Eye-tracking-aided Characterization of Saccades and Antisaccades in SYNE1 Ataxia Patients – A Pilot Study

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Abstract

Background
SYNE1 ataxia is an autosomal recessive hereditary condition, the main characteristic features of which are gait and limb ataxia and cerebellar dysarthria. Previous reports revealed that the clinical phenotype of SYNE1 ataxia is more complex than the first published cases with pure cerebellar signs. The aim of this study was to characterize the eye movement alterations of the first diagnosed Hungarian SYNE1 ataxia patients.

Results
Saccades and antisaccades were examined with eye tracker device in 3 SYNE1 (one patient has two frameshift mutations [c.8515_8516insA, p.Met2839Asnf*53 and c.11594_11595insG, p.Glu3866*] in compound heterozygous state, whereas two subjects have a splicing variant [c.23146-2A=G] in homozygous state), 6 Friedreich ataxia (FA) patients and 12 healthy controls. Besides that, detailed clinical phenotyping and comprehensive neuropsychological assessment were implemented as well in all patients with ataxia.

In addition to the characteristic cerebellar alterations, pyramidal signs and polyneuropathy were observed at least in 2 SYNE1 ataxia patients without any other underlying reason. The eye tracking assessment revealed hypometric saccades in the longer amplitude (18.4°) saccadic paradigm in all SYNE1 patients, whereas 2 out of 3 SYNE1 subjects performed slow saccades as well. In the antisaccade task, higher incorrect ratio of antisaccades were demonstrated in SYNE1 patients compared to healthy controls, showing inverse correlation with working memory test results. The corresponding data of FA patients dispersed in a wide range partially overlapping with control data.

Conclusions
The current study draws attention to the presence of eye movement disorders in patients with SYNE1 ataxia and demonstrates that alterations in the antisaccade paradigm may be related to working memory deficits.

Background
Autosomal recessive cerebellar ataxias (ARCA) belong to a continuously expanding group of hereditary neurodegenerative disorders. Recently, more than 100 genes have been identified which can cause ARCA including the SYNE1 gene (OMIM 608441). SYNE1 is one of the largest genes in the human genome, located in 6p25 chromosome and containing 146 exons [1]. This huge gene encodes a peptide of about 8797 amino acids, known as Nesprin 1 (Nuclear envelope spectrin 1) [1]. This is a member of spectrin family proteins and its major function is to link the plasma membrane to the actin cytoskeleton [2]. Nesprin 1 has three domains including the N-terminal actin binding domain (also called calponin homology domain), the multiple spectrin repeats and the C-terminal KASH domain (also knowns as Klarsicht domain) [1]. In 2007, Gros-Louis et al. reported 26 French-Canadian families from Quebec, Canada with slowly progressive pure cerebellar hereditary ataxia caused by truncating mutations of the SYNE1 gene. The name of this disease was autosomal recessive cerebellar ataxia type 1 (ARCA1), also known as spinocerebellar ataxia, autosomal recessive 8 (SCAR8), or recessive ataxia of Beauce [1]. In the following years, the SYNE1 ataxia was observed almost exclusively in Quebec province, Canada [1, 3]. From 2013, some sporadic cases were reported as well outside the French-Canadian population [4–7]. In 2016, Synofzik and Mademan et al. described 33 non-Canadian patients with SYNE1 ataxia from a large multi-centre study, which delineated that mutations of SYNE1 gene are much more common causes of ARCA than previously thought [2, 8]. Besides its frequency, the clinical phenotype was also more complex compared to the first described pure cerebellar disease. Most of the newly identified patients had extracerebellar neurological signs including upper and lower motoneuron symptoms and non-neurological abnormalities including scoliosis, pes cavus or respiratory dysfunction with severe manifestation. Only a small portion of these subjects showed classical pure cerebellar phenotype [2, 8].

Moreover, mutations of SYNE1 gene have been associated with arthrogryposis multiplex congenita, Emery-Dreifuss muscular dystrophy 4, dilatative and hypertrophic cardiomyopathy, intellectual disability, blepharospasm, autism spectrum disorder and schizophrenia [9–16].

