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Autonomic neuropathy in patients with HIV: course, impact of disease stage, and medication

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The purpose of this article is to examine the prevalence, degree, and natural course of pupillary neuropathy (PANP), cardiovascular autonomic neuropathy (CANP), and sensorimotor neuropathy (SNP) and to study the impact of disease stage and medication on neuropathy in 61 consecutive patients with HIV. PANP, CANP, and SNP were assessed by standardized test procedures. Overall prevalence of PANP, CANP, and SNP were 66%, 15%, and 15%, respectively. The maximal pupillary area (pupillary measure, $p < 0.0001$) and the lying-to-standing ratio (cardiovascular measure, $p < 0.0001$) were abnormal as compared with control subjects. The changes in CD4+ T-lymphocytes and respiratory sinus arrhythmia percentile during 2 years of follow-up correlated significantly ($r = 0.758$, $p = 0.007$). Patients with CANP were more often in an advanced disease stage than patients without CANP ($p = 0.004$). SNP, but not PANP or CANP, was associated with the intake of the neuropathogenic drugs dideoxycytidine, dideoxyinosine, and 2′,3′ didehydro-2′,3′ dideoxythymidine ($p < 0.05$). Autonomic and sensorimotor neuropathy are frequent in patients with HIV, and progression of CANP may put patients at risk for unexpected cardiorespiratory arrest.

Key words: HIV, autonomic neuropathy, sensorimotor neuropathy.

Neuropathies of different types and locations are common in patients with human immunodeficiency virus (HIV) as a result of the neurotropic properties of the virus itself [1–5], complement activation of surface-bound gp120 glycoprotein on nerves [6,7], widespread infection with other neurotropic microorganisms such as cytomegalovirus [8], malnutrition in advanced disease stages, and the neuropathogenic anti-retroviral medication. In addition to the problem of painful sensorimotor neuropathy, cardiovascular autonomic neuropathy (CANP) has severely affected patients with HIV through postural hypotension, interval prolongation between Q- and T-waves in electrocardiography, and the negative sequelae of both conditions [9,10]. Unexpected cardiorespiratory arrest has demonstrated the life-threatening potency of CANP in patients with HIV [10,11]. In cross-sectional studies, prevalence of CANP was reported as 5% to 70%, depending on the definition of autonomic neuropathy [3,11–20]. However, little is known about other forms of autonomic neuropathy such as pupillary autonomic neuropathy (PANP), the influence of anti-HIV medication on autonomic neuropathy, or the natural course of CANP or PANP. Therefore, it was the aim of the present study to examine the prevalence, degree, and natural course of PANP, CANP, and for comparison, sensorimotor neuropathy (SNP), and to study the impact of disease stage and medication on PANP, CANP, and SNP.

Patients and methods

Patients

Sixty-one patients with HIV and complete datasets were included in the cross-sectional study. Eleven patients were observed for a median of 24 months (range, 10–34 months) for the longitudinal cohort study. All patients were referred to the Department of Internal Medicine of the University Medical Center at Regensburg between 1994 and 1998. All patients entered the study consecutively without further selection. All patients were fully informed about the purpose of the investigations and gave informed consent to participate. Patients with other causes of peripheral neuropathy such as diabetes mellitus and alcohol-associated neuropathy, genetically determined neuropathy, and drug or toxin neuropathy were excluded. We particularly excluded patients with tumors (and patients who had received tumor therapy) or patients with overt opportunistic infections such as tuberculosis. Of the 61 patients with HIV, 13 had clinically overt encephalopathy. Table 1 gives the clinical parameters of the patients studied. Twenty-three patients received no anti-retroviral therapy, 7 received monotherapy (in 1994), 10 took two drugs, 19 took a triple drug therapy, and 2 took four different anti-retroviral drugs. Among the 38 patients who took anti-retroviral drugs, 21 took neurotoxic anti-retroviral drugs (2′,3′ didehydro-2′,3′ dideoxythymidine [D4T], 10; dideoxycytidine [DDC], 11; D4T/dideoxyinosine [DDI], 1). The patients took no other drugs that alter autonomic nervous function. For comparison, 223 control subjects from two previous studies were included for standardization of autonomic nervous function examination [21,22].

