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Importance of Laboratory Clinical Investigation in the Diagnosis of Immune Vasculitis with Neurological Manifestation

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Summary. In this study 23 cases of immune vasculities with predominance of neurological symptoms were analysed. Besides patient history and neurological examination, myelotomy is the most relevant means of diagnosis in immune vasculitis. For this reason myelotomy should be intergrated in routine diagnostic methods if the diagnosis immune vasculitis is discussed. Other laboratory parameters have no great relevance in the diagnosis of immune vasculitis. A higher specificity of antibody tests, especially in the case of ANA, might be able to replace myelotomy in the diagnosis of immune vasculitis. The relevance of laboratory parameters in the diagnosis of immune vasculitis in neurological patients was examined.

Key words: Immune vasculitis - Neurological manifestation - Laboratory investigation

Introduction

During the last few years immunological diagnosis has gained importance in neurological disease, though its application is less established than in internal medicine, since neurological manifestations appear more manifold even when concerning brain damage alone. In general, the diagnosis cannot rely on a biopsy which is only rarely indicated for in the CNS and as the disease need not spread to organs other than the CNS, normal results may be obtained from internal organ biopsies. Consequently, diagnosis of immunological disease of the CNS can only be derived from clinical criteria and laboratory values.

Material and Methods

This study primarily concerns patients with neurological symptoms. The various means of diagnosis in the cases of 23 patients with immunological disease were reviewed in retrospect. The immunological laboratory data were especially examined with regard to the immunological aspects of the neurological patients. Furthermore the contribution of different biopsies to diagnosis was investigated. Patients who were admitted for clinical treatment to the Department of Neurology in Hamburg from February 1975 until June 1982 were tested. The reports on these patients were checked according to the following three aspects:

1. whether or not the clinical diagnosis of immunological disease was determined or assumed on the basis of history and clinical findings;
2. whether antibodies were found,
3. and whether or not a myelotomy or other biopsies were performed.

Only those patients who satisfied at least one of these conditions were included in the study. The following examinations were therefore performed on 122 patients: clinical data, laboratory data, biopsies, electroencephalogram (EEG), electromyogram (EMG), and antibody tests following corticosteroid therapy with or without other immunosuppressive therapy. One or more of the following antibodies were determined: antinuclear antibodies (ANA), smooth muscle antibodies (SMA) and antimitochondrial antibodies (AMA). In 23 cases the diagnosis of immune vasculitis was made. In spite of some positive findings in the remaining 99 patients cases of immune vasculitis could not be ascertained. In this study the records of the 23 selected patients were analysed. The average age of these patients was 48 years (SD = ±3), the percentage of female patients was 83% ($n=19$), compared to 17% ($n=4$) of males.

Case Reports

Case No. 1, B.K., was a 45-year-old male first admitted in 1979 with a single left adversive seizure. His neurological status was normal though he was very adipose with mildly elevated blood pressure and had hyperlipidaemia type IV. An EEG showed focal alteration in the right precentral-parietal region, EMG revealed a possible myopathic pattern. CSF analysis showed a disturbed barrier function with protein 851 mg/l, IgG 113 mg/l, albumin 520 mg/l and a cell count of 3 cells/mm^3. Cranial computer tomography showed decreased density in the white substance of both hemispheres, controls showed additional hypodense areas fronto-parietal. A carotid angiogram showed on the right side, changes in the vessel wall of the posterior temporal artery with changes in caliber, and on the left changes in caliber of the internal carotid artery. A cerebral scintigram showed small circulation disturbances on the left hemisphere.

Laboratory findings were as follows: erythrocyte sedimentation rate (ESR) 55-108 mm, discrete normochrome anaemia, serum iron 9.4 µmol/l, antibody tests negative, C_3- protein 1.9 g/l, γ-GT 66 U/l. Myelotomy revealed immunogenetic hyperergic changes in the mesenchyme with distinct vasculitis; the skin biopsy was normal.

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This patient slowly improved with corticosteroid therapy, though dose reduction resulted in increased pathological findings on CCT and hyperreflexia of the right leg with discrete paresis. Therefore corticosteroid therapy was continued for some months, until the development of osteroporosis with a fracture of the first lumbar vertebral body following a fall. Anticonvulsive therapy as prescribed for a new seizure (left cerebral Jackson seizure). Myelotomy showed no sign of vasculitis.