After reviewing the clinical phenotype of the previously published 168 SYNE1 ataxia patients, the detailed characterization of eye movements has not been performed so far; only the occurrence of gaze-evoked nystagmus, slowing of saccades, broken up smooth pursuits, strabism and square-wave jerks were reported [1–4, 17–19].

In this paper we aimed to characterize the saccadic and antisaccadic eye movements of 3 Hungarian SYNE1 ataxia patients and to compare them with the same parameters of Friedreich ataxia (FA) patients and healthy subjects in addition to detailed clinical phenotyping and comprehensive neuropsychological assessment.

Patients And Methods

Participants
3 SYNE1, 6 Friedreich ataxia patients and 12 healthy controls were enrolled in the study. The patients underwent a detailed diagnostic approach including neurological examination, laboratory and radiological investigations to exclude acquired causes of ataxia. Scale for the Assessment and Rating of Ataxia (SARA) scores were recorded in all cases. After obtaining written, informed consent, genomic DNA was extracted from peripheral blood leukocytes by standard protocol. First, according to recent guidelines on the management of sporadic ataxias without known secondary etiology [20], the most common repeat expansion hereditary ataxias (spinocerebellar ataxia 1, 2, 3, 6, 7 and FA) were tested. These examinations reinforced the diagnosis of FA in six patients. All of
them have homozygous GAA repeat expansions in the first intron of the FXN gene. In the additional three patients, targeted gene analysis followed by new generation sequencing were performed.

For proband AT-04, whole exome sequencing (WES) was performed with SureSelectXT Human kit All Exon v7 (Agilent, Agilent Technologies, Santa Clara, CA) according to the manufacturer’s instruction and paired-end sequenced (2x100 bp) on HiSeq 1500 (Illumina, San Diego, CA, USA). Prioritized variants were validated in the proband, proband’s parents and brother by amplicon deep sequencing performed using Nextera XT Kit (Illumina) and sequenced on HiSeq 1500 (Illumina).

For subjects AT-05 and AT-06 a total of 60 ng of genomic DNA was used for library preparation and sequenced with Trusight One clinical exome kit (Illumina) on Illumina MiSeq platform. The clinical exome kit covers the coding region of 4813 clinically relevant, disease-associated genes. The 150 bp paired reads were aligned to the GRCh37.75 human reference genome by Burrows Wheel Aligner (BWA v0.7.9a) software. The variants were called by Genome Analysis Toolkit HaplotypeCaller (GATK v3.5) best practice; annotated by SnpEff and VariantStudio softwares. Variants were filtered based on severity and frequency against public variant databases including dbSNP, ClinVar, ExAC, EVS and an in-house clinical exome database of 140 unrelated Hungarian patients.

Eye tracking

Recording system

The used system and paradigm were described in a previous study [21]. The assessment was performed in a well-lit room. Subjects sat in front of the monitor and their head were fixed at 60 cm distance from the screen. We used a Tobii TX300 eye tracker and tasks were programmed in Psychophysics Toolbox V 3.0.12, under MatLab. Before every paradigm a five-points calibration was performed.

Saccade task

Subjects accomplished a visually guided saccade task as described here: a black cross appeared at the center of the screen and 1.2-2 seconds later it jumped to the right or left side of the screen. The background was grey and the distances of displacement of the cross were 9.2° or 18.4° horizontally. All measurements were repeated 20 times in a pseudorandom order, this means 80 measurements per subject. The participants had to shift their gaze to the new position of the target as fast and accurate as they can. There was a break in halftime of the task to prevent subjects tearing and/or tiring.

Antisaccade task

In the antisaccade task the composition was similar to the visually guided saccade paradigm, however, the participants had to direct their gaze to the opposite direction (e.g. if the target appeared in the left side, they had to look to the ride side). Only horizontal movements were recorded such as in the saccade task. There was also a pause in half of the trial.

