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Video-Oculography Assessment in Neurodegenerative Ataxias and Niemann Pick Type C

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ABSTRACT

Introduction: Deceleration of vertical saccades, an early and characteristic finding of Niemann-Pick Type C (NP-C), may help diagnosis. Our aim in this study was to demonstrate the role of video-oculography (VOG), in the differential diagnosis of ataxia syndromes, particularly of NP-C, using this technique in the evaluation of saccadic velocity and smooth pursuit gain of ataxia patients.

Methods: We recruited consecutive 50 ataxia patients and 50 healthy control subjects who were age and sex-matched with the patient group. Saccadic eye movements and smooth pursuit eye movements for different angles and different directions from patients and healthy subjects were recorded by using VOG.

Results: Saccadic eye movement velocity and smooth pursuit gain values of the patients were significantly lower in all directions and at all angles as compared to healthy subjects. In the patient group, 3 cases out of 50 were selected as suspected NP-C, based on the dissociation between their markedly impaired vertical saccadic velocity and near normal to slightly impaired horizontal one and relatively intact smooth pursuit eye movements; the diagnoses in all 3 cases were confirmed with positive genetic testing, and thereupon Miglustat treatment was started.

Conclusion: Our findings support that cerebellar pathology in degenerative ataxia patients is associated with both impaired saccadic velocity and smooth pursuit gain, whereas in NP-C, only the impaired vertical saccades as opposed to relatively preserved other eye movements are seemingly a diagnostic marker for the entity. We conclude that recording of eye movements could be useful for differential diagnosis and monitorization of the treatment of ataxia syndromes as an easy and objective method.

Keywords: Degenerative ataxias, niemann-pick type c, saccadic velocity, smooth pursuit, video-oculography

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INTRODUCTION

Niemann-Pick Type C (NP-C) is an autosomal recessive lipid storage disorder caused by mutation of genes that encoding NP-C1 and NP-C2 proteins (1). These two proteins are involved in cellular trafficking of sterols and required for cholesterol exits from lysosomes (2). Impairment of NP-C1 and NP-C2 genes results in accumulation of unesterified cholesterol and glycosphingolipids in late endosomes and lysosomes (3). Although the estimated incidence of disease is 1/104.000 live births, recent database analyses suggested that the incidence of adult-onset form may be as high as 1/19.000–1/36.000 (4,5). The clinical features of NP-C are heterogeneous and can range from neonatal fatal neurovisceral symptoms to a mild neurodegenerative disease. In adult-onset forms, progressive neurological deficits like cognitive impairment, ataxia, dystonia and major psychiatric findings are the main clinical characteristics of the disease (6).

Saccades are the explosive movements of both eyes that aim to place the object of interest to the fovea for clear vision. Multiple regions of the central nervous system (CNS) are involved in the control of specific features of saccadic eye movements like velocity, amplitude, and duration (7). A variety of disorders that disturb this complex neural circuitry cause impairment of saccadic eye movements in particular ways that can give clues about the affected area (8,9). Vertical supranuclear saccade palsy (VSSP) describes the predominant vertical saccadic impairment due to selective involvement of burst neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF)(10). On the other hand, vertical supranuclear gaze palsy (VSGP) that corresponds to dysfunction of both smooth pursuit and saccades caused by an impairment of the rostral midbrain and its connections was highlighted as one of the earliest and prominent findings of NP-C (11,12). Vertical supranuclear gaze palsy has been shown to be present in 46.9 – 70% of NP-C patients while VSSP has been shown to be present in 98.2 % in a cross-validated study (13).

Highlights

- **Disruption of the vertical saccades is a distinctive feature of Niemann Pick Type C.**
- **Videooculography provides objective information in the diagnosis of Niemann Pick Type C.**
- **Videooculography is a rapid technique that can be used in the differential diagnosis of ataxia.**

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Especially in a busy clinical practice, the oculomotor examination is usually limited to the observation of eye movements while following a slowly moving target, which corresponds to smooth pursuit. Lack of information about saccades can lead to delayed diagnosis of certain diseases like in the case of NP-C. Improvements in technology allow us to easily quantify eye movements at the bedside with non-invasive techniques, evaluation of saccades can be an important diagnostic tool for helping to distinguish degenerative disorders of CNS at an early stage.

