Recovery from spontaneous confabulations parallels recovery of temporal confusion in memory

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Article abstract—Background: In previous studies, the authors found that patients with spontaneous confabulation differ from those with nonconfabulating amnesia by 1) temporal context confusion (TCC) in memory based on an inability to suppress intrusions of currently irrelevant memory traces into ongoing thinking; and 2) lesions involving the orbitofrontal cortex, basal forebrain, or amygdala and perirhinal cortex. Objectives: To study the long-term clinical course of spontaneous confabulations, determine whether TCC in memory also parallels the clinical course of spontaneous confabulations, and study the impact of lesion site on clinical course. Methods: Eight patients with spontaneous confabulation were re-examined 18 months after onset. Tests of memory and executive functioning and measurement of TCC in memory were again applied. MRI according to a standard protocol was performed to determine areas of permanent damage. Results: Seven patients eventually stopped confabulating. TCC, but not common memory or executive tests, precisely paralleled the course of spontaneous confabulations. Patients with isolated, less extensive, orbitofrontal lesions stopped confabulating first and had the best neuropsychological outcome. Patients with basal forebrain lesions continued to confabulate for several months and remained amnesic. One patient with extensive orbitofrontal damage and perirhinal cortex damage continues to confabulate after more than 3 years, continuing to confuse memory traces. Conclusions: Temporal context confusion in memory is not only the sole feature reliably separating patients with spontaneous confabulation from those with nonconfabulating amnesia in the acute stage, it is also the only feature that precisely parallels the clinical course of spontaneous confabulations. Most patients eventually stop confabulating but duration of confabulations depends on the lesion site.

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Some patients with amnesia fail to adjust their behavior to ongoing reality. They confabulate about their recent doings and produce plans for the day that ignore their current condition (e.g., hospitalization). Occasionally, they act according to their false beliefs. The confabulations are typically composed of the patient's past experiences and habits.1-4 We have used the term “spontaneous confabulations” to describe this condition.3,4 Spontaneous confabulations are distinct from the provoked confabulations (intrusions) elicited in memory tests.3,5-7 Provoked confabulations were considered a less severe form of the disorder producing spontaneous confabulations.8-11 We found, however, that the two types of confabulations doubly dissociate.3 Provoked confabulations are produced both by amnesic subjects3,5,9,11 and healthy people10 when they fail to recollect an imprecise memory. Provoked confabulations never guide a patient’s behavior, as seen in spontaneous confabulations.

In previous studies, we compared patients with spontaneous confabulation with nonconfabulating subjects having similar deficits in free recall (termed “nonconfabulating amnesics” in the previous studies).3,4,12 We found that these two groups did not differ on several measures of memory (three continuous recognition tasks with meaningful designs, meaningless designs, and nonwords; learning and delayed recognition [both hits and false positives] on a verbal memory test; and delayed recall of the complex figure of Rey14), indicating that they cannot be distinguished in terms of “true amnesia” with impaired information storage versus “frontal memory failure” with impaired free recall despite intact information storage.15-17 Furthermore, the groups did not differ on measures of executive functioning (verbal nonverbal fluency,19 color–word interference20).3,4,12 Patients with spontaneous confabulation also had no increased tendency to fill gaps in memory as measured with a questionnaire containing fake questions about nonexistent items.3 The only feature separating patients with spontaneous confabulation from those with nonconfabulating amnesia and healthy controls was an inability to distinguish between currently relevant information and memory traces lacking current behavioral relevance. In the second of two runs of a continuous recognition task composed of the same set of pictures, patients with spontaneous confabulation failed to distinguish between item
recurrences within the second run (targets) and the reappearance of items that they had last seen in the first run, 1 hour earlier (distracters).\(^3\) In a recent study, we found that patients with spontaneous confabulation fail to suppress currently irrelevant memory traces, which may then guide their behavior.\(^3,4\)

Patients with nonconfabulating amnesia have lesions involving the posterior medial temporal lobe or the neocortex, whereas those with spontaneous confabulation have lesions in anterior limbic areas, particularly orbitofrontal cortex, basal forebrain, amygdala and perirhinal cortex, or medial hypothalamus.\(^3,4,21,22\)

In the current study, the course of eight patients with spontaneous confabulation is described. All patients had failed our task measuring the confusion of memory traces during the confabulatory stage. We considered the following questions: 1) What is the clinical course of patients with spontaneous confabulations? 2) Is recovery from spontaneous confabulations associated with recovery in distinguishing between currently relevant and previously encountered but currently irrelevant information, using our task to measure temporal confusion in memory? 3) Is recovery from spontaneous confabulations dependent on the lesion site?

