Diphtheritic Polyneuropathy

Clinical Analysis of Severe Forms

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Background: Diphtheritic polyneuropathy (DP) is a dangerous complication of diphtheria, especially its severe forms with bulbar, respiratory tract, and circulatory disturbances. However, the clinical picture of severe forms of DP is practically unknown.

Objective: To investigate the clinical features and peculiarities of the course of severe forms of DP.

Patients: Thirty-two patients with severe forms of DP.

Results: The first symptoms of DP developed in most patients 3 to 5 weeks after the onset of diphtheria. The cranial nerves were involved in all patients, most frequently nerves IX and X (32 patients); VII (28 patients); III, IV, and VI (27 patients); and XI (27 patients). One third of the patients had quadriplegia. The remaining patients had quadripareses. Of the 32 patients, 24 underwent artificial ventilation. All patients had sensory signs, proprioceptive more often than superficial. Autonomic disturbances were observed also in all patients. Only 2 of the 32 patients died.

Conclusions: A direct indication for tracheotomy and artificial ventilation in patients with DP is a decrease of the vital capacity of the lungs below the traditional 16 mL/kg body weight or the development of the paralytic closure of the larynx against the background of the increasing weakness of the respiratory muscles. Characteristic of severe forms of DP is the phenomenon of the oppositely directed change in the neurological symptoms in the second month of the disease: the restoration of the function of the cranial nerves against the background of the further increase of the motor disturbances in the extremities and trunk. Special attention and care should be taken of patients during the period of the appearance of the episodes of vascular collapses—between the fourth and seventh weeks of DP.

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RESULTS

LATENCY AND THE FIRST SYMPTOMS OF DP

From 1990 to 1995, the epidemic of diphtheria broke out in the former Soviet Union. The number of patients reached 90% of all cases documented in the world during this period. More than 125,000 humans were infected with diphtheria, and 4000 of them died. More than 97,000 cases with 2500 fatal outcomes took place in Russia, where the epidemic was accompanied by a pronounced increase in the number of patients with one of its most dangerous complications, diphtheritic polyneuropathy (DP). The incidence of DP is directly proportional to the severity of diphtheritic intoxication, and it may occur in 68% of the total number of diphtheritic patients. The most dangerous are the severe forms of DP, with bulbar, respiratory tract, and circulatory disturbances. Mortality due to these forms of DP surpassed 50%, even in the specialized hospitals. Although paralysis of the diaphragm was known earlier as a sign leading to 100% lethality of patients with DP (without artificial ventilation [AV]), the data on clinical manifestations of severe forms of DP and the life-threatening role of respiratory insufficiency in this disease are scarce. The high diphtheritic lethality resulted from the inefficiency of respiratory therapy during previous epidemics, most of which broke out before the 1950s, when the modern devices of AV became widespread. This article describes the clinical presentation and the course of the disease in the patients with severe forms of DP, most of whom had the respiratory tract disturbances and needed AV.

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SUBJECTS AND METHODS

The subjects were 32 patients with severe forms of DP (18 men and 14 women; mean±SD age, 44±4 years; age range, 21-54 years) admitted to our hospital from January 1, 1990, to December 31, 1997. All patients had toxic diphtheria with cervical subcutaneous fat edema spread down to the clavicles and below them (28 and 4 patients, respectively). Laboratory diagnostic testing was performed, with microbiological isolation of the causative pure culture of diphtheria and identification of its basic morphological, biochemical, and toxic features in infectious disease hospitals. Bacteriologic tests revealed Corynebacterium diphtheriae gravis in 24 patients and Corynebacterium diphtheriae mitis in 6. In 2 patients, diphtheria was diagnosed in the infectious inpatient departments based on clinical and epidemiological data. Only 1 of 32 patients was vaccinated with a single dose of antitoxin 1 year before infection.