Case No. 2, A.D., was a 42-year-old female who, 7 days preceding admission, noticed hypaesthesia of the right cheek spreading to the right shoulder and arm. This was followed by nausea, vomiting, vertigo, dysphagia and hoarseness. The neurological findings were failure of the V^{th} nerve on the right and of the IX^{th} and XII^{th} nerves on the left. Inexhaustible nystagmus was observed with a rotary component on viewing to the right more than to the left, with Horner's syndrome on the left and dysarthry.

The EEG was normal, IgG value in CSF elevated and CCT normal. Laboratory findings were: ESR 27–52 mm, ANA and SMA positive in repeated samples, IgM 292 mg/100 ml and myelotomy revealed immune vasculitis. A spontaneous remission occurred within a few weeks.

Case No. 3, H.R., was a 48-year-old male suffering from progressive strokes over 3 days, with hemiparesis beginning in the right arm and somnolence. His neurological status was hemiplegia, hypalgesia and hypaesthesia, homonymous hemianopsia on the right side and predominantly sensory dysphasia. An EEG revealed general alterations and focal disturbance in the left temporo-parieto-occipital area. CCT showed hypodensity in the area of the left medial cerebral artery. An angiogram showed an obstruction of the left internal carotid artery at the bifurcation.

Laboratory findings were as follows: ESR 95–127 mm, white blood cell count increasing from 15 000/mm^3 to 30 000/mm^3, CRP positive, γ-globulin 21.2%, immunoelectrophoresis normal, liver enzyme activities, including γ-GT, enhanced, lipid metabolism type IIa disturbance and SMA positive. Myelotomy revealed immunogenetic vasculitis with a suspicion of chronicity.

Following signs of enhanced cerebral pressure an angiogram revealed displacement of the anterior cerebral artery to the right, and CCT showed disseminated bleeding in the infarct region. Under high-dose corticosteroid therapy the CCT findings improved and recovery of consciousness occurred within 2½ months. Death occurred suddenly due to acute heart and circulatory failure. No postmortem was performed.

Table 1. Results of antibody tests in patients with immune vasculitis (ANA, SMA, AMA)[a]

Results	Positive	Negative
Number of patients ($n=23$)	12 (52%)	11 (48%)

[a] ANA: Antinuclear antibody
SMA: Smooth muscle antibodies
AMA: Mitochondria antibodies

Table 2. Distribution of positive antibody test results according to ANA, SMA, AMA in patients with immune vasculitis

Antibody	ANA	SMA	AMA
Total number ($n=14$)	9 (64%)	4 (29%)	1 (7%)

Table 3. Comparison of antibody test results from different institutes[a] in patients with immune vasculitis

Results	Equal	Different
A. ANA		
Comparison between		
a) Laboratory I and II ($n=5$)	3 (60%)	2 (40%)
b) Laboratory I and III ($n=5$)	3 (60%)	2 (40%)
c) Laboratory II and III ($n=10$)	6 (60%)	4 (40%)
B. SMA		
Comparison between		
a) Laboratory I and II ($n=1$)	1 (100%)	–
b) Laboratory I and III ($n=2$)	1 (50%)	1 (50%)
c) Laboratory II and III ($n=1$)	1 (100%)	–
C. AMA		
Comparison between		
a) Laboratory I and II ($n=2$)	2 (100%)	–
b) Laboratory I and III (–)	–	–
c) Laboratory II and III ($n=1$)	1 (100%)	–

[a] Laboratory I: Universitätskrankenhaus Eppendorf;
Laboratory II: Allgemeines Krankenhaus Buchholz;
Laboratory III: Abteilung für klinische Immunpathologie der Universitäts-Kinderklinik Hamburg

Results

A. Laboratory Results

Of the patients 52% ($n=12$) displayed antibodies at some time, the remaining 11 patients did not display antibodies at any time (Table 1). A total of 48 antibody tests were performed on the 12 patients with positive findings, 28 of these antibody tests were positive, 20 were negative. In some cases different antibodies were found simultaneously, e.g. against ANA and SMA. For this reason there are a larger number of positive antibody results in Table 2 than the number of patients. Table 2 demonstrates that ANA were found more often than SMA and AMA. The antibody tests were performed either simultaneously or within a short period (maximum 14 days) of time in different institutes.[1] The comparison of antibody test results

1 a. Abteilung für Immunologie, Medizinische Klinik Universitäts-Krankenhaus Hamburg-Eppendorf, Direktor: Prof. Dr. Thiele. b. Allgemeines Krankenhaus Heidberg and afterwards Kreiskrankenhaus Buchholz, Direktor: Dr. Maintz. c. Abteilung für Klinische Immunpathologie: Universitäts-Kinderklinik Hamburg, Direktor: Prof. Dr. Fischer

between the different institutes is found in Table 3. Of the 20 ANA tests, 12 (60%) were in agreement between centres with and 8 tests (40%) differing. In only 4 cases was an antibody test performed during corticosteroid therapy with or without other immunosuppressive therapy. In 1 case the antibodies had disappeared, while antibody levels in the other 3 patients were still measurable, in 2 of these patients they were reduced.