**Methods.** All patients had produced spontaneous confabulations at the time of first testing and were re-examined after 1 to 2 years with our task to measure temporal confusion in memory. In addition, MRI was performed to determine permanent lesion sites. The study was approved by the Ethical Committee of the Medical School of the University of Bern.

**Patients.** Eight patients who had been hospitalized in our Division for Neuropsychological Rehabilitation during the early stage after brain injury were included. All of them had qualified as “spontaneous confabulators” according to our definition;\(^3\) i.e., they produced confabulations in discussions and spontaneously (e.g., invented plans for the day) and occasionally acted on the basis of these confabulations (an indication that their confabulations were indeed spontaneously generated). The following are typical examples of spontaneous confabulations by hospitalized patients:

1) Patient 3, a retired diplomat, interrupted the physician’s visit, saying that he was sorry that he had to stop the conversation; he had to give a talk at a conference in a few minutes. He also apologized for not being able to offer a cup of tea; his secretary had the day off.

2) Patient 6, a housewife, packed her suitcase in the morning and told the nurse that she was about to go home to feed her baby (her “baby” was 35 years old at the time).

3) Patient 7, a previous pastime hunter, came to the attending physician’s office and asked whether he could use the phone; he had arranged a deer hunt that same afternoon and would just like to inform his wife about it.

4) Patient 8, a tax accountant, suddenly ran away from the ward. When asked by the nurse why he was running away he responded that he was in hurry; the taxi, which would bring him to a business meeting with another financial expert, was waiting outside.

Other examples of spontaneous confabulations can be found in our previous articles.\(^3,21,23\) Similarly to delusions, spontaneous confabulations represent false beliefs that are unshakably accepted as being true.\(^24\) However, unlike delusions (e.g., beliefs that one’s thoughts are being controlled or that one is being persecuted or poisoned), spontaneous confabulations always have a valid memory component—that is, they can virtually always be traced back to real events in the patient’s life.\(^3,4,21,23,25\) In addition, the patients involved in this study had no history of a psychiatric disorder, which is commonly present in delusional patients.\(^24,25\)

All patients had normal focused attention and sleep-wake cycle when first tested (a confusional state was an exclusionary criterion in the initial study). All five patients with spontaneous confabulation from the initial study\(^3\) again participated in the current follow-up study (table, Patients 1, 3, 6, 7, 8). Two additional patients with spontaneous confabulation had participated in a study on disorientation\(^22\) (Patients 2 and 4), in which the first five patients had also participated. One patient (no. 5) had not been involved in any previous study.

**Follow-up.** All patients were contacted by telephone after approximately 18 months and asked to participate in a follow-up examination. The history given by the patients was complemented by an extensive interview with family members or caregivers. The interview covered current occupation and lifestyle, necessity for support in daily activities, and changes in habits. For the patients who had remained spontaneous confabulators when they left our Division (Patients 6, 7, and 8), the interview also aimed to determine the duration or persistence of spontaneous confabulations. General questions to detect spontaneous confabulations (e.g., “does he occasionally wrongly pretend to go to an appointment?”) and specific questions about types of confabulations that the patients had produced while hospitalized in our Division (e.g., “does he occasionally prepare himself to go for an invented deer hunt?”) were asked.