Diphtheria was located in the stomatopharynx (23 patients), the stomatopharynx and the larynx (3 patients), the stomatopharynx and the nose (4 patients), the nose and the larynx (1 patient), and the stomatopharynx and hand skin (1 patient). Treatment with antitoxin was delayed because of the untimely admission of the patients into the infectious disease clinics (Figure 1). Three patients received no specific treatment. In addition to antitoxin, the patients in the infectious disease clinics received antibiotics, cardiovascular drugs, and corticosteroid hormones. The early phase of diphtheria was accompanied by soft palate (15 patients) and accommodation (8 patients) pareses, which lasted for no more than 2 weeks. The somatic complications (myocarditis and nephrosis) were observed in 30 and 27 of the patients, respectively. On average, the symptoms of DP were manifest 30 days after the onset of diphtheria. At the time of hospital admission, 15 patients needed AV, while other patients either were bedridden or could walk no more than 5 m. Nine more patients needed AV during the first 2 weeks after admission. In total, AV was performed in 24 of the patients.

Neurological status and vital capacity (VC) were determined daily in all patients. A radiological examination of diaphragm motility was performed 2 to 3 times during inpatient treatment. Data are given as mean±SD unless otherwise indicated.

shorter in the patients with the most severe neurological disturbances, which dictated AV (Figure 2).

THE BASIC SYMPTOMS OF DP

All patients had pareses of motor cranial nerves, weakness of respiratory and abdominal muscles, quadriparesis and quadriplegia with areflexia and muscular hypotonia, peripheral sensory disturbances, pain syndrome in the arms and legs (mostly pronounced to the end of DP month 2), and autonomic disturbances. Half of the patients had sensory ataxia.

CRANIAL NERVE DISTURBANCES

The bilateral disturbances of cranial nerves III, IV, VI, VII, IX, and XII were most frequently observed (Table 1). The clinical signs of lesions in cranial nerves I, II, and VIII were absent. The oculomotor disturbances were manifested as ptosis, anisocoria, and diplopia (Table 2). These abnormalities were observed in all patients undergoing AV and in half of the other patients. The oculomotor disturbances during DP were short compared with those of other cranial nerves. The sensory and motor functions of cranial nerve V were disturbed in 17 and in 11 of the patients, respectively. Palpation of the trigger zones of cranial nerve V was painful in 13 of the patients undergoing AV during the development of DP symptoms. A lesion of the facial nerves was observed in 28 of the patients, including all patients undergoing AV and 4 not undergoing AV. A lesion of cranial nerves IX and X was manifested during weeks 3 to 5 of diphtheria by dysphonia, dysphagia, respiratory insufficiency, and asphyxia. Dysphagia was combined with excessive salivation and regurgitation of fluid food via the nose.

Table 1. Cranial Nerve Disturbances in 32 Patients With Diphtheritic Polyneuropathy

<table>
<thead>
<tr>
<th>Cranial Nerves</th>
<th>Duration of Involvement, wk</th>
<th>Frequency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IX and X</td>
<td>7-8</td>
<td>32 (100)</td>
</tr>
<tr>
<td>VII</td>
<td>7-8</td>
<td>28 (88)</td>
</tr>
<tr>
<td>III, IV, and VI</td>
<td>5-7</td>
<td>27 (84)</td>
</tr>
<tr>
<td>XI</td>
<td>7-9</td>
<td>27 (84)</td>
</tr>
<tr>
<td>XII</td>
<td>7-8</td>
<td>23 (72)</td>
</tr>
<tr>
<td>V</td>
<td>6-7</td>
<td>17 (53)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients.
and 33 ± 4 days, respectively. Only 2 patients with paralytic laryngospasm were 62 ± 4 and 50 ± 3 days, while the durations of AV were 50 ± 3 and 38.2 ± 5.3 mL/kg. In the other 9 patients, the paralytic laryngostenosis with 50% narrowing of the laryngeal lumen (n = 10). In 5 of the 14 patients, the paralytic laryngospasm developed on day 22 of DP (on the average), and the slope of the regression line significantly differs from 0, indicating that Y tends to decrease as X increases (95% confidence interval, −1.25 to −0.47; r = −0.63; r2 = 0.39). We used statistical software (STATISTICA 99; StatSoft Inc, Tulsa, Okla) for the calculations.