Clinical and laboratory parameters

All patients had a thorough clinical examination by an experienced clinical immunologist. The stage of the disease

Table 1. Clinical characteristics of HIV patients studied

n	61
Age (y)	36.6 ± 1.2 [21–66]
Gender (f/m)	13/48 (21.3/78.7)
Disease duration (y)	7.5 ± 0.5 [0.1–15]
CD4+ T-lymphocytes (cells/µl)	272.4 ± 25.9 [6–700]
Stage according to CDC (number of patients)	A1: 3, A2: 20, A3: 1 B1: 0, B2: 6, B3: 11 C1: 0, C2: 3, C3: 17

Data are given as mean ± SEM, with percentages in parentheses and ranges in brackets.
CDC = Centers for Disease Control and Prevention.

was classified according to the 1993 revised classification system for HIV infection of the Centers for Disease Control and Prevention (CDC) [23]. CD4+ T-lymphocyte count was measured using routine fluorescence-activated cell sorter analysis in the Department of Laboratory Medicine in our hospital.

Autonomic nervous system examination

CANP was assessed using the following test battery, which included standardized tests based on 120 control subjects [21]: variation coefficient of 150 heart beat intervals while in the supine position, heart rate variation during six deep breaths per minute (respiratory sinus arrhythmia test, R-R max - R-R min or expiration - inspiration), respiratory vector measure according to Weinberg *et al.* [24], blowing into the mouthpiece of a manometer for 15 seconds to maintain a pressure of 40 mm Hg (Valsalva test, R-R max/R-R min), and heart rate response to standing up (lying-to-standing test, R-R max/R-R min). For all calculations, we used the exact percentile values for each patient, derived from a study by Ziegler *et al.* [21]. A test result was abnormal if the result was below the fifth percentile. An overall diagnosis of CANP was made if two or more of the five individual test results were abnormal.

PANP was assessed using the following test battery, which was based on 103 control subjects [22]: latency time of pupillary light reflex for the parasympathetic portion and maximal pupillary area in darkness for the sympathetic portion of the pupillary autonomic nervous system. Exact percentile values were used for each test [22]. A test result was abnormal if the result was below the fifth percentile. An overall diagnosis of PANP was made if the result of either test was abnormal [25].

Clinical neurological examination

The neurological investigator was trained in clinical neurological examination for several years. The investigation partly followed a neurological disability score, which was recommended earlier [26]. Peripheral SNP was clinically assessed using five measures: vibratory perception with a standard tuning fork (left and right: great toe, medial malleolus, medial epicondyle of the femur), ability to discriminate two temperatures by means of cold (22°C) and warm (30°C) metal discs (left and right: back of the foot, tibia, back of the hand, fingers), discrimination perception (modality: light touch; left and right: back of the foot, tibia, back of the hand, fingers), reflexes (biceps brachii, triceps brachii, quadriceps femoris, triceps surae), and muscular force (hand shut with a dynamometer, climbing a chair, walking on the heels, walking on tiptoe). For each of the five test groups, a patient could obtain a score of 100 points, which meant that the function was completely normal. The total neurological score was the sum of the five individual scores divided by 5. Overall SNP was diagnosed if the score of two of the five individual tests was below 70 points. In contrast to the autonomic nervous function examination, the diagnosis of SNP was not based on age-related values and not standardized by means of percentiles.

Statistical analysis

Multiple group means were compared by one-way analysis of variance using the statistical package SPSS [27]. The homogeneity of variances was tested by the Cochrans and Bartlett-Box test. Percentages were compared by the Chi-square test using the Yates continuity correction. Correlations were expressed mathematically by the Spearman rank correlation coefficient. In the follow-up analysis, group means were compared by the Wilcoxon matched-pairs signed-rank test. Values were expressed as mean ± standard error of mean, and the significance level was $p < 0.05$.

Results

Prevalence and degree of PANP

With respect to the pupillary test parameters (latency time and maximal pupillary area), 45.9% of all patients with HIV had a test result below the fifth percentile of control subjects in both subtests (Table 2). Overall prevalence of PANP was 65.6%. Prevalence of pathological test results was similar in the different CDC groups. Compared with control subjects (whose mean localization occurred at the 50th percentile), patients with HIV had significantly prolonged pupillary latency time (percentiles, 50.0 ± 1.6 vs 33.1 ± 5.5; $p < 0.001$) and smaller maximal pupillary area in darkness (percentiles, 50.0 ± 1.6 vs 20.6 ± 3.7; $p < 0.0001$).