Memory and executive functions. The same learning and executive tests as in the initial study were applied: California Verbal Learning Test,\(^13\) verbal fluency,\(^18\) nonverbal fluency,\(^19\) and color–word interference.\(^20\)

**Temporal context confusion.** Temporal context confusion (TCC) was tested as described in the previous studies.\(^3,22\) Briefly, subjects are given two runs of a continuous recognition task with 120 pictures. The task is composed of 80 pictures from Snodgrass and Vanderwart,\(^26\) 8 of which are randomly selected to be target items—i.e., to be presented repeatedly within a run. Unknown to the patients, the 120-picture series actually consists of six blocks with 20 pictures each. Each block contains the eight target items (which are thus repeated five times after initial presentation) and 12 distracter items that are not repeated in other blocks. All pictures are presented on a computer screen for two seconds. For each picture, the subjects are requested to respond to the question: “Have you already seen precisely this picture in this run?” Answers are recorded by the examiner pressing the appropriate response key and are immediately followed by presentation of the next picture.

One hour after the first run, a second run with the same
design is made. The run is composed from the same 80 pictures. The only differences from the first run are that item order is changed (new random order) and that eight different items from the same picture series function as targets; thus, eight distracter items from the first run now serve as the target items, while the target items from the first run are now among the distracters. Subjects are instructed to “forget that they have already seen the pictures before” and to answer the question: “Have you already seen precisely this picture in this run?” for each picture. The idea behind the task is that false familiarity with a distracter item (i.e., a false positive response) is based on an inability to distinguish between the item’s previous occurrence in the first rather than the second run, i.e., TCC.

Two types of data analysis were performed: analysis of a composite score of TCC, as used in our first group study; and analysis of the suppression of memory traces, as explored in our most recent study. Composite score of TCC. In our initial study, we defined TCC as the increase of the relative amount of false positives in the second over the first run:

$$\text{TCC} = (FP_{2}/\text{Hits}_{2}) - (FP_{1}/\text{Hits}_{1}),$$

where $FP_{1,2} =$ false positives in run 1 or 2; $\text{Hits}_{1,2} =$ hits in run 1 or 2. This measure separated all patients with spontaneous confabulation from all patients with nonconfabulating amnesia and normal control subjects in the acute stage; i.e., when the patients were still spontaneously confabulating.

Suppression of memory traces. In our most recent study using a similar task with four runs, patients with spontaneous confabulation specifically differed from those with nonconfabulating amnesia and healthy controls by an increase of false positive responses from run to run, indicating that they failed to suppress interference by items seen in previous runs, which were irrelevant (nonrepeated) in the current run.

To explore whether the ability to suppress currently irrelevant items recovers when patients cease to confabulate, the same group analysis as in the recent study was made with the current set of data. The change of hits and false positive responses from the first to the second run was studied both for the data obtained during the confabulatory stage and when the patients had stopped confabulating. Their performance was compared with that of the series of patients with nonconfabulating amnesia and control subjects involved in the original, acute study.

Lesion analysis. To determine areas of permanent damage, all patients received a follow-up MRI after 1 to 3 years. MRI was obtained on a 1.5-T imager (Magnetom Vision; Siemens Medical System, Erlangen, Germany) using a dedicated head coil. Brain images were acquired in the coronal, sagittal, and axial planes using conventional spin-echo T1-weighted, turbo spin-echo T2-weighted, and turbo inversion recovery magnitude (TIRM) sequences (TIRM sequence distinguishes better between gray matter, white matter, and CSF than conventional T1-, T2-, or proton density–weighted images). Lesion sites were determined with the use of Damasio and Damasio’s templates and the atlas of Nieuwenhuys et al. To summarize lesion areas, the lesions were referred to a composite axial slice containing the hippocampus, amygdala, and basal forebrain, and to the midsagittal plane, similarly to our previous lesion studies.

