protein contents (see tab. 1). High protein contents with meningeosis neoplastica may be specified by detection of tumour-like cells.

Therefore, it is useful to look for specific quantities in the CSF to determine the cause of a radicular syndrome.

Specific Laboratory Quantities of Radicular Syndromes

The following disease specific quantities were investigated at different stages of radicular syndromes:

1. Quantities of the acute state

Detection of bacteria in CSF by testing for bacterial antigens or by culturing any bacteria present may be helpful in some cases. Detection of free antigens was restricted by the antibodies available and the test sensitivity. Some therapeutic measures (34, 35) also affect the ability to produce bacteria cultures. *Borrelia* cultures were found to be positive only in $< 20\%$ of the cases showing the clinical signs of tick borne polyneuritis (36).

D-Lactate, a bacterial metabolite (37, 38), is of low relevance in the diagnosis of neuropathies or radicular syndromes.

2. Quantities of subacute and chronic state

Antibodies specific to bacteria and viruses were determined in CSF using quantified ELISA, and subtracting the portion of specific serum antibody that had permeated into CSF as a consequence of radicular syndromes or CNS diseases. The calculation was performed

a) with the aid of the barrier indicator albumin (39, 40)

b) by comparing the IgG contents of CSF and serum samples (36), or assaying a specific antibody in CSF and serum (41, 42). A comparative evaluation of these procedures is still lacking.

Detection of oligocloncal bands specific to bacteria and viruses in CSF, by applying different blotting procedures (43, 44), eliminates the effect of specific serum antibodies permeated through the blood-brain barrier into CSF. Using quantitative methods, this effect cannot be reliably extrapolated by arithmetical procedures. Moreover, the diagnostic sensitivity of *Borrelia burgdorferi* detection proved to be highly dependent on tested antigen (41).

3. Bacterial or viral DNA or RNA may be detected by the polymerase chain reaction (PCR) in CSF during all stages of inflammation. The PCR test of *Borrelia burgdorferi* was more sensitive in CSF samples than in blood (45, 46) (and still more sensitive in urine (47)). *Borrelia burgdorferi* and *Treponema pallidum* infections may be reliably discriminated by the PCR test, but not with ELISA tests, because of cross-reacting antibodies (48, 49). Further investigations are needed to determine whether PCR tests for viral and bacterial infections (cf. l. c. (50)) are more sensitive and give a positive earlier response than the procedures discussed above.

In summary, an efficient laboratory diagnosis is a valuable aid for confirming the clinical discrimination between pseudoradicular and radicular syndromes. Normal findings with non-specific and specific methods in CSF and blood indicate the presence of a pseudoradicular syndrome not accompanied by a nerve root disorder. Laboratory findings may also classify radicular syndromes into inflammatory and non-inflammatory forms with or without blood-nerve barrier disturbances. Mainly non-specific methods are used in the daily routine because most of the specific methods are still under investigation.

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