Prevalence and degree of CANP

Overall prevalence of CANP was determined to be 14.8% (Table 2). It was significantly higher in CDC group C as compared with CDC group A. The most frequently abnormal test result occurred in the lying-to-standing test (mixed sympathetic and parasympathetic), followed by the respiratory vector measure (mixed sympathetic and parasympathetic), the Valsalva ratio (mixed sympathetic and parasympathetic), the variation coefficient (parasympathetic), and the respiratory sinus arrhythmia (mixed sympathetic and parasympathetic). Figure 1 gives the mean percentiles ± standard error of mean of the five cardiovascular test parameters in the different CDC groups. With respect to all subtests, it is obvious that the mean percentile level was lower in CDC group C than in the other groups (Fig. 1).

Table 2. Prevalence of autonomic and sensorimotor neuropathy in patients with HIV

Function test	Prevalence			
	Overall *n* = 61	CDC A *n* = 24	CDC B *n* = 17	CDC C *n* = 20
Pupillary function				
latency time*	28 (45.9)	11 (45.8)	8 (47.1)	9 (45.0)
maximal pupillary area*	28 (45.9)	12 (50.0)	6 (35.2)	10 (50.0)
overall pupillary neuropathy	40 (65.6)	15 (60.0)	10 (58.8)	13 (65.0)
Cardiovascular function				
variation coefficient*	2 (3.3)	0 (0)	0 (0)	2 (10.0)
respiratory sinus arrhythmia*	0 (0.0)	0 (0)	0 (0)	0 (0)
respiratory vector measure*	13 (21.3)	3 (12.5)	4 (23.5)	6 (30.0)
Valsalva ratio*	6 (9.8)	1 (4.1)	2 (11.8)	3 (15.0)
lying-to-standing ratio*	27 (44.3)	6 (25)	9 (52.9)	12 (60.0)†
overall cardiovascular neuropathy	9 (14.8)	0 (0)	3 (17.6)	6 (30.0)†
Sensorimotor function				
vibration perception‡	4 (6.6)	1 (4.1)	1 (5.9)	2 (10.0)
reflex status‡	2 (3.3)	0 (0)	0 (0)	2 (10.0)
temperature perception‡	3 (4.9)	1 (4.1)	2 (11.8)	0 (0)
discrimination perception‡	18 (29.5)	5 (20.8)	5 (29.4)	8 (40.0)
muscular force‡	19 (31.1)	8 (33.3)	4 (23.5)	7 (35.0)
overall sensorimotor neuropathy	9 (14.8)	1 (4.1)	2 (11.8)	6 (30.0)

Percentages are given in parentheses.
CDC = Centers for Disease Control and Prevention.
*Patients with a test result below the 5th percentile.
†$p < 0.05$ for the comparison between group CDC A and CDC C.
‡Patients with a test result of less than 70 points.

The differences between CDC groups A and C were statistically significant for the Valsalva test and the lying-to-standing test. Compared with control subjects (whose mean localization occurred at the 50th percentile), the lying-to-standing test results were severely abnormal for patients with HIV (mean percentile for control subjects [21] vs mean percentile for all patients with HIV, 50.0 ± 1.4 vs 29.6 ± 4.2; $p < 0.001$). The mean percentile of the respiratory sinus arrhythmia test for patients with HIV was significantly higher than that for control subjects (mean percentile for control subjects [21] vs mean percentile for all patients with HIV, 50.0 ± 1.4 vs 78.7 ± 3.0; $p < 0.001$), which was the result of 19 patients having test results above the 95th percentile (hyperreflexia).

Prevalence of SNP

Table 2 gives the overall prevalence of SNP and the percentages of patients with HIV who scored less than 70 points in the individual neurological tests. The highest prevalence of neuropathic changes was found in the muscular force (31.1%) and discrimination perception (29.5%) tests. There was no patient with symptoms of overt sensorimotor neuropathy such as unsteadiness in walking, diffi-