Since Miglustat has been approved as a disease-modifying therapy for NP-C that slows progressive neurological damage, early diagnosis and initiation of treatment are crucial for stabilizing the disease (14). Vertical supranuclear gaze palsy is a reliable finding despite the heterogeneity of NP-C phenotype, however it becomes clinically apparent later in the course of disease. Examination of saccades with eye tracking systems provides an advantage to detect early deterioration of vertical saccades even if it is not clinically obvious (15).

In this study, we aimed to quantify the eye movements of degenerative ataxia patients with unknown etiology by using video-oculography (VOG) in order to reveal accompanying eye movement abnormalities that suggest NP-C and evaluate the clinical usefulness of VOG in the differential diagnosis of degenerative ataxias.

METHODS

Subjects

Fifty degenerative ataxia patients, consecutively admitted to the movement disorders outpatient clinic of İstanbul Üniversitesi, İstanbul Tıp Fakültesi, Nöroloji Anabilim Dalı were included in this study. All cases were screened for spinocerebellar ataxia (SCA) 1, 2, 3, 7, 17 and Friedreich's ataxia, celiac disease, and vitamin E deficiency and were found negative. No abnormality was found in routine biochemistry tests. Patients with a history of using any medications that could affect eye movements were excluded. Gender– and age-matched 50 healthy controls (HC) (27 males, 23 females) with no prior neurological disease history were included in this study.

All patients were examined by a neurologist for evaluation of clinical features. The International Cooperative Ataxia Rating Scale (ICARS) was used to assess the severity of ataxia which is scored from 0 to 100. The study protocol was approved by the Istanbul University clinical research ethics committee (2015/1863). The written informed consents were obtained from all participations.

Video-oculography

Eye movements were recorded with a video-based eye-tracking system (EyeSeeCam®, Munich, Germany) that contains a camera with two integrated infrared light-emitting diodes (IRLED), an inertial measurement unit (IMU) and a calibration laser, a google frame that this camera can be attached. A display positioned 40 cm away from the patient provides visual stimuli which the test person can fixate or follow. For measuring 3D eye movements, limbus was used as a marker and recordings were obtained from left eye only. A laptop with EyeSeeCam software was used for quantifying eye movements. The procedure was performed in a dimly lit room, and a chinrest was used to support and stabilize the head. The instrument was calibrated for each participant. After the calibration step, patients and control subjects were instructed to look at a visual target that is displayed on the screen 5 times running at 60 Hz (upward, downward, right and left directions) with 10° and 20° amplitude for the examination of reflexive saccades. The smooth pursuit was also evaluated with a stimulus with a ±10° amplitude that moves horizontally and vertically without a break from the central position. MATLAB (Matlab 7.10, The MathWorks, Natick, MA) was used for analyzing raw data and it provided high-order information. The following saccadic parameters were analyzed: 1) Peak velocity: defined as the maximal velocity during the saccade. 2) Latency: defined as the interval between target presentation and when the eye velocity reached 5°/s. 3) Amplitude: Position of the eye at the start of the saccade and the position of the final gaze shift. Smooth pursuit gain was calculated from the ratio of eye velocity to target velocity. Values lower than mean – 2.5 SD of healthy controls were considered pathological for patients.

Statistical Analysis

Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) program version 26 software (IBM Inc, Chicago, IL, USA) with 95% confidential interval and the significance level was set at $p<0.05$. The variables were investigated using visual (histograms) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Mann-Whitney U test was utilized for analyzing non-parametric variables and student t-test for parametric ones. The correlation coefficients and their significance were calculated using Pearson correlation coefficient.

RESULTS

Subject Characteristics

Twenty-three female and 27 male patients and age and sex-matched 50 healthy controls (mean age 38.2±10.9, $p=0.975$) enrolled in this study. The clinical characteristics of patients are presented in Table 1.