Data acquisition and processing

Data recording began when the target jumped to the periphery and stayed there for one second. The recording frequency was 300 Hz and both eyes were registered separately. We used a semi-automatic in-house made script to define parameters of saccades as described in a previous study [21]. The following parameters were measured: peak velocity, latency, amplitude, gain and duration. In the saccade task, we assessed the main sequence relationships of duration versus amplitude and peak velocity versus amplitude using the linear model [22]. Additionally, in the antisaccade paradigm the incorrect ratio of antisaccades was also examined, which is a quotient showing the incorrectly executed antisaccades.

Neuropsychological assessment

The enrolled ataxia patients were assessed via cognitive examination performed by trained neuropsychologists. The global cognitive performance was measured by the Addenbrooke's Cognitive Examination (ACE) including the Mini-Mental State Examination (MMSE). The executive function was evaluated by verbal and semantic fluency tests. In addition, the working memory and the ability of maintenance and manipulation of information were estimated by the Backward Digit Span Task (BDST) and the Listening Span Task (LST). The quality of information planning and visuoconstructional and visual organizational abilities were assessed by the Rey Complex Figure Test (RCFT).

Result

Patients

The mean age of SYNE1 ataxia patients was 38.3 years (35-43 years), similar to that of the FA group: 41.5 years (16-60 years). The mean age at eye tracking examination of healthy subjects was 40.0 years in the saccade paradigm and 40.25 years in the antisaccade task. The SARA scores showed remarkable variability in both groups of ataxia cases (SYNE1: 12-23.5 points, FA: 12-30.5 points).
The detailed demographic and genetic data with clinical phenotype of SYNE1 ataxia patients are summarized in Table 1. The first symptom of AT-04 subject was gait ataxia at the age of 15 years. He also had delayed puberty in this period. Later, slurred speech also appeared and his gait imbalance progressed. There was no neurological disease in his family. The neurological examination revealed gaze-evoked horizontal nystagmus, cerebellar dysarthria, bilateral Babinski sign, gait ataxia and severe lower limb ataxia and mild numbness in the upper extremities. Sometimes stimulus sensitive myoclonic jerks could be observed as well. He had strabism and myopia with negative fundoscopy. Electroneurography showed mild axonal sensory polyneuropathy. Currently, the patient needs sticks as walking aids because of the progression of his symptoms. Laboratory examination did not find pathological abnormalities. Skull MRI was performed after sixteen years of disease course and displayed moderate cerebellar atrophy with preserved brainstem and supratentorial structures (Figure 1/a-b).

Table 1
Demographic, clinical and genetic data of SYNE1 ataxia patients

| Patient code | Age (years), gender | Mutation (cDNA) | Protein change or variant type | Age at onset (years) | Gait ataxia | Upper limb ataxia | Lower limb ataxia | Dysarthria | GEN | UMN | LMN | PNP | SA |
|--------------|---------------------|-----------------|-----------------------------|---------------------|------------|------------------|------------------|-----------|-----|-----|-----|-----|----|
| AT-04        | 35, M               | c.8515_8516insA | p.Met2839Asnfs*53          | 15                  | +++        | ++               | +++              | ++        | Y   | Y   | N   | mild | 23.|
|              |                     | c.11594_11595_insG | p.Glu3866*                |                     |            |                  |                  |           |     |     |     |     |     |
| AT-05        | 43, F               | c.23146-2A>G    | Splicing                   | 30                  | +++        | ++               | +++              | ++        | N   | Y   | N   | N   | 25.|
| AT-06        | 37, F               | c.23146-2A>G    | Splicing                   | 14                  | ++         | +                | +                | +         | N   | Y   | N   | MSMN| 12.|

+: mild, ++: moderate, +++: severe, ASN: axonal sensory polyneuropathy, DM: diabetes mellitus, F: female, GEN: gaze-evoked nystagmus, HC: hypercholester male, MSMN: mixed sensorimotor polyneuropathy, N: not present, PNP: polyneuropathy, SARA: Scale for the Assessment and Rating of Ataxia, UMN: upper m present

WES of AT-04 patient revealed a compound heterozygote state in SYNE1 gene NM_033071.3:c.8515_8516insA, p.Met2839Asnfs*53 and NM_033071.3:c.11594_11595insG, p.Glu3866* (Figure 2/a). The c.8515_8516insA variant located in exon 55 out of 146 was inherited from the mother of the proband, while c.11594_11595insG located in exon 71 was inherited from the father, and both variants were absent in the healthy brother of the proband. Both frameshift variants were not found in the gnomAD database (www.gnomad.broadinstitute.org) and are predicted to cause loss of the full-length SYNE1 protein (8750 amino acids).