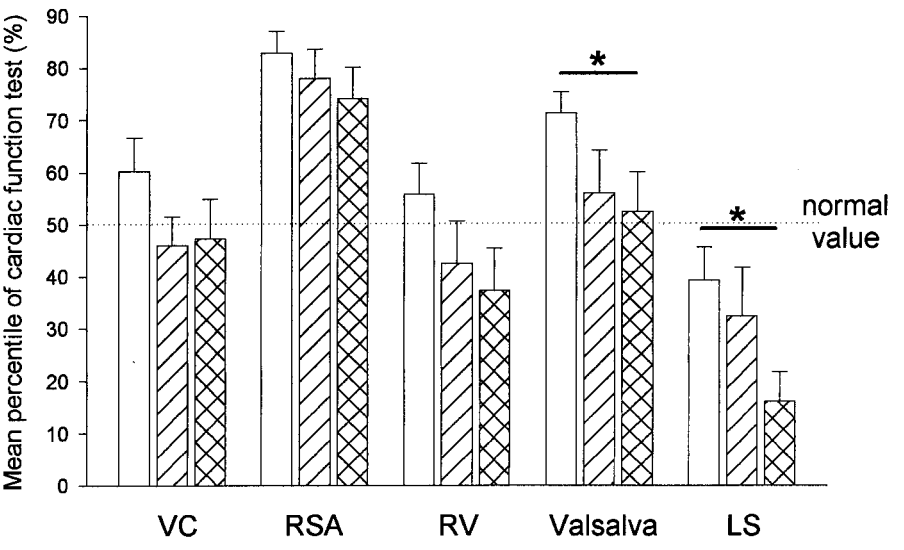

Figure 1. Degree of cardiovascular autonomic nervous dysfunction in patients with HIV. The average percentile localizations of patients with HIV for cardiovascular autonomic nervous function test results are shown (CDC group A, unshaded bars; CDC group B, hatched bars; CDC group C, cross-hatched bars). The mean percentile localization of control subjects is indicated by a dotted line at the 50th percentile. The data are given as mean ± standard error of mean. VC, variation coefficient; RSA, respiratory sinus arrhythmia measure; RV, respiratory vector measure; Valsalva, test result of the 15-second 40 mm Hg Valsalva maneuver; LS, lying-to-standing ratio.

culty identifying objects in hands, numbness, prickling pain, or burning feet.

Impact of CDC disease stage on PANP, CANP, and SNP
The prevalence of CANP in patients with AIDS was significantly higher than in patients with HIV but without AIDS (30.0% vs 7.5%, p = 0.0212). The difference in mean percentile values between the two groups was most obvious in the lying-to-standing test (with AIDS vs without AIDS, 16.1 ± 5.6 vs 36.3 ± 5.4; p = 0.0218). Patients with CANP had significantly lower CD4+ T-lymphocyte cell counts than patients without CANP (Fig. 2A). The prevalence of CANP was significantly higher in patients with advanced CDC disease stage than in patients without it (Fig. 2B). No significant differences were found for overall PANP, overall SNP, or individual PANP or SNP subtests.

Natural course of PANP, CANP, and SNP during 2 years of follow-up
Eleven patients were followed up for 23.3 ± 2.4 months (median, 24 months; range, 10–34 months). The CDC disease stage and the CD4+ T-lymphocyte count (228 ± 62 vs 186 ± 58, p = 0.30) did not significantly change during the 2-year follow-up. Overall PANP, overall CANP, and overall SNP did not change significantly during the short follow-up period of 2 years. However, in the cardiovascular respiratory sinus arrhythmia test, a deterioration of autonomic function correlated to a decrease in CD4+ T-lymphocytes (rank correlation coefficient = 0.758, p = 0.007, data not shown). No correlations were found for other subtests.

Impact of neuropathogenic medication on PANP, CANP, and SNP
DDC, DDI, and D4T are known to be the most potent neuropathogenic drugs used for treatment of patients with HIV [28]. We divided the 61 patients into two groups according to whether they were treated with or without DDC, DDI, and/or D4T. Twenty-one patients took DDC, DDI, and/or D4T and did not differ from patients without these drugs in their CDC disease stage (n = 40). The two groups did not differ in PANP or CANP or individual PANP or CANP subtests (Table 3). However, the total neurological score was significantly lower and the percentage of patients with SNP was significantly higher in the group of patients taking DDC, DDI, and/or D4T than in the group of patients not taking neuropathogenic drugs (Table 3). Patients taking DDC (n = 11) did not significantly differ from patients taking DDI (n = 10) in the prevalence of PANP, CANP, or SNP.