Video-oculography Examination Results

Velocity of saccadic eye movement and smooth pursuit gain values were significantly lower in patients for all directions compared to healthy controls (Table 2 and 3).

Mean vertical saccadic velocity rates of eight patients were significantly low (less than mean – 2.5 SD) compared to controls. Among these 8 patients, 3 have a high suspicion of having NP-C according to NP-C suspicion index (a total risk prediction score of >70)(16). Primary exon and junction sequencing of the NP-C1 and NP-C2 genes revealed NP-C1 mutation in these three patients.

Patient 1: Nineteen years old female patient who had ataxia for 5 years and complained of swallowing difficulties for the last year. Her systemic examination indicated splenomegaly and dysarthria, appendicular and truncal ataxia, and choreiform movements of hands were detected in neurological assessment. Abdominal ultrasonography (USG) revealed an increased size of the spleen. Her NP-C suspicion index score was 80. Genetic sequencing revealed a heterozygote S945L mutation in the NP-C1 gene. Cholestan-3β, 5α, 6β-triol (C-triol), and 7-ketocholesterol (7-KC) levels were found to be elevated in the patient's serum (39.16 ng/mL and 102.09 ng/mL, respectively). The patient was diagnosed as NP-C and started on Miglustat treatment.

Patient 2: Twenty-six years old female patient who had progressive ataxia for 14 years. Neurological examination showed dysarthria, appendicular and truncal ataxia, and splenomegaly have been found in her abdominal USG. Her NP-C suspicion index score was 80. The sequencing study of NP-C1 and NP-C revealed homozygote p. P1007A (c. 3019C >G) mutation in NP-C1 gene. The patient started on Miglustat treatment after NP-C diagnosis.

Patient 3: Twenty-five years old male patient complained of progressive ataxia for 5 years. His neurological examination revealed dysarthria, brisk deep tendon reflexes, and appendicular and truncal ataxia. Splenomegaly

Table 1. Clinical characteristics of patients

	Patients n=50 (%)
Age	38.3±11.51
Gender	
Female	23(46)
Male	27(54)
Duration of ataxia (years)	9.36±5.73
Onset symptom	
Imbalance	40(80)
Dysarthria	2(4)
Tremor	4(8)
Myoclonus	2(4)
Dizziness	1(2)
Psychosis	1(2)
Accompanying symptoms	
Dysphagia	2 (4)
Dystonia	1(2)
Pyramidal signs	12(24)
Hepato/splenomegaly	4(8)
Polyneuropathy	9(18)
Seizure	3(6)
ICARS score (total)	32.18±15.20
Posture and gait disturbance	12.02±8.22
Kinetic function	16.10±6.95
Speech disorder	2.13±0.87
Oculomotor disorders	1.93±1.26
Consanguineous marriage of parents	28(56)
Positive family history	29(58)

ICARS: International Cooperative Ataxia Rating Scale.

was observed in abdominal USG. His NP-C suspicion index score was 80. Homozygote N169I mutation in NP-C1 gene has been detected in an exon sequencing study. Miglustat treatment was started after NP-C diagnosis.

Although saccadic velocities of NP-C patients were under a lower bound of 95% CI values of healthy controls for all directions, deterioration of vertical saccades was more prominent than horizontal saccades (Figure 1a and 1b). Smooth pursuit gain values were within 95% CI limits for two cases, only patient 3 had a slightly lower smooth pursuit gain value (Figure 2).

We re-examined patient 2 after 3 months of Miglustat treatment and repeated her eye movement recordings. Her ICARS score was found to be decreased by 6 points, horizontal saccadic velocities were elevated, and found to be within 95% CI limits of controls (Figure 3).

DISCUSSION

Degenerative ataxias are rare chronic diseases of the CNS with a progressive course. When all ataxias are evaluated together, the prevalence has been reported as 15–20:100 000. It is estimated that there are between 50 and 100 different genetic and molecular causes of ataxia in this group (17). Therefore, clinical differential diagnosis will include many diseases in degenerative ataxia patients unless there are other clinical and laboratory findings accompanying cerebellar findings. Narrowing the molecular targets to be screened for differential diagnosis of degenerative ataxias with the help of additional diagnostic tests would be cost-effective and it would also shorten the time for the diagnosis.