<table>
<thead>
<tr>
<th>Oculomotor Disturbances</th>
<th>Duration of Involvement, wk</th>
<th>Frequency*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convergence disturbance</td>
<td>5-7</td>
<td>20 (62)</td>
</tr>
<tr>
<td>Accommodation</td>
<td>4-7</td>
<td>17 (53)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>4-6</td>
<td>16 (50)</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>4-6</td>
<td>16 (50)</td>
</tr>
<tr>
<td>Pupillary light reflex</td>
<td>5-6</td>
<td>9 (28)</td>
</tr>
<tr>
<td>Anisocoria</td>
<td>5-6</td>
<td>8 (25)</td>
</tr>
<tr>
<td>Partial ptosis</td>
<td>5-7</td>
<td>6 (19)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients.

Figure 3. Duration of latency and time of quadriparesis regression. In 29 patients, we attempted to predict the day of onset of quadriparesis (Y) from the day diphtheritic polyneuropathy started (X) using simple regression analysis. X (mean ± SD, 30.3 ± 6.9 days) and Y (mean ± SD, 61.9 ± 9.4 days) are normally distributed (according to the Shapiro-Wilks W test) continuous variables. The assumptions of simple linear regression were verified. The slope (−0.86) of the regression line significantly differs from 0, indicating that Y tends to decrease as X increases (95% confidence interval, −1.25 to −0.47; r=−4.19; P<.001; Y=87.87−0.86X; r=−0.63; r2=0.39). We used statistical software (STATISTICA 99; StatSoft Inc, Tulsa, Okla) for the calculations.

The motor disturbances in the extremities were observed during weeks 2 to 3 of DP, and they slowly developed during weeks 6 to 9, reaching the maximum on day 51 ± 10 of DP. Proximal quadriparesis was revealed in most patients (n = 26). In 11 of the patients, quadriplegia was observed, while other patients had pronounced quadrapareses. All patients had muscular hypotonia and tendinous areflexia. The patients could walk only 4 months after the onset of DP. There was an inverse relationship between DP latency and the period needed to restore motor function: a longer latency corresponded to earlier regression of motor disturbances (Figure 3).

**SENSORY DISTURBANCES**

All patients demonstrated hypoesthesia and hyperesthesia, disturbances in joint position sense, tactile discrimination, and vibration. Hypoesthesia and hyperesthesia accompanied by the elements of hyperpathia of the distal parts of the extremities (usually to the level of the upper thirds of the forearms and legs) were maximal on day 47 ± 13 of DP. The joint position sense, tactile discrimination, and vibration were most frequently disturbed in the distal regions to the level of the elbow and knee joints. They were most pronounced on days 52 ± 11 and 42 ± 12 of DP, respectively. Sensory ataxia was observed in half the patients.

**AUTONOMIC DISTURBANCES**

The autonomic disturbances were observed in all patients. They included sinus tachycardia (32 patients); arterial hypotension (32 patients) leading to collapses (11 patients); retention of urine (11 patients); pronounced xeroderma and hyperkeratosis (24 patients); and hyper-
emia and hyperhidrosis in the face, neck, and chest, at the background of the general paleness of the skin (20 patients). A sudden decrease of arterial pressure occurred during weeks 4 to 7 of DP, and it continued for 3 to 10 days (Figure 4). During this period, all patients needed continuous injections of dopamine hydrochloride. In 2 patients, cardiac intensive care was needed, although an electrocardiogram revealed neither short-term damage to the myocardium nor arrhythmia. Retention of urine developed on day 37 ± 4 of DP, and it was observed in 10 patients undergoing AV and in 1 not undergoing AV. In all these patients, persistent catheterization of the urinary bladder was needed for 5 to 14 days.

