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Presentation of Graves' orbitopathy within European Group On Graves' Orbitopathy (EUGOGO) centres from 2012 to 2019 (PREGO III)

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ABSTRACT

Background Graves' orbitopathy (GO) is subject to epidemiological and care-related changes. Aim of the survey was to identify trends in presentation of GO to the European Group On Graves' Orbitopathy (EUGOGO) tertiary referral centres and initial management over time.

Methods Prospective observational multicentre study. All new referrals with diagnosis of GO within September–December 2019 were included. Clinical and demographic characteristics, referral timelines and initial therapeutic decisions were recorded. Data were compared with a similar EUGOGO survey performed in 2012.

Results Besides age (mean age: 50.5±13 years vs 47.7±14 years; p 0.007), demographic characteristics of 432 patients studied in 2019 were similar to those in 2012. In 2019, there was a decrease of severe cases (9.8% vs 14.9; p<0.001), but no significant change in proportion of active cases (41.3% vs 36.6%; p 0.217). After first diagnosis of GO, median referral time to an EUGOGO tertiary centre was shorter (2 (0–350) vs 6 (0–552) months; p<0.001) in 2019. At the time of first visit, more patients were already on antithyroid medications (80.2% vs 45.0%; p<0.001) or selenium (22.3% vs 3.0%; p<0.001). In 2019, the initial management plans for GO were similar to 2012, except for lid surgery (2.4% vs 13.9%; p<0.001) and prescription of selenium (28.5% vs 21.0%; p 0.027).

Conclusion GO patients are referred to tertiary EUGOGO centres in a less severe stage of the disease than before. We speculate that this might be linked to a broader awareness of the disease and faster and adequate delivered treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Changes in presentation of Graves' orbitopathy (GO) due to epidemiological and therapeutic modifications are assumed. The European Group On Graves' Orbitopathy (EUGOGO) provides specified centres offering interdisciplinary treatment.

WHAT THIS STUDY ADDS

⇒ Referral time to EUGOGO centres after first diagnosis of GO is shorter and in a less severe stage of the disease than before.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Awareness of GO and knowledge of the existence of specialised centres must be kept high among physicians, as this seems to be beneficial for the management of affected patients and the course of the disease, especially regarding severity.

INTRODUCTION

Graves' orbitopathy (GO), also called thyroid eye disease, is the most frequent extrathyroidal manifestation of Graves' disease; although less frequently, it may also occur in association with chronic autoimmune thyroiditis.[1] With an estimated incidence of 0.54–0.9 cases/100 000/year in men and 2.67–3.3 cases/100 000/year in women,[2 3] it is a relatively rare disease.[1] Although most patients with Graves' disease have no or only mild ocular involvement at diagnosis,[1 4] the prevalence of GO at all stages of Graves' disease is 25%–40%.[1] The aetiology of GO, a disease of autoimmune origin, is thought to be based on a complex interaction between genetic predisposition (endogenous, unmodifiable) and environmental (exogenous, modifiable) influences.[1 5–7] Smoking[8 9] is the most important risk factor; others include thyroid dysfunction,[10–12] radioiodine treatment,[13 14] elevated thyrotropin thyroid-stimulating hormone (TSH) receptor antibodies (TRAbs),[15 16] oxidative stress[17–19] and

hypercholesterolaemia.[20] Most patients present with a bilateral disease, starting with inflammatory changes in the periorbital region (active phase), followed by stabilisation (plateau phase) before burning out/fibrotic stage (inactive phase).[1] Classification and treatment decisions are based on activity, severity and duration of GO.[21] In 2000, the European Group On Graves' Orbitopathy (EUGOGO) performed an observational study on the clinical characteristics of newly referred patients to tertiary EUGOGO centres.[22] A similar study followed in 2012 and provided a data-based possibility to investigate changes in the clinical presentations of GO over the years,[23] and an assumed decline in severity of GO[24 25] could be confirmed.[23] Improvement of diagnostic and therapeutic options with awareness of possible risk factors might improve the prognostic outcome in GO within years. The demographic characteristics, including smoking rates, were similar between 2000 and 2012,[23] however, shorter referral times to tertiary centres after first diagnosis of GO were reported,[23] probably due to an increased awareness of the disease.

The aim of the current study was to once again investigate patient characteristics, referral timelines and treatment strategies in consecutive newly referred patients with GO seen at the EUGOGO centres in 2019 and compare these findings with the data generated by the EUGOGO group in 2012.[23]

METHODS

Study design

This survey was a prospective observational multicentre study.