Nonspecific immunological parameters could only be found in a very low percentage: C-reactive protein 20%, rheumatoid factors 5%, antistreptolysin titre 15%. The mean value of C_3-protein was 1.30 g/l (SD = ± 0.10 g/l) which exceeded the normal value of 0.55 to 1.20 g/l. The ESR, another nonspecific parameter, was elevated in 65% of the patients; 35% had normal values (female 10–25 mm, male 6–20 mm). A raised white blood cell count (> 10 000/mm^3) was found in 9% of the patients, a low white blood cell count (< 4800/mm^3) in 17%, and 74% of the patients had a normal white cell count (between 4800 and 10 000/mm^3). A lymphocytosis (more than 30% lymphocyte in the differential blood cell count) was found in 65% of the patients; 39% of the patients had a hypergammaglobulinaemia (> 17.0%); α- and β-globulins were usually normal. Immunoelectrophoresis showed IgM to be elevated in 26% (> 280 mg/ml) and reduced in 22% (< 60 mg/100 ml) of patients; 22% of the patients showed deviations for both IgA and IgG (IgA 90 to 450 mg/100 ml; IgG 800 to 1800 mg/100 ml). The axilla body temperature (> 37°C) was elevated in 13 patients (57%); 10 patients (43%) had normal temperatures.

B. CSF

Table 4 shows the results of CSF analysis. On reviewing the results, total protein values (normal: 310–530 mg/l) and IgG values (normal: 3–43 mg/l) both deviate from standard values in 55% of the cases, whereas cell count values (normal: up to 5 cells/mm^3), γ-globulin values (normal: 2%–11%) and albumin values (normal: 50–320 mg/l) were mainly found at standard levels.

C. Electrophysiology

Most of the patients had alterations in EEG patterns. Normal EEG's were only found in 3 of the 23 patients (13%). Most of the pathological alterations were focal (in 15 patients, equivalent to 65%), though 5 patients (22%) showed generalized alterations. EMG results ($n = 14$) were normal in 1 patient (7%), 7 patients (50%) had a mononeuropathy, 4 patients (29%) had a polyneuropathy, and 2 patients (15%) had a myopathy.

D. Biopsy

A review of the evaluation of myelotomy and other biopsy results is given in Table 5. The diagnosis immune vasculitis was histologically proven in 19 cases (86%) based on positive myelotomy material).[2] In 3 cases (14%) myelotomy material showed nonspecific inflammatory mesenchymal changes which did not allow a definite interpretation as to whether or not an immune vasculitis existed. No negative biopsy material results were found. Besides myelotomies other biopsies of skin, muscle and sternal bone were performed in order to either state diagnosis or specific other organ involvement (Table 6).

2 In most cases myelotomy was performed in AK Heidberg. The results were evaluated by Prof. Georgii and colleagues at the University clinics in Hannover

Table 4. Results of CSF analysis in neurological patients with immune vasculitis

Results	Normal	Raised
A. Cell count ($n = 20$)	15 (75%)	5 (25%)
B. Total protein ($n = 20$)	9 (45%)	11 (55%)
C. γ-Globulin ($n = 19$)	14 (74%)	5 (26%)
D. IgG ($n = 20$)	9 (45%)	11 (55%)
E. Albumin ($n = 20$)	13 (65%)	7 (35%)

Table 5. Results of myelotomy and other biopsies in neurological patients with immune vasculitis

Results	Positive	Nonspecific and/or uncertain	Negative
A. Myelotomy ($n = 22$)	19	3	–
B. Skin biopsy ($n = 10$)	1	4	5
C. Muscle biopsy ($n = 9$)	–	1	8
D. Sternal bone biopsy ($n = 4$)	–	–	4

It can be concluded that myelotomy is of main importance in the diagnosis of immune vasculitis in neurological patient cases. According to this study skin biopsy is of next greatest importance following myelotomy in the diagnosis of immune vasculitis. However only half of all skin biopsies showed pathological findings, and most of them were difficult to interpret.