Impact of HIV encephalopathy on PANP, CANP, and SNP
Thirteen patients had various degrees of overt HIV encephalopathy. These patients had significantly lower CD4+ cell counts than patients without HIV encephalopathy (92 ± 29 µl vs 322 ± 28 µl, p = 0.0001). However, there was no difference in the prevalence of CANP, PANP, or SNP between the two groups.

Discussion

Patients with HIV frequently had PANP, CANP, and SNP, and the pupillary autonomic function was severely affected. To our knowledge, this is the first study to systematically examine pupillary autonomic function in patients with HIV. The prevalence of PANP is high and exceeds the prevalence found by the same technique for other diseases such as diabetes mellitus (about 40%) [25], systemic lupus erythematosus (30%) [29], systemic sclerosis (21%) [29], Crohn disease (21%) [30], and ulcerative colitis (21%) [30]. Because central nervous system involvement is common in patients with HIV, [2] the high prevalence of pupillary autonomic disorders may be a sign of central nervous system alterations. Pupillary autonomic function tests investigate a more central portion of the autonomic nervous system. The afferent part of the reflex loop consists of the retina, the optic nerve, and the central visual pathways, which are often altered in patients with HIV [2,4]. However, patients with clinically overt encephalopathy did not differ from patients without it in pupillary test parameters in this study. This indicates that alterations of the pupillary reflex loop are not

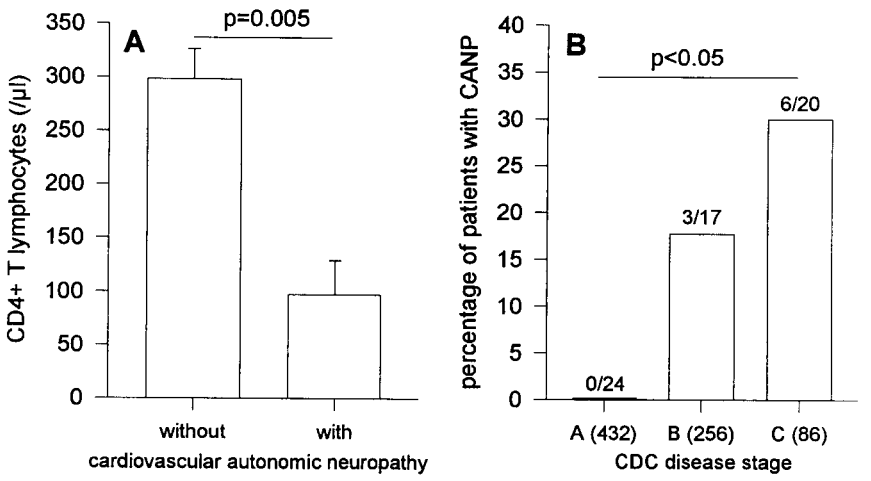

Figure 2. Disease stage and cardiovascular autonomic neuropathy. **(A)** CD4+ T-lymphocyte count in patients with and without cardiovascular autonomic neuropathy are shown. The data are given as mean ± standard error of mean. **(B)** Percentage of patients with CANP in the three groups of CDC disease stages A to C. The number of patients with CANP is given on the bars. The mean number of CD4+ T-lymphocytes per microliter is given in parentheses.

Table 3. Association of neuropathogenic drugs (DDC, 3TC, D4T) and sensorimotor or autonomic nervous function

Function test	Without neuropathogenic drugs (n = 40)	With neuropathogenic drugs (n = 21)	p
Pupillary function			
latency time*	40.1 ± 10.0	28.9 ± 6.6	ns
maximal pupillary area*	23.1 ± 5.0	16.2 ± 5.5	ns
patients with overall pupillary neuropathy	25 (62.5)	13 (61.9)	ns
Cardiovascular function			
variation coefficient*	55.2 ± 4.9	45.9 ± 6.2	ns
respiratory sinus arrhythmia*	76.8 ± 4.1	82.2 ± 4.1	ns
respiratory vector measure*	49.4 ± 5.4	39.4 ± 7.0	ns
Valsalva ratio*	59.1 ± 5.0	64.1 ± 5.7	ns
lying-to-standing ratio*	28.4 ± 5.3	31.8 ± 7.0	ns
patients with overall cardiovascular neuropathy	6 (15.0)	3 (14.3)	ns
Sensorimotor function			
total neurological score†	89.7 ± 0.8	85.6 ± 2.2	0.037
patients with overall sensorimotor neuropathy	2 (5.0)	7 (33.3)	<0.01