Patients

All the newly referred GO patients to the EUGOGO sites from 1 September 2019 to 31 December 2019 were prospectively included in this survey. This time frame was same as that used in the previous two EUGOGO surveys.[22 23] Patients were assessed using the EUGOGO case record form (CRF), which includes demographic data and a detailed ophthalmological and endocrine assessment.[26]

Assessments

Ophthalmic signs were assessed according to established EUGOGO protocols.[27] The EUGOGO group has adopted a well-defined protocol for the clinical assessment of GO using a photographic atlas.[28] All members of the group are trained in using the protocol and undergo regular refresher courses using real patients with GO.[29] Patients were classified as 'active' or 'inactive' based on a Clinical Activity Score (CAS) (active=CAS≥3/7) and the overall clinical impression by the examining clinicians, as in our previous studies[22 23] (overall clinical impression of activity took account of the CAS, but in addition, interpreted it in the context of whether lid swelling was due to true inflammatory lid oedema as opposed to congestive, non-inflammatory oedema or fatty prolapse and presence or absence of clear history of recent change in symptoms). To allow comparability with the 2012 data, the classification of mild, moderate and severe from the previous studies[22 23] was chosen instead of the official EUGOGO classification of severity[21] mild, moderate-to-severe and sight-threatening. At the end of the first evaluation, the clinicians recorded the immediate treatment plan for GO. If various therapies were thought to be necessary (eg, decompression followed by eye muscle surgery), only the first treatment option in the chronological sequence proposed was recorded. Patients' CRF data were entered pseudonymously in a prespecified table by each centre and send to AS and CRH who double checked the data. In this way confidentiality was preserved.

In order to access the potential bias of new centres (NC) included in the 2019 cohort, we comparedpatient characteristics obtained in 2012 and 2019 of the centres who participated in both studies PREGO II and III (old centres, OC).

Table 1 Number of patients referred to different EUGOGO centres between September and December 2019 and comparative data from 2012 study[23]

		No of patients	
Centre	Country	2012	2019
Ankara	Turkey	15	41
Belgrade	Serbia	17	23
Brussels	Belgium	13	8
Cardiff	UK	7	–
Essen	Germany	48	31
Exeter	UK	–	8
Göttingen	Germany	–	26
Lyon	France	37	–
Mainz	Germany	21	60
Milan	Italy	42	34
Munich	Germany	–	28
Newcastle	UK	13	–
Odense	Denmark	6	12
Olten	Switzerland	14	24
Pisa	Italy	27	62
Valencia	Spain	–	18
Varese	Italy	9	10
Warsaw	Poland	–	30
Zagreb	Croatia	–	17
Total		269	432

EUGOGO, European Group On Graves' Orbitopathy.

Statistical analyses

The data, including differences between the 2012 study and the current study, were compared by standard two-sample t testif normally distributed or Mann-Whitney-U test for continuous variables and Pearson χ^2 test or Fisher's exact test for categorical variables. Comparisons for time intervals were made using Wilcoxon rank-sum test. Analysis was performed with SPSS V.25.[30]

RESULTS

Number of patients, centres and referral time

A total of 432 CRFs were returned from 16 participating EUGOGO centres, compared with 269 CRFs from 13 centres in 2012 (table 1). In 2019, 10 centres, contributing with 305 patients, had also participated in the 2012 study (OC), whereas six centres which contributed with 127 patients were participating for the first time (NC). The mean number of patients seen by centre per month was 5.2 for the 2012 cohort and 6.8 for the 2019 cohort. Comparing this number only for OC, it was 5.3 in 2012 and 7.6 in 2019. The time interval from the first diagnosis of GO to referral to EUGOGO centres was shorter in 2019 (median: 2 (0–350) month vs 6 (0–552) month; p<0.001). At presentation to an EUGOGO centre, the duration of eye symptoms or thyroid symptoms in general was similar in 2019 and 2012.

Table 2 Demographic characteristics of patients referred in EUGOGO centres between September and December 2019 and comparative data from the 2012 study

	2019		2012		
	%	N	%	N	P value
Age	50.5±13.1		47.7±14.0		0.007
Female	79.2	342/432	77.3	208/269	0.564
Caucasian	95.8	414/432	95.2	256/269	0.306
Smoking rates					
Current smoker	37.2	160/430	40.3	108/268	0.211
Ex-smoker	24.2	104/430	27.6	74/268	
Never smoked	38.6	166/430	32.1	86/268	

EUGOGO, European Group On Graves' Orbitopathy.