The age at onset of AT-05 patient was 30 years and her first complaint was gait ataxia, whereas the first symptom of her sister (patient AT-06) appeared at 14 years of age and it was gait abnormality as well. The neurological examination of both patients revealed cerebellar dysarthria and brisk tendon reflexes with bilateral Babinski signs. The truncal ataxia was moderate in the younger patient (AT-06) and was severe in the elder subject (AT-05). After 11 years of disease course patient AT-05 can walk only with aids. Mild upper limb and moderate lower extremity incoordination developed in the younger sister, whereas her sibling had moderate superior and severe inferior limb ataxia. The AT-05 patient has obesity, diabetes mellitus, hypertension and hypercholesterolemia, but ophthalmological and cardiological investigations were negative. The AT-06 subject also has the same metabolic disorders, moreover, she has excavated foot and the electromyography delineated multifocal sensorimotor mixed type polyneuropathy. The skull MRI showed moderate cerebellar and very mild cerebral cortical atrophy in both patients (Figure 1/c-f). Their parents do not have ataxia and the younger patient has two healthy children.

In AT-05 and AT-06 patients the same homozygous NM_182961.3:c.23146-2A>G alteration of the SYNE1 gene was detected. This intronic variant was not found in the gnomAD. It causes a TAG – TGG codon change in the Intron 128 – Exon 128 boundary resulting in an abnormal splicing variant (Figure 2/b). The presence of these mutations was confirmed by targeted Sanger sequencing. Segregation analysis identified this variant in heterozygous state from both parents of the patients.

**Eye tracking**

**Saccades**

The pooled data of leftward and rightward saccades were analyzed (Table 2). There was not any relevant difference between the three groups of examined subjects in the saccadic latencies and durations regarding both of the shorter (9.2°) and the longer (18.4°) saccade paradigms. The peak velocities of saccades of AT-05 and AT-06 patients were smaller than the HC subjects and FA patients. However, the peak velocities of the saccades of AT-04 patient were similar to the subjects of HC and FA groups. In the 9.2° saccade task AT-04 patient demonstrated hypermetric saccadic eye movements, whereas the another two SYNE1 ataxia patients showed hypometric saccades. Nevertheless, in the 18.4° saccade task all SYNE1 ataxia subjects performed smaller saccadic
amplitudes and gain than the healthy controls (Figure 3/a). The amplitudes and gain of saccades of FA patients were in a similar range to that of the HC group. Figure 4 displays the main sequence relationships using the linear model. The duration vs. amplitude diagram (Fig. 4/a) shows that saccades of SYN1 ataxia patients are hypometric and their duration is longer than in FA or HC groups. The peak velocity vs. amplitude graph (Fig. 4/b) reinforces that the saccades of SYN1 patients are hypometric and their peak velocity is smaller than in HC or FA groups.