The analysis of follow-up scans was compared with the acute scans used in the original studies to verify the reliability and prognostic value of the acute lesion analysis.
Results. Clinical course. The table summarizes the duration of confabulations and the neuropsychological and social outcome in the eight patients. Duration of confabulations varied widely. Three patients ceased to confabulate after less than 3 months (Patients 1, 2, and 3); two of them had a full neuropsychological recovery. Only two patients continued to spontaneously confabulate for 2 and more years (7 and 8). Vocational outcome was directly dependent on neuropsychological outcome; only the two patients with full neuropsychological recovery kept their jobs, although one patient (Patient 1) had severe marital problems and lost his job after 1 year due to personality changes with lack of respect for social hierarchies and loss of creativity.29 All other patients had continuing memory impairment and lost their jobs. One long-term confabulator (Patient 7) now lives alone in his home and visits a day care center. The only continuing confabulator (Patient 8) lives in an adult care center, where he leads an unrestricted life and makes trips to the nearby town. He often tells people that he has to go to a business meeting, considering himself to be in business as an accountant, or he stands guard at the entrance of the adult care center, pretending that he is in the civil service.

Behavioral observations. Several patients were still hospitalized in our unit when they ceased to confabulate. Whereas during the acute stage, the patients were entirely convinced about the veracity of their confabulations and typically had no insight into their memory problem, several patients expressed skepticism for their own memory as they improved. Some patients apparently became increasingly conscious of their “bad memory” and would make remarks like: “People tell me that I make mistakes.” However, conscious insight into the failure of their memory was independent of the production of spontaneous confabulations; patients acknowledging their bad memory would nevertheless confabulate and be at risk of inadvertently leaving the hospital, e.g., in the idea of going to a business meeting. Skepticism toward their memory typically increased toward the end of the confabulatory stage. For example, a patient, who was at the very end of his confabulatory stage, was questioned at noon about his activity in the morning. He responded that he had been in Zürich (about 150 kilometers from Bern). When asked whether he was sure about this, he admitted: “I have the sure feeling that I was in Zürich this morning; but now that you ask me, I have no idea how I got there and how I came back. I know that I cannot trust my memory.” Another patient, who had been a florid confabulator for months but now produced very rare confabulations, spontaneously complained: “You know, it is very annoying: I have the feeling of switching between two realities.”

Memory and executive functions. As expected, the group of patients generally improved on measures of memory (figure 1, a through d) and frontal executive functioning (figure 1, e through g). However, none of the measures paralleled the course of all spontaneous confabulators: ei-
ther clinical improvement (cessation of confabulations) was
associated with constant or worse test performance at
follow-up (see figure 1, a, b, c, e, and g), or test perfor-
mance improved despite continuing confabulation (see fig-
ure 1, c, d, and e).

Temporal context confusion. As seen in figure 2, TCC
perfectly paralleled the clinical course of all patients. All
patients who had ceased to confabulate at follow-up had
markedly improved and mostly normal TCC (normal TCC
defined as the range of the nonconfabulating patients’ and
healthy subjects’ TCC in the initial study).3 Only Patients
7 and 8, who continued to confabulate, remained clearly in
the abnormal range (session 2 in figure 2). These two pa-
tients were again examined after 3 years (session 3 in
figure 2). Patient 7 had ceased to confabulate; TCC was
now normal. Patient 8, who continued to confabulate, still
had increased TCC.

Figure 3 shows that patients with spontaneous confab-
ulation (both in the acute stage and after cessation of sponta-
neous confabulations), other patients with amnesia, and
normal control had a constant hit rate from run 1 to run 2
(figure 3a). However, in contrast to the other patients with
amnesia and control subjects, the patients with spontaneous
confabulation had a steep increase of false positive responses from run 1 to run 2 in the confabulatory stage
(figure 3b). After cessation of spontaneous confabulations,
this increase of false positives was much more discrete.
This result agrees with our recent study, demonstrating
that—in the confabulatory stage—patients with spontane-
ous confabulation have a specific inability to suppress false
positives in the second and later runs; they fail to sup-
press information that they have seen in the first run but
that has no relevance in the second run (distracters). Re-
covery from spontaneous confabulations is accompanied by
improvement of this suppression capacity.