Demographic characteristics

Patients were significantly older in the 2019 cohort as compared with the 2012 cohort(mean age: 50.5±13 years vs 47.7±14 years; p=0.007). Other demographic characteristics including gender, ethnicity and smoking rates were similar in the two cohorts (table 2).

Medical history

As compared with the 2012 cohort, more patients in the 2019 cohort were already treated with antithyroid drugs (ATD) (80.2% vs 45.0%; p<0.001) at the time of referral to an EUGOGO centre. Fewer patients in the 2019 cohort had a combined treatment of ATD and levothyroxine (LT4) (block and replace) (6.3% vs 22.0%; p<0001). In the 2019 cohort, more patients were on selenium treatment (22.3% vs 3.0%; p<0.001), beta-blockers (18.7% vs 10.0%; p=0.002) and systemic steroids (15.1% vs 4.1%; p<0.001) at the time of the first visit at an EUGOGO centre. Other treatments for hyperthyroidism were similar (table 3). In the 2019 cohort, 52.6% were using artificial tears at referral (this information was not collected in 2012). In the medical history provided at referral, the 2019 cohort showed a higher prevalence of glaucoma (13.1% vs 5.6%; p 0.002), diabetes (8.9% vs 3.7%; p 0.010), dermopathy (3.2% vs 0.8%; p 0.037)and other concomitant diseases (52.0% vs 39.8%; p 0.003).

Ophthalmic symptoms and findings

Ophthalmic symptoms were similar in the two cohorts (table 4), except grittiness, which was less often reported by the patients in 2019 (45.4% vs 54.3%; p 0.019). There were more active cases in 2019 compared with 2012 (41.3% vs 36.6%; p 0.217), but the difference was not statistically significant (table 4). Also, activity according to CAS (CAS≥3/7) as well as the total CAS score showed no significant differences between the two cohorts. The distribution of severity changed from 2012 to 2019: there was a reduction of mild and severe cases but an increase of moderate cases (mild 50.3% vs 60.6%, moderate 39.9% vs 24.5%, severe 9.8% vs 14.9%; p<0.001) (table 4).

Imaging was performed less frequently in the 2019 cohort (19.2% vs 43.1%; p<0.001). CT was used 43.4%, MRI 38.6%. In 18.1% of the cases, it was not recorded if imaging was CT or MRI based, and this made it impossible to determine, which of the two technique was the preferred one within the EUGOGO centres.

Table 3 Endocrinological history of patients referred in EUGOGO centres between September and December 2019 and comparative data from the 2012 study

	2019		2012		P
	%	N	%	N	value
Thyroid disease					
Graves	89.9	381/432	94.1	253/269	0.054
Others (Hashimoto, primary hypothyroidism, no thyroid disease)	10.1	43/432	5.9	16/269	
Laboratory findings					
Elevated TRAb	74.8	234/313	80.5	157/195	0.134
fT3					
Normal	75.6	59/78	73.6	190/258	0.561
High	19.2	15/78	23.3	60/258	
Low	5.1	4/78	3.1	8/258	
Thyrotropin					
Normal	45.9	50/109	49.5	138/279	0.809
High	15.6	17/109	15.1	42/279	
Low	38.5	42/109	35.5	99/279	
Comorbidites					
Glaucoma	13.1	55/420	5.6	15/267	0.002
Diabetes	8.9	38/429	3.7	10/267	0.010
Other concomitant diseases	52.0	219/421	39.8	88/221	0.003
Visible goitre	13.1	55/421	16.9	45/267	0.169
Dermopathy	3.2	13/411	0.8	2/266	0.037
Family history of autoimmune thyroid disease	33.3	113/400	38.7	99/256	0.157
Family history of other autoimmune disease	9.5	36/380	7.2	18/251	0.312
Any previous/current anti-thyroid treatments					
Anti-thyroid drugs (ATD)	80.2	337/420	45.0	118/262	<0.001
Radioiodine	15.1	63/417	17.9	47/262	0.330
Thyroidectomy	24.1	102/423	22.7	59/260	0.671
Previous/current steroids	15.1	63/416	4.1	11/269	<0.001
Oral	28.6	18/63	0.0	0/11	
Intravenous	58.7	37/63	0.0	0/11	
Not available	12.7	8/63	100.0	11/11	
Current medication					
Methimazole	34.5	148/429	26.0	70/269	0.019
Carbimazole	12.0	51/424	17.8	48/269	0.033
Propylthiouracil	3.0	13/427	3.7	10/269	0.629
Block and replace (any ATD plus T4)	6.3	13/208	22.0	28/127	<0.001
T4 substitution (without ATD)	33.1	143/432	39.4	106/269	0.090
Selenium	22.3	94/421	3.0	8/269	<0.001
Beta blocker	18.7	79/422	10.0	27/269	0.002

EUGOGO, European Group On Graves' Orbitopathy.