Table 2. Mean velocity of saccades in patients compared to healthy controls

		N	Mean velocity (°/sn)	Standart deviation	P
10° right	Patients	50	291.24	80.79	<0.001
	HC	50	352.12	72.13	
10° left	Patients	48	289.02	101.07	<0.001
	HC	50	381.56	87.99	
10° upward	Patients	50	251.46	123.91	0.001
	HC	50	323.16	73.93	
10° downward	Patients	50	266.76	105.76	<0.001
	HC	50	382.04	83.76	
20° right	Patients	50	388.66	123.82	<0.001
	HC	50	477.36	93.71	
20° left	Patients	49	373.51	130.49	<0.001
	HC	50	479.62	96.96	
20° upward	Patients	50	322.72	126.33	<0.001
	HC	50	446.76	104.13	
20° downward	Patients	50	334.70	122.49	<0.001
	HC	50	447.02	94.71	

HC: Healthy controls.

Table 3. Smooth pursuit gain values in patients and healthy controls

		N	Mean smooth pursuit gain value	Standart deviation	P
10° right	Patients	50	0.58	0.29	<0.001
	HC	50	0.83	0.18	
10° left	Patients	50	0.59	0.28	<0.001
	HC	50	0.82	0.19	
10° upward	Patients	50	0.50	0.30	0.001
	HC	50	0.69	0.20	
10° downward	Patients	50	0.42	0.26	<0.001
	HC	50	0.63	0.23	

HC: Healthy controls.

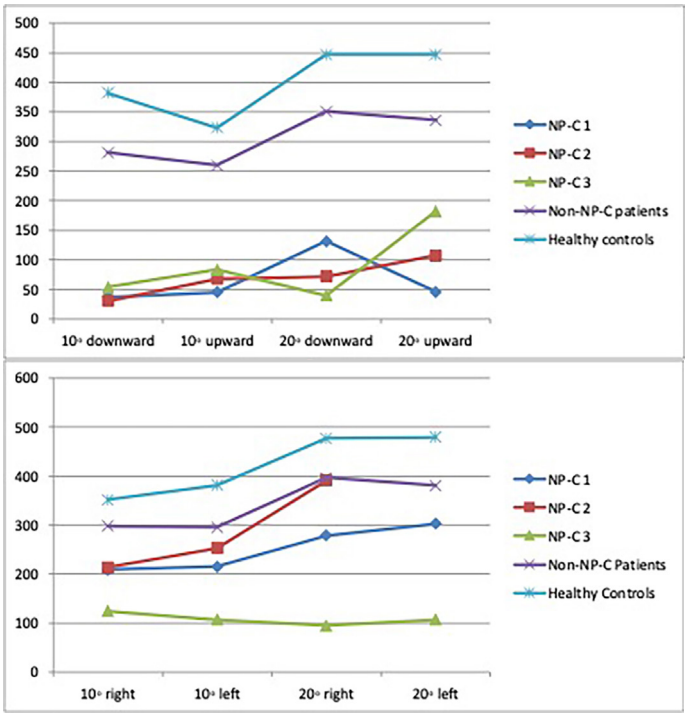

Figure 1. a, b. Vertical saccadic velocity (°/sn) of healthy controls, non-NP-C and NP-C cases **(a).** Horizontal saccadic velocity (°/sn) of healthy controls, non-NP-C and NP-C cases **(b).**

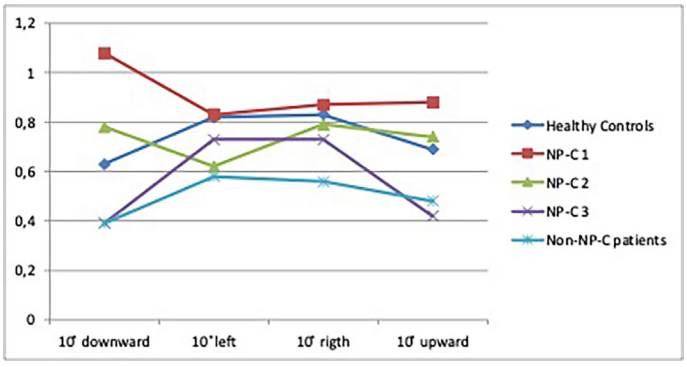

Figure 2. Smooth pursuit gains of healthy controls, non-NP-C and NP-C cases.