CEREBROSPINAL FLUID

Cerebrospinal fluid (CSF) was examined in 27 patients, and CSF pressure was measured with open-tube manometry in 24 patients at different periods of the disease (days 17-68 of DP). In 9 of the patients, the CSF pressure was enhanced from 200 to 440 mm H$_2$O. The CSF protein level was 0.103 ± 0.073 g/dL (range, 0.015-0.283 g/dL), and it did not depend on the duration and severity of the disease. Albumin-cytologic dissociation was observed in 21 of the patients. The CSF cell count did not surpass 12 cells per cubic millimeter (lymphocytes and neutrophils).

COURSE OF THE DISEASE

Disturbance and recovery of neurological functions during DP were characterized with certain regularities. The cranial nerves were affected first, cranial nerves IX and X being disturbed most severely. Nasal feeding was needed as early as day 11 of DP (on average). The duration of nasal feeding varied from 26 to 87 days. As a whole, functional recovery of the cranial nerves was accomplished during weeks 5 to 10 of DP. The motor disturbances appeared during weeks 2 to 3 of DP, and they slowly aggravated to day 51 ± 10 of DP. Quadriplegia was observed in 11 patients, while other patients had severe quadripareses. Regression of motor disturbances began on day 61 ± 12 of DP. Thus, the phenomenon of counterchanges of the neurological symptoms was observed during the second month of the disease: the functional recovery of cranial nerves developed simultaneously with aggravation of motor disturbances in the trunk and extremities. The regress of sensory disturbances started during weeks 12 to 14 of DP.

OUTCOME OF THE DISEASE

Despite severity and a long-term character of the neurological disorders, a virtually complete regression of neurological symptoms was observed in 30 patients. Two patients died of the development of pneumonia complicated by pyopneumothorax and acute cardiovascular insufficiency combined with hemorrhagic syndrome.

Analysis of the development and the course of severe forms of DP showed that neurological symptoms resulted from the toxic forms of diphtheria. None of our patients was treated with antidyphtheritic serum on day 1 of the occurrence of diphtheria. It is known that diphtheria toxin penetrates into Schwann cells and binds to them as early as 1 hour postinjection, inducing the latent development of polyneuropathy. A severe lesion of the peripheral nervous system caused by the diphtheria toxin led to the development of DP accompanied with disturbances of the vital functions. Our data corroborate the existence of a direct relationship between the intensity of diphtheritic intoxication and the probability of the development of severe neurological disorders, thereby stressing the importance of immediate administration of the antidyphtheritic serum.

It was believed that manifestation of neurological disorders in the most immediate period of diphtheria foreshadowed the development of DP. However, less than half of our patients had the neurological disturbances (such as paresis of the soft palate and accommodation disorder) in the immediate phase of diphtheria, although all patients had somatic complications (myocarditis and/or nephrosis). It seems that cardiac and renal disturbances, not the early neurological symptoms, are most indicative of the possibility of DP development.

In all patients, DP was clinically manifested after some latency, which varied from 18 to 46 days. Other data attest to a pronouncedly greater period of 5 to 16 weeks between the onset of diphtheria and the manifestation of the first DP symptoms.

This longer latency probably resulted from a mild course of the disease in the described patients, in whom the most vital functions were not disturbed. We saw, for the first time to our knowledge, the existence of the reverse relationship between DP latency and the onset of the regression of neurological symptoms: the longer the latency, the earlier the regression of motor disturbances. Correspondingly, the most severe clinical forms of DP were observed in the patients with a short latency.

Many studies showed that the first symptoms of DP are paresis of the soft palate and paresthesia in the distal parts of the extremities. Patients with paresthesia on the face, gingivae, and tongue are rarely described. By contrast, we observed these symptoms accompanied with paresis of the soft palate and paresthesia in the distal parts of the extremities in 24 of our patients. Previously, the sensory disturbances were reported only for the innervation area of cranial nerve V. By contrast, we revealed not only the sensory abnormalities of cranial nerve V but also the corresponding motor disturbances of cranial nerve V, which can be explained by the severity of the disease.
It is generally considered thataccommodation disturbances are characteristic of DP, while malfunction of extracranial muscles is a rare symptom lasting for no more than 2 weeks.4,9,10 In our study, these abnormalities were observed in 27 of the patients for 5 to 8 weeks, and half of these patients had accommodation paresis and a lesion of the extraocular muscles. A lesion of the facial nerve was revealed in 28 of the patients during weeks 7 to 8 of DP, while other researchers4,10,11 observed similar lesions in 8% to 35% of patients; these lesions lasted for no longer than 3 weeks.