Discussion

In the last few years the importance of diagnosis of immunological diseases has increased, and new possibilities of clinical diagnostics and therapeutics have been developed for routine work in various disciplines of medicine. One aspect of the importance of this development is the diversity of symptoms on account of one basic disease being manifest in different organs. The neurological aspect of apoplexy, for example, is often considered as an entity in itself with less attention to diagnostics than to the usual stroke therapy. However, if the diagnosis of immune vasculitis as a systemic disease with its first clinical manifestation in the cerebrum, were to be stated, other therapeutic implications would result. This is clearly shown by our case reports.

Even though immune vasculitis is relatively seldom found among neurological cases, it is probably not recognized often enough. The search for parameters supporting diagnosis of immune vasculitis continues. This study is a first review with special orientation to everyday neurological aspects as far as this is statistically possible considering the low number of

patients. From 122 patients initially selected for this study, immune vasculitis could only be verified in 23 cases. For a clinician there are no "typical" characteristics of immune vasculitis. Cerebral symptoms caused by vascular complications in patients of middle age attract attention, yet immune vasculitis can become manifest at any age. Nonimmunogenic diseases may produce similar symptoms and neuropathological findings are often nonspecific and disseminated. A large number of patients in whom immune vasculitis was suspected suffered from multiple sclerosis. Also, the pathological laboratory parameters—with the exception of biopsy findings—are more or less nonspecific, as was shown in a comparison of all 122 patients [20].

Among the present data antibodies were found in about half of the patients with immune vasculitis. Of all antibody tests performed on patients who at least once had had positive antibody tests only 58% were positive. The antibody tests consisted of ANA, SMA and AMA; ANA were found much more often than SMA and AMA. A striking fact was that antibody test results performed in three different laboratories differed a great deal from each other in some cases. When comparing antibody tests from different laboratories one must also consider the fact that different antigens and test systems were used [6, 9], which may lead to varying test results. ANA are antibodies which act against very different cell core components, such as nucleolar substances, histones and RNA. This explains for one part the fact that a relatively high percentage of patients have antibodies against different cell core components, e.g. ANA, compared to other specific antibodies. Furthermore it is understandable that deviations occur between laboratories using different test systems. This is true for all three antibody groups which were examined in this study, especially for ANA. Differentiation of antibodies is now possible, for instance by the haemagglutination test, the indirect immunofluorescent technique and radioimmunoassay [8, 16, 23–25]. As an example, it is now possible to serologically differentiate between lupus erythematosus and Sharp syndrome [17, 22]. However, it is possible that in cases of immune vasculitis which had been verified by biopsy, no antibodies have been found in blood samples. This may be the result of the laboratory test systems employed failing to measure antibody levels. Conversely, people appearing clinically healthy may have positive antibody tests [9, 18] or have nonimmunogenetic diseases [21]. If antibodies are used in diagnostics, antibody tests must be performed frequently and at best in several institutes. Positive test results may support and induce further immunological diagnostic measures. As far as these few cases may be commented on these antibody proof methods may be continued after beginning with corticosteroid and/or immunosuppressive therapy as usually conducted in cases of immune vasculitis [5, 13, 15, 19]. These few cases show that antibody tests may be positive during or after such therapies. Similar results have been noted in the literature [14].

The following general laboratory criteria may support the diagnosis of immune vasculitis without claim of specificity: subfebrile patient temperatures, elevation of ESR of C_3-complement and of lymphocyte cell count. The value of γ-globulin may be elevated; IgM, measured by immunoelectrophoresis, and white cell count may be altered. It is not obligatory that these values deviate from standard levels in immune vasculitis. This fact makes these nonspecific diagnostic methods more relative.

A similar statement can be made concerning neurological examinations such as EEG, EMG and CSF analysis. Even though they are relatively nonspecific criteria, their value for the diagnosis of organ manifestation is undisputed. The results of these neurological examinations are in concordance with those of other authors [11, 12]. Gottwald [7] described general or focal EEG alterations in cases of lupus erythematosus; Herrmann and Kunze [10] pointed out that in cases of discrete myopathic EMG findings, an immune vasculitis could be proved by biopsy.

Myelotomy as developed by Burkhardt [2, 3] remains the most important diagnostic method in the diagnosis of immune vasculitis. Immune vasculitis could be verified using myelotomy in 86% of cases with this disease, 14% showed chronic, nonspecific inflammatory involvement of mesenchyme. In the present study there were 3 cases of immune vasculitis which were not proven by myelotomy, showing that the diagnosis of immune vasculitis could not be proven in 100% of cases [4], as published in cases of pseudo-lupus erythematosus and Sharp disease [1]. However, the diagnosis immune vasculitis was positive on the basis of clinical symptoms either with typical findings in skin biopsy or with frequently positive antibodies or with several of these factors combined.

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