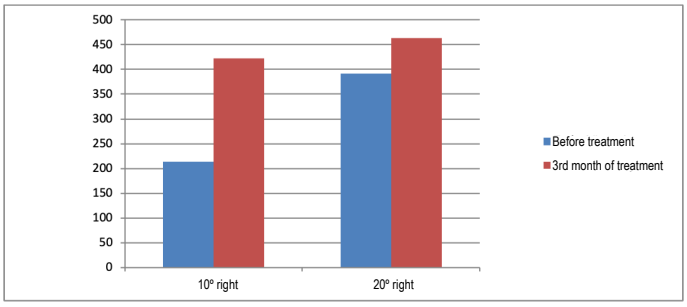

Figure 3. Horizontal saccadic velocity of patient 2 before and after treatment.

Examining eye movements is an essential step for evaluating patients with movement disorders. A better understanding of the functional anatomy of the ocular motor system provides clues in the differential diagnosis of movement disorders, especially in the diagnosis of rare diseases (18). Eye movement abnormalities could reveal the affected neural network in certain diseases besides their prognostic value. Smooth pursuit is dominantly a reflexive movement whereas saccades could be a component of behavioral functions (19). Eye movements have a special role in the diagnosis and follow-up of NP-C patients, as supranuclear gaze palsy is highly specific for the disease and provides the possibility of early diagnosis and initiation of treatment (4,20). However, in busy clinical setups, evaluation of saccades may be skipped or not comprehensively evaluated.

Advances in the technology for the assessment of eye movements have led us to go beyond observation and we are now enabled to measure and record certain parameters related to eye movements with sensitive methods. Recent studies with eye tracking systems have shown that these techniques are easily applicable and reliable methods in the differential diagnosis of ataxia syndromes (21–24).

In NP-C patients, impairment in vertical saccades is more prominent compared to horizontal saccades and smooth pursuit, and these abnormalities are well-correlated with the neuropathological findings of the disease as the neuronal loss mainly seen in riMLF while the interstitial nucleus of Cajal was spared at the early stages (12). Frontal regions associated with eye movements are also affected in the advanced stages of the disease (25,26). In a study Abel et al. performed with 9 NP-C cases and 10 healthy controls, they investigated the correlation of MRI findings of patients with eye movement abnormalities and found that saccadic gain value was well correlated with disease severity and anatomical findings (27). Furthermore, they demonstrated the reduction in cerebellar white and gray matter volumes was associated with saccadic gain and motor impairment in NP-C patients (28). In another study comparing 2 neurological, 3 pre-neurological NP-C cases, and 77 healthy controls, a decrease in vertical saccade peak velocity was demonstrated in all cases, although it was more pronounced in neurological cases, and therefore, the monitoring of vertical saccade velocities is suggested as an essential tool for detection of neurological findings even at the stage they are not yet clinically evident (29). Similarly, typical oculomotor findings were shown in VOG studies in heterozygous NP-C cases (30).

In a prospective multicontinental cross-sectional study, Bremova et al. assessed 72 NP-C patients with VOG. They reported that 98.2% of patients' vertical saccade peak velocities were below the 95% CI of the controls' peak velocity. However, only 46.9% of patients had lower smooth pursuit gain than 95% CI of controls. In this study, they demonstrated the decreased mean peak velocity in NP-C patients compared to healthy controls (HC) for both rightward and leftward saccades (NP-C vs. HC, 244.6°/s vs. 449.8°/s for the right, 240°/s vs. 429.8°/s for the left, p<0.001). On the other hand, they have reported that vertical velocity smooth pursuit gain shows no differences between NP-C and HC (0.544 vs. 572, respectively, p=0.435) whereas horizontal smooth pursuit gain was lower in NP-C patients compared to HC (0.619 vs. 0.812, p<0.001). They also indicated that horizontal saccadic peak velocity and latency, vertical saccadic duration and amplitude were correlated to disease severity and could be used as a biomarker for clinical trials. In conclusion, they suggested that vertical supranuclear saccade palsy (VSSP) is cardinal symptom of NP-C, but not VSGP (31).