Lesion analysis. Figure 4 demonstrates that the out-
come depended on the lesion site. Orbitofrontal lesions had
fastest and—in Patients 1 and 2—complete recovery. In
Patient 1, the chronic scan showed, in addition to frontopolar
damage, left temporal polar damage. The acute scan of
Patient 2 showed marked right frontal edema impinging
on the medial orbitofrontal cortex; the definitive lesion in
the chronic scan appears markedly smaller. Basal fore-
brain lesions, even if only partial (Patient 5), were associ-
ated with confabulations lasting for months up to a year
(Patients 4, 5, and 6); all these patients remained amnesic.
Whereas these conclusions can be derived from both the
acute and the follow-up scan, the prolonged course in Pa-
tient 7 and the negative outcome in Patient 8 can only be
explained by the follow-up scan. Patient 7 apparently had
more severe diffuse axonal injury, evidenced by marked

Figure 2. Course of temporal context confusion in memory
(TCC). The dashed line indicates the worst performance of
any healthy control or nonconfabulating amnesic involved
in the original study.3 At session 1, all patients were con-
fabulating. At session 2, all but two patients (7 and 8) had
stopped confabulating. These two patients were again exam-
ined at session 3 after 3 years; Patient 7 (●) had ceased to
confabulate, Patient 8 (□) was still confabulating. ○ = Tran-
sient confabulators (nonconfabulating at session 2).

Figure 3. Analysis of suppression. a, Hits; b, false positive responses in the
first and the second run of the continuous recognition task. Spontaneous con-
fabulators have the same hit rate in both runs—both in the acute, confabu-
laratory stage (all eight patients; ●) and after cessation of confabulations at
follow-up (“recovered confabulators,” Patients 1 to 7; ○); in contrast, their
false positive rate increases steeply from the first to the second run during the
acute, confabulatory stage, but much less so after cessation of confabulations.
The data of the other, nonconfabulating amnesics (□) and normal controls (△)
are taken from the original study.3
atrophy (figure 5), than was expected on the basis of the acute scan. In particular, what appeared to be discrete hemorrhages of the right amygdala (figure 5a) and the left anterior insula (figure 5b) in the acute scan turned out to be virtual destruction of the entire right amygdala (figure 5e) and extended damage of the left perirhinal and anterior insular cortex in the follow-up scan (figure 5g). In Patient 8, the follow-up scan confirms the partial sparing of the basal forebrain, which appears to be atrophied (figure 6). However, it demonstrates additional right perirhinal damage and, in particular, extensive orbitofrontal damage; the lesion extends dorsally to the anterior horn of the lateral ventricles on both sides and undercuts the prefrontal connections of the thalamus (figure 6, c and f).

**Discussion.** In previous studies, we found that the only feature distinguishing patients with spontaneous confabulation from those with nonconfabulating amnesia and healthy controls was a confusion of memory traces based on an inability to suppress currently irrelevant memories.3, 4 The current follow-up study shows that this failure also precisely parallels the clinical course of patients with spontaneous confabulation. Patients who recover from spontaneous confabulations regain their ability to distinguish between currently relevant and previously encountered but currently irrelevant information (TCC, figure 2) and—more specifically—to suppress memory traces that lack current behavioral relevance (false positives in figure 3b). The patients who had not recovered at first (Patient 7) or second follow-up (Patient 8) continued to fail on our task (see figure 2).

As expected for any deficit after brain injury, com-
mon memory and executive tasks improved in the patient group as whole. However, none of the tested functions reliably paralleled the course of all patients. This agrees with our previous finding that common executive and memory tests do not distinguish between patients with spontaneous confabulation and those with nonconfabulating amnesia in the acute stage. Studies concluding that confabulations emanate from the combination of an amnesia with frontal executive failures examined only single cases or groups of patients with a common etiology of brain damage (usually rupture of an anterior communicating artery aneurysm). We also have found that some patients with spontaneous confabulation store normal amounts of information (thus, a failure to store enough information is not necessary). In comparison with patients with nonconfabulating amnesia, those with spontaneous confabulation do not have an indiscriminate tendency to fill gaps in memory, as suggested before. Self-monitoring also does not appear to play a significant role. We observed a patient who confabulated spontaneously although he closely monitored his responses in test situations.