### Table 2

| 9.2° saccades | 18.4° saccades |
|---------------|---------------|
| Subjects      | Peak velocity (°/s) | Latency (s) | Amplitude (°) | Duration (s) | Gain | Peak velocity (°/s) | Latency (s) | Amplitude (°) | Duration (s) | Gain |
| AT-04         | 343.18         | 0.16        | 10.27         | 0.069         | 1.117 | 384.95         | 0.19        | 13.87         | 0.079         | 0.754 |
| AT-05         | 219.14         | 0.27        | 7.434         | 0.076         | 0.808 | 279.08         | 0.27        | 11.48         | 0.087         | 0.624 |
| AT-06         | 215.87         | 0.18        | 7.02          | 0.073         | 0.763 | 280.26         | 0.22        | 15.16         | 0.104         | 0.824 |
| Median FA     | 316.45         | 0.20        | 9.18          | 0.071         | 0.998 | 431.13         | 0.23        | 16.49         | 0.088         | 0.896 |
| (range)       | (264.62-382.63)| (0.18-0.31) | (7.86-11.83)  | (0.066-0.856) | (0.085-1.285)| (320.27-555.22)| (0.21-0.34) | (14.35-20.85) | (0.083-0.104) | (0.780-1.133) |
| Median HC     | 269.20         | 0.18        | 8.45          | 0.069         | 0.919 | 363.93         | 0.20        | 16.75         | 0.091         | 0.911 |
| (range)       | (233.54-333.55)| (0.17-0.21) | (7.99-9.21)   | (0.059-0.869) | (0.079-1.001)| (321.89-505.69)| (0.17-0.26) | (15.12-17.29) | (0.075-0.102) | (0.822-0.940) |

### Antisaccades

The pooled data of leftward and rightward antisaccades were evaluated as well (Table 2). There was no remarkable difference between the groups with regard to the peak velocities, latencies and durations of antisaccades. The incorrect ratios were higher in the SYN1 and FA patients than in the HC group. However, there was a slightly overlapping range in the 9.2° antisaccades within the SYN1 and HC subjects, whereas this was not detected in the longer antisaccades (Figure 3/b).

### Neuropsychological assessment

The neuropsychological assessment of FA and SYN1 patients are summarized in Table 3. The cognitive performance of ataxia patients was compared with the data of age- and education-matched standards of the literature [23-25]. The global cognition was mildly reduced only in two FA patients (AT-11 and AT-20), whereas the other subjects demonstrated normal ACE and MMSE scores. The LST results showed mild abnormalities in all SYN1 patients and in one FA patient, whereas the BDST results were decreased more prominently in both patient groups. These alterations indicate the impairment of working memory and the ability of maintenance and manipulation of information. Surprisingly, the fluency test scores were in normal range, only AT-04 patient demonstrated mild deficit in the verbal fluency test. In addition, the RCFT results were equal to the standard outcomes, only AT-05 patient showed a mild impairment.
In this paper we describe the clinical phenotype and characteristics of saccades and antisaccades of the first genetically confirmed Hungarian \textit{SYNE1} patients caused by novel mutations. The cerebellar symptoms of these patients involved moderate to severe gait and lower limb ataxia and mild to moderate upper limb ataxia and dysarthria. Extracerebellar involvement was present as well because all subjects have pyramidal signs and two of the three patients have some kind of polynuropathy. Moreover, AT-04 patient had strabismus, tactile sensitive myoclonic jerks and delayed puberty. In summary, the clinical phenotype of subjects is not pure cerebellar in contrast to that of described in the first French-Canadian population by Gros-Louis et al. [1], and similar to that of the later reported cases [2, 8]. This symptomatic variability suggests that \textit{SYNE1} gene plays an important role in the normal functioning of the nervous and musculoskeletal systems in a broader range. Consequently, the mutations of this gene can cause symptoms and signs within a large spectrum, but obvious genotype-phenotype correlation cannot be established [2].

The eye tracking examination revealed hypometric saccades in the 18.4° paradigm in all \textit{SYNE1} patients and in two out of three in the 9.2° task. Saccadic dysmetria is a cerebellar symptom and it is a common eye movement abnormality in hereditary ataxies [26]. This is not a specific symptom for any type of inheritable ataxia, but there may be a higher proportion of hypo- or hypermetric saccades, serving as a supporting feature of the disease. In addition to the accuracy, the velocity is another important characteristic of saccades. Previous case reports described slowing of saccades in a part of Friedreich ataxia, but there may be a higher proportion of hypo- or hypermetric saccades, serving as a supporting feature of the disease. In addition to the dysmetria is a cerebellar symptom and it is a common eye movement abnormality in hereditary ataxies [26]. Consequently, the mutations of this gene can cause symptoms and signs within a large spectrum, but obvious genotype-phenotype correlation cannot be established [2].