We showed, for the first time to our knowledge, the development of 2 variants of laryngeal paralysis during weeks 3 to 5 of DP; these were manifest as laryngospasm and 50% laryngostenosis. Laryngoscopy revealed the role of laryngeal paralysis in the development of respiratory tract disturbances during DP. In 5 of the patients, laryngospasm was the major reason to start AV, although the mean VC of these patients was 38 mL/kg, and paresis of respiratory muscles did not reach the critical level. Therefore, extrathoracic obstruction of the airways resulting from laryngeal paralysis can be fatal even before the development of pronounced paresis of the respiratory muscles. Laryngeal paralysis during DP is the reason to start AV, even in patients with a sufficient VC. Laryngospasm is an unfavorable factor in the course of DP.

Respiratory muscle pareses are the life-threatening neurological problem during DP. In one patient, we observed the total respiratory paresis unknown, to our knowledge, in the medical literature. Malfunction of the respiratory muscles was manifest during weeks 1 to 3 of DP, and it attained its maximum only during weeks 3 to 4, which dictated the use of long-term AV (43 days on average). Therefore, AV of patients with DP who have a combination of bronchopulmonary pathological features and pronounced long-term malfunction of respiratory muscles must be performed via tracheotomy without the intubation stage.

Dysfunction of the cranial nerves appeared earlier and developed more rapidly than quadriparesis, which is a typical feature of DP. This period of DP is sometimes referred to as the “cranial stage.”12 Quadriplegia in patients with DP is reported extremely rarely.10,11 In our study, it was observed in 11 of the patients. In most of these patients (n=26), the proximal type of quadriparesis developed. In contrast, the distal type of quadriparesis is characteristic of less severe forms of DP.10,15 In our patients, the maximum of motor disturbances was observed at the end of month 2 of DP, after which regression of motor disturbances started, so the patients could walk without assistance 2 months later. Satisfactory reversibility of neurological disorders during diphtheria is well-known, although such long-term disturbances were observed rarely.4,10,15 The self-restricting course of DP indicates that the immune cells do not actively participate in the development of the pathological process, as evidenced by the absence of inflammatory changes in the nerves.4,15 The prolonged course of neurological disorders reflects the peculiarities of remyelination, which does not restore the myelin even 2 months after the onset of DP.14 Analysis of severe forms of DP revealed the phenomenon of the opposite changes of neurological symptoms during the second month of the disease: functional recovery of cranial nerves proceeded simultaneously with the development of motor disturbances in the extremities. This phenomenon is probably explained by peculiarities of damage and remyelination in different nerves,14,15 and further study should elucidate its nature. The proprioceptive disturbances were also observed in the patients without vital functional disorders.1,4,7,10,11 However, these disturbances were much more prolonged and pronounced in patients with severe DP.

The monitoring of basic variables of systemic hemodynamics showed that weeks 4 to 7 of DP is the period when the circulatory collapses are most probable. The absence of immediate myocardial damage and arrhythmic episodes during this period indicates that a lesion of the autonomic nerve fibers is the main cause of the sudden decreases in arterial pressure.

The modern methods of intensive care made it possible to prevent death in our patients and to study the course of severe forms of DP aggravated by respiratory insufficiency. The unfavorable economic conditions in many countries combined with high migration and communication without intensity increase the probability of new diphtheria outbreaks. Neurologists should always keep in mind the possibility of a diphtheritic cause of polyneuropathy. The timely diagnosis of DP is a prerequisite for the rational treatment and beneficial outcome of this disease, even in the most severe cases.

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REFERENCES