We used a stringent definition of spontaneous confabulations, which requires that patients also occasionally act on the basis of their beliefs. To the patients, their false memories appear to be genuine and to relate to ongoing reality. Their basic problem is that they fail to extract from their memory the information that pertains to “now,” a failure based on an inability to suppress memory traces and mental associations that have no current behavioral relevance. Thus, they act on the basis of information that does not relate to ongoing reality. This failure, as described by our definition, concerns all aspects of thinking, action planning, and behavior; the confabulations are simply the verbal manifestation.

Our experiment is different from traditional temporal order and recency tasks that examine knowledge about when a specific item was presented in relation to other items (e.g., in the first or second of two word lists; more or less recently than other items). This capacity is not required by our task, in which target items are defined by their own previous occurrence within the same test run, irrespective of their temporal relation with other items. The specificity of our task is corroborated by the following observations. First, patients with spontaneous confabulation have been found to fail in traditional temporal order tasks, but the tasks do not distinguish them from patients with nonconfabulating amnesia. In contrast, our task not only reliably distinguishes patients
with spontaneous confabulation from those with non-confabulating amnesia, but also precisely parallels their clinical course, as indicated by the current study. Secondly, the pure failure on traditional temporal order tasks is typically associated with lateral prefrontal cortex (LPFC) damage. In contrast, focal LPFC lesions alone never produced failure in our task. It appears that the dorsolateral prefrontal cortex is not critical to the function whose defect causes spontaneous confabulations: the suppression of currently irrelevant memory traces.

The ability to suppress currently irrelevant memory traces apparently depends on anterior limbic structures. In previous studies, we found that patients with spontaneous confabulation, in contrast to those with nonconfabulating amnesia, had lesions involving the medial orbitofrontal cortex or its connections, the basal forebrain, the amygdala and perirhinal cortex, or the medial hypothalamus. Patients with nonconfabulating amnesia did not have damage to these structures; their lesions involved the posterior medial temporal lobe and the neocortex. For the current study, follow-up MRI was done to determine more precisely the impact of the lesion site (areas of permanent damage) on the clinical course.

Patients with isolated orbitofrontal lesions confabulated for the shortest period. Two of three patients even regained normal memory functions. However, only one patient remained fully socially integrated in the long term (Patient 2). One patient (Patient 1) had increasing marital problems and lost his job after 1 year, despite full (measurable) neuropsychological recovery. His wife reproached him for being a different, blunt person; his employer described a lack of respect for social hierarchies and loss of creativity. Anterior orbitofrontal lesions may induce subtle but socially incapacitating personality changes even when results on common neuropsychological tests are normal.

Basal forebrain lesions were associated with a prolonged confabulatory stage of up to 1 year. These patients remained amnesic but manage to live with their families with no particular supervision. We have observed a similar course in a patient with a lesion of the right capsular genu, which interrupted connections between the dorsomedial thalamic nucleus and the orbitofrontal cortex. One patient (Patient 7) confabulated for almost 2 years. The follow-up MRI demonstrates virtually complete destruction of the right amygdala and severe left perirhinal and anterior insular damage (see figure 5). However, additional diffuse brain damage has to be assumed given the marked atrophy. Although his memory never fully recovered, he now leads an independent life.

Only one patient continues to spontaneously confabulate after more than 3 years (Patient 8). His lesion spares the basal forebrain, which appears to be atrophied. Follow-up MRI shows an extremely extensive orbitofrontal lesion that reaches so far dorsally as to interrupt thalamo-prefrontal connections, including the anterior limbic connections to dorsolateral prefrontal cortex (see figure 6). The patient is able to execute complex action plans (e.g., trips to town), a capacity thought to require an intact dorsolateral prefrontal cortex, but his action plans are often inappropriate for current reality.

We have seen a similar long-term course in a patient with an anteromedial hypothalamic granuloma (neurosarcoidosis). She produced typical spontaneous confabulations for 3 years until her death. It is possible that the progressive nature of the lesion continuously interfered with compensation. Alternatively, the anteromedial hypothalamus might make a specific contribution to the integration of ongoing re-
ality into thinking and action planning, a contribution that cannot be made by another component of the anterior limbic system.