The antisaccade assessment delineated greater rate of incorrectly accomplished antisaccades in both FA and \textit{SYNE1} patients compared to healthy subjects, whereas the other parameters were in similar ranges. This observation raises the suspicion of cognitive impairment, because strong correlation was demonstrated between antisaccades and working memory [27]. The neuropsychological assessment revealed that the global cognitive performance was normal in \textit{SYNE1} patients, whereas the executive functions were impaired, especially the working memory. The performance of the examined \textit{SYNE1} subjects in BDST and LST paradigms inversely correlated with the errors in the antisaccade tasks, i.e., the most severely affected patient in working memory tests (AT-06) performed the highest error rate in antisaccade paradigm (Fig. 5). Similar relationship was not detected in the FA group. This finding draws attention to the major role of working memory in the performance of antisaccades, and confirms that executive dysfunction is a prevalent neuropsychological abnormality in hereditary ataxias as a part of the cerebellar cognitive and affective syndrome [28].

### Table 3

**Neuropsychological assessment of \textit{SYNE1} and Friedreich ataxia patients.**

| Patient code | Age (years) | Education (years) | ACE (93.7±4.3) | MMSE (28.8±1.3) | LST | BDST | Verbal fluency | Semantic fluency | RCFT copying | RCFT recall |
|--------------|-------------|--------------------|----------------|-----------------|-----|------|----------------|-----------------|--------------|------------|
| \textit{SYNE1} patients | | | | | | | | | | |
| AT-04 | 35 | 14 | 89 | 29 | 2 (3.38±0.79)* | 4 (5.88±1.1)* | 10.5 (17.61±5.42)* | 14 (17.25±3.96) | NA | NA |
| AT-05 | 43 | 14 | 93 | 29 | 2.33 (3.38±0.79)* | 3 (5.88±1.1)* | 14.5 (17.61±5.42) | 17 (17.25±3.96) | 35 (31.1±3.6) | 15 (23.7±5.2)* |
| AT-06 | 37 | 12 | 89 | 29 | 2 (3.38±0.79)* | 2 (5.88±1.1)*** | 16 (17.61±5.42) | 14 (17.25±3.96) | 36 (31.1±3.6) | 21.5 (23.7±5.2) |
| Friedreich ataxia patients | | | | | | | | | | |
| AT-08 | 23 | 12.5 | 93 | 30 | 3 (3.45±0.89) | 4 (5.88±1.1)* | 14.5 (16.13±5.65) | 11 (15.84±4.51) | 26 (31.1±3.6) | 24 (23.7±5.2) |
| AT-11 | 57 | 16 | 87* | 27 | 2.33 (3.11±0.61)* | 3 (5.34±0.96)* | 12 (11.02±4.98) | 16 (13.77±4.05) | 36 (29.2±4.2) | 26.5 (15.5±5.5) |
| AT-12 | 60 | 17 | 95 | 29 | 3 (3.11±0.61) | 2 (5.34±0.96)*** | 15.5 (11.02±4.98) | 20 (13.77±4.05) | 34 (29.2±4.2) | 27 (15.5±5.5) |
| AT-20 | 16 | 10 | 88 | 26* | 2.66 (3.33±0.59) | 5 (5.88±0.96) | 13.5 (13.83±4.31) | 14 (13.44±3.52) | 36 (31.1±3.6) | 26 (23.7±5.2) |
| AT-21 | 59 | 14 | 94 | 30 | 3 (3.11±0.61) | 5 (5.34±0.96) | 15 (11.02±4.98) | 14 (13.77±4.05) | 32 (29.2±4.2) | 17.5 (15.5±5.5) |
| AT-22 | 34 | 15 | 96 | 30 | 3.3 (3.38±0.79) | 4 (5.88±1.1)* | 16.5 (16.13±5.65) | 21 (15.84±4.51) | 34 (31.1±3.6) | 21 (23.7±5.2) |

*slight deficit, **moderate deficit, ***severe deficit, ACE: Addenbrooke’s Cognitive Examination, BDST: Backward Digit Span Task, LST: Listening Span Task, MMSE: Mini-Mental State Examination, NA: not available, RCFT: Rey Complex Figure Test.