Data are given in mean ± SEM, and percentages are in parentheses.
ns = not significant.
*Values are given in mean percentile ± SEM.
†The total neurologic score is the sum of the five individual scores of vibratory perception, reflex status, temperature perception, discrimination perception and muscular force divided by 5 (given in mean ± SEM).

inevitably associated with encephalopathy, and vice-versa. We have not investigated the optic nerve by specific ophthalmologic tests, which should be done in future studies because optic neuritis may frequently be present in these patients [4]. Pupillary function examination seems to be a tool for the investigation of alterations of the visual pathways. The prognostic implications regarding morbidity and mortality need to be explored in prospective studies.

By means of the same standardized techniques, the 15% prevalence of CANP was found to be in the range known for other diseases such as systemic lupus erythematosus (10%) [29] and systemic sclerosis (16%) [29], but it was significantly higher than the prevalence known in Crohn disease (0%) [30] and ulcerative colitis (5%) [30] and significantly lower than the prevalence known in diabetes mellitus (approximately 25%) [31]. The most abnormal cardiovascular function test results were yielded by the mixed parasympathetic–sympathetic lying-to-standing test, which was also shown to be the most severely affected function in patients with diabetes mellitus, systemic lupus erythematosus, and systemic sclerosis [29,31]. It is obvious that the mean percentiles of various cardiovascular subtests were lower in CDC group C than in any other subgroup. Patients with overt AIDS had CANP significantly more often, and patients with CANP had lower CD4+ T-lymphocyte counts than patients without CANP. This clearly indicates that cardiovascular function, as compared with pupillary or sensorimotor function, for which no such association was found, is more vulnerable to current disease processes. These data confirm a recently published study in which HIV progression was significantly associated with more severe cardiovascular autonomic dysfunction [32]. The same has been demonstrated for nerve conduction velocity in the peroneal, median, and sural nerves [33]. We have not investigated other reasons for cardiovascular dysfunctions such as deficiency of adrenal hormones (epinephrine, aldosterone), and we did not perform echocardiography. Therefore, we are not able to exclude adrenalitis and symptomatic cardiomyopathy, which have been found in patients with HIV [34–36].

Progression of cardiovascular dysfunction during a follow-up of 24 months seems to be slow and has minimal, non-significant changes [32]. Including data on PANP, CANP, and SNP, we were able to confirm that there was no progression of autonomic or sensorimotor nervous dysfunction during 24 months, which may depend on the constant overall HIV disease stage in our patients. However, the number of patients in the follow-up was relatively low, which may have lead to a bias in the selection of patients with HIV. At the second visit, 24 months later, patients may have died as a consequence of cardiovascular autonomic dysfunction, and these patients could have been lost to follow-up.

Using similar standardized techniques, the 15% prevalence of SNP was found to be higher than the prevalence of Crohn disease (4%), ulcerative colitis (5%), and systemic lupus erythematosus (7%) in patients of the same age, but it was comparable with the prevalence known in diabetes mellitus and similar disease duration (approximately 17%) [29–31]. SNP, in contrast to PANP and CANP, was more prevalent in patients taking anti-retroviral drugs with known neurotoxic effects such as DDC, DDI, and/or D4T. This may indicate that the myelinated fibers of sensorimotor nerves are more severely affected than non-myelinated autonomic nerve fibers by these drugs.

In conclusion, PANP, CANP, and SNP are relevant complications in patients with HIV. The high prevalence of PANP, as compared with the prevalence of other diseases, is

probably the result of the strong central nervous system neurotropism of HIV with multiple lesions at specific central nervous system localizations and at the optic nerve. Altered cardiovascular autonomic function is significantly associated with HIV progression, which may indicate an important risk for sudden death in these patients. Cardiovascular autonomic function testing may identify patients with increased risk of cardiorespiratory arrest, which seems to be especially high if additional proarrhythmogenic factors are present, such as anesthesia during surgical interventions [10,11]. Furthermore, a clinical examination of sensorimotor function may help to identify patients with particular risk for overt sensorimotor nervous dysfunction after administration of neuropathogenic anti-retroviral medication.

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