Similar to this large prospective study, we also found a decrease in the mean peak velocity of 3 NP-C patients compared to our health controls (NP-C vs. HC, 255°/s vs. 477.4°/s for the right, 205°/s vs. 479.6°/s for the left). In our HC cohort, the vertical smooth pursuit gain value was 0.660, while horizontal smooth pursuit gain calculated as 0.825. In NP-C cases, these values were recorded as 0.715 and 0.765, respectively. These differences between literature and our results probably arose due to our lower sample size.

Disease progression in NP-C is largely associated with neurological symptoms (1). Considering that the main problem in NP-C is lipid

accumulation in lysosomes, treatment studies focused on reducing cellular cholesterol, but these treatment options did not have an effect on neurological symptoms (32).

Miglustat has been shown to slow the progression of neurological symptoms and is the only treatment approved by the FDA in 2009 as a disease-modifying therapy for NP-C (33). It reversibly inhibits glycolipid synthesis via the glucosylceramide synthase enzyme (34). Observational prospective cohort studies have proven that the patients under Miglustat treatment have stable or improved neurological findings (35–37). As Miglustat has been started to use in clinical practice, the need for monitoring the treatment outcomes has emerged. Patterson et al. used horizontal saccadic eye movement (HSEM) velocity as the primary endpoint to investigate the efficacy of Miglustat with 29 NP-C cases and found improvement in HSEM velocity besides improvement in swallowing capacity and a slower deterioration in the ambulatory index in some cases (14). Abel et al. have reported improvement in gain and the interval between self-paced saccades under Miglustat treatment (38). Among our 3 NP-C cases, we could only assess one patient's eye movement records before and after treatment and we could observe improvement in her ICARS score as well as horizontal saccadic velocities within 3 months.

These results indicate that Miglustat has a positive effect at multiple sites in the CNS. In the light of this information, it can be predicted that early recognition of neurological involvement and initiation of early treatment will provide a significant advantage in disease progression.

The examination of eye movements is of great importance in neurological practice and provides valuable clues related to the anatomical areas it is associated with. However, especially in regions with a high patient load, as is often the case in our country, there may not always be the opportunity to perform a detailed eye examination in routine practice. This situation can result in the oversight of diseases with the potential for early diagnosis and treatment, such as NP-C. This study demonstrates that the rapid and objective evaluation of eye movements with VOG (Video-Oculography) can assist in the diagnosis and emphasizes its usability in daily practice considering the conditions in our country.

In conclusion, we demonstrated the use of VOG as a scanning method for degenerative ataxia patients in the case of suspicion of NP-C. This method is a valid, non-invasive, and easily applicable method that provides objective findings of early-stage NP-C, which can be a challenge, particularly in adult-onset cases. Therefore, there is a chance to start on a disease-modifying therapy, which can be a very helpful method in clinical practice in terms of early diagnosis and early treatment. In addition, its use as an objective parameter in treatment follow-up makes this method more valuable.

The main limitations of our study are the low number of cases which made it impossible to compare our results statistically with other degenerative ataxia cases. In addition, anatomical correlation with the affected areas of the cases could not be achieved. However, the algorithmic approach starting with the eye movement abnormalities has been detected at an early stage and subsequent suspicion of diagnosis with NSI could lead us to confirmation of genetic diagnosis. We suggest that screening degenerative ataxia patients with no clear etiological background by using VOG may be a cost-effective method for NP-C diagnosis.

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Ethics Committee Approval: The study protocol was approved by the Istanbul University clinical research ethics committee (2015/1863).

Informed Consent: Written informed consent was obtained from all participants.

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Data Availability Statement: The raw data of this retrospective study are not publicly available due to ethical restrictions.

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