Why does recovery from spontaneous confabulations occur at all? The capacity to distinguish between memory traces (experiences) that have current behavioral relevance and mental associations that have no current relevance is obviously essential for any purposeful action planning. This capacity is probably not specific to humans. Animals with orbitofrontal lesions show similarities to our patients' behaviors: they fail to suppress previously established habits and continue to react to stimuli that are no longer rewarded. Selection of currently relevant memory traces—that is, of information that needs to be integrated into ongoing behavior—may have the same mechanism in animals as in humans, except that humans draw from much more complex memory representations spanning much longer periods of time. From a teleologic point of view, such an essential capacity deserves to be protected by redundant organization. Our data indicate that the system subserving this capacity is indeed anatomically redundant, as most patients with spontaneous confabulation eventually regained the ability to adjust their behavior to ongoing reality. The system is further protected by the fact that complete destruction of all anterior limbic structures is very unlikely; the most common etiologies (trauma, hemorrhage from an anterior communicating artery aneurysm) do not normally destroy all components of this system. The observation of Patient 8, who continues to spontaneously confabulate after more than 3 years, indicates that recovery may be impossible when the anterior limbic system lacks connection with other areas implicated in the planning of behavior, particularly the dorsolateral prefrontal cortex.

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References

Distinctive pathologic findings in proximal diabetic neuropathy (diabetic amyotrophy)

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Article abstract—Objective: To investigate the pathogenesis of proximal diabetic neuropathy (PDN) with nerve and muscle biopsies. Background: Recent evidence suggests that nerve ischemia secondary to immune-mediated vasculopathy rather than diabetic microangiopathy may be responsible for PDN. Method: Fifteen patients with PDN and two diabetic controls underwent nerve and muscle biopsy and clinical, electrophysiologic, and laboratory evaluation. There were eight men and seven women between 49 and 79 years of age with type II diabetes. All had progressive, painful, asymmetric, proximal weakness with duration of 5 weeks to 12 months. None had evidence of systemic autoimmune disorder. Results: Four patients showed the distinctive findings of polymorphonuclear small-vessel vasculitis affecting epineurial vessels with transmural infiltration of postcapillary venules with polymorphonuclear leukocytes. Immunoglobulin M (IgM) deposits were found along the endothelium and intramurally in affected vessels. IgM staining was seen in the subperineurial space and in the endoneurium. Activated complement deposition was seen along endothelium of small vessels. Three of these four patients were evaluated within 6 weeks of onset of PDN, and the fourth patient during acute flare of PDN 6 months after the initial onset. Six patients showed “perivasculitis” with mononuclear cell infiltrates around small epineurial vessels without vasculitis (fibrinoid necrosis or transmural inflammation). One patient showed recanalized vessels with transmural lymphocytes without fibrinoid necrosis, possibly suggesting healed vasculitis. Conclusion: These distinctive pathologic findings support that proximal diabetic neuropathy has an immune-mediated inflammatory basis and suggest that polymorphonuclear vasculitis with immune complex and complement deposition may be the primary event in the acute phase of proximal diabetic neuropathy.

Proximal diabetic neuropathy (PDN) or diabetic amyotrophy is a rare complication of type II diabetes that causes subacutely evolving, painful, asymmetric, proximal weakness. It often leads to significant disability and is characterized by slow improvement over a protracted period. The pathogenesis of PDN is unknown. Emerging evidence suggests that it may be due to immune-mediated vasculopathy (vasculitis or perivasculitis) causing ischemic nerve injury. The factors responsible for inducing an immune response against the vessels supplying the nerves are not well understood. Humoral as well as T cell-mediated processes seem to be involved. An autoimmune basis is further supported by observation that immune-modulating therapies such as IV immunoglobulin (Ig) may be useful in the treatment of PDN. We further investigated the pathogenesis of PDN.

Materials and methods. Sixteen patients with PDN were identified from the Neuromuscular Clinic at the University of Minnesota in Minneapolis between June 1997 and January 1999. One patient did not undergo biopsy as the symptoms were mild and nonprogressive. Fifteen patients who underwent biopsy were included in this study. All patients presented with progressive, painful, asymmetric, proximal weakness. The duration of symptoms ranged from 5 weeks to 12 months.