In ACE and MMSE the lower normal threshold values of the normal population are in the brackets.

In LST, BDST, verbal fluency, semantic fluency, RCFT copying and RCFT recall the age- and education-matched lower threshold values of the normal population are in the brackets.

### Discussion

The eye tracking examination revealed hypometric saccades in the 18.4° paradigm in all \textit{SYNE1} patients and in two out of three in the 9.2° task. Saccadic dysmetria is a cerebellar symptom and it is a common eye movement abnormality in hereditary ataxies [26]. This is not a specific symptom for any type of inheritable ataxia, but there may be a higher proportion of hypo- or hypermetric saccades, serving as a supporting feature of the disease. In addition to the accuracy, the velocity is another important characteristic of saccades. Previous case reports described slowing of saccades in a part of \textit{SYNE1} patients, however these observations were based exclusively on physical examinations [1–4, 18, 19]. Our findings, obtained by fine eye tracking assessment, confirmed the clinical observations of some earlier publications, i.e., high frequency of slow saccades can be detected in \textit{SYNE1} ataxia.

The antisaccade assessment delineated greater rate of incorrectly accomplished antisaccades in both FA and \textit{SYNE1} patients compared to healthy subjects, whereas the other parameters were in similar ranges. This observation raises the suspicion of cognitive impairment, because strong correlation was demonstrated between antisaccades and working memory [27]. The neuropsychological assessment revealed that the global cognitive performance was normal in \textit{SYNE1} patients, whereas the executive functions were impaired, especially the working memory. The performance of the examined \textit{SYNE1} subjects in BDST and LST paradigms inversely correlated with the errors in the antisaccade tasks, i.e., the most severely affected patient in working memory tests (AT-06) performed the highest error rate in antisaccade paradigm (Fig. 5). Similar relationship was not detected in the FA group. This finding draws attention to the major role of working memory in the performance of antisaccades, and confirms that executive dysfunction is a prevalent neuropsychological abnormality in hereditary ataxias as a part of the cerebellar cognitive and affective syndrome [28].
Conclusions

In conclusion, this paper demonstrates the detailed neurological assessment of the first Hungarian $SYNE1$ ataxia patients with novel pathogenic mutations. The eye tracking investigation detected some interesting alterations regarding both saccades and antisaccades of these subjects, including saccadic hypometria and increased errors of antisaccades. The main weakness of this study is the low case number. Nevertheless, these pilot findings point out the importance of device-aided examination of eye movements in ARCA. Hopefully in the near future, these parameters can be investigated in a larger number of $SYNE1$ patients to be able to draw statistical conclusions as well.

Abbreviations

ACE – Addenbrooke’s Cognitive Examination (ACE)
ARCA – autosomal recessive cerebellar ataxias
ARCA1 – autosomal recessive cerebellar ataxia type 1
BDST – Backward Digit Span Task
FA – Friedreich ataxia
HC – healthy controls
LST – Listening Span Task
MMSE – Mini-Mental State Examination
RCFT – Rey Complex Figure Test
SARA – Scale for the Assessment and Rating of Ataxia
SCAR8 – spinocerebellar ataxia, autosomal recessive 8
WES – whole exome sequencing

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patients for the participation in this study (Regional Human Biomedical Research Ethics Committee of the University of Szeged registration number is 44/2016). All procedures performed in this study involving human participants were in accordance with the ethical standards of the Regional Human Biomedical Research Ethics Committee of the University of Szeged and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets used and/or analysed in the current study are available in this paper.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

LSZ examined the patients and wrote the manuscript. GSZ and BK performed the eye-tracking examination of the subjects. BK set up the eye-tracking aided device and established the methods of the study. VLN and NSZ performed the neuropsychological examination of the patients. ZM, TK, MR and RP carried out
the new generation sequencing of the SYNE1 patients. GV analysed the data and made the diagrams. PK and AS had important recommendations to the manuscript. ZD was the major contributor in writing the manuscript.

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