Therapeutic decisions

Initial management plans were similar in 2012 and 2019. However, there was less indication for eyelid surgery in 2019 (2.4% vs 13.9%; p<0.001). Selenium supplements were offered to more patients in 2019 (28.5% vs 21.0%;p 0.027). For all results on therapeutic decisions (see table 5).

Differences in patients' presentation comparing only EUGOGO centres which took part in both 2012 and 2019 surveys

Most of the differences noted in the whole cohort in 2019 *vs* 2012 were also present when only OC were analysed. At difference, there were fewer indications of steroid treatment (26.6%

Table 4 Ophthalmic symptoms and findings of patients referred in EUGOGO centres between September and December 2019 and comparative data from the 2012 study

	2019		2012		
	%	N	%	N	P value
Painful oppressive feeling behind globe	38.9	167/429	39.2	89/227	0.944
Gaze evoked pain	26.1	112/429	27.5	74/269	0.683
Excessive watering	48.8	209/428	53.2	143/269	0.266
Photophobia	51.2	215/420	46.8	126/269	0.265
Grittiness	45.3	194/428	54.5	146/268	0.019
Double vision	44.0	190/432	40.8	109/267	0.412
Relative afferemt pupillary defect	1.9	7/363	2.0	4/199	1.000
Abnormal colour test	4.5	16/357	6.7	16/240	0.245
Lid lag in down gaze	41.8	153/366	46.1	112/243	0.296
Upper eye lid retraction	58.4	220/377			*
Exophthalmos (mm, mean, SD)	20.7±3.6		20.7±3.5		0.763
Lagophthalmus	14.4	62/430	17.4	46/265	0.299
Bell phenomenon positiv	75.0	273/364	75.3	113/150	0.937
Keratopathy or ulcer	11.6	47/402	13.9	37/266	0.464
Optic nerve swelling	1.3	5/381	2.3	4/174	0.688
Choroidal folds	0.8	3/375	0.0	0/221	0.299
Clinical evidence for DON at least one eye (including equivocal)	5.8	23/397	7.1	19/268	0.500
Right eye (incl.equivocal)	4.5	18/397	5.6	15/268	0.536
Left eye (incl. equivocal)	5.1	20/396	4.9	13/267	0.916
Imaging performed	19.2	83/432	43.1	116/269	<0.001
CT	43.4	36/83	0.0	0/116	
MRI	38.6	32/83	0.0	0/116	
Not available	18.1	15/83	100.0	116/116	
Severity					
Mild	50.3	216/429	60.6	163/269	<0.001
Moderate	39.9	171/429	24.5	66/269	
Severe	9.8	42/429	14.9	40/269	
Activity (based on CAS)					
Inactive (CAS <3)	61.3	264/431	66.8	179/268	0.139
Active (CAS ≥3)	38.7	167/431	33.2	89/268	

*No comparison possible, as information on upper eye lid retraction was not collected in the 2012 cohort.
CAS, clinical activity score; DON, dysthyroid optic neuropathy; EUGOGO, European Group On Graves' Orbitopathy.

Table 5 Therapeutic decisions of patients referred in EUGOGO centres between September and December 2019 and comparative data from the 2012 study

	2019		2012		
	%	N	%	N	P value
Watchful monitoring	66.0	277/420	44.9	120/267	<0.001
Local measures	58.7	247/421	59.9	160/267	0.744
Steroids	25.8	108/419	30.3	81/267	0.192
Oral*	2.9	3/105			
Intravenous	97.1	102/105			
Steroids if moderate	39.9	65/163	50.0	33/66	0.161
Oral*	4.8	3/63			
Intravenous	93.7	59/63			
Orbital irradiation	5.5	22/421	7.9	21/267	0.163
Surgical decompression	12.4	52/421	16.5	44/267	0.128
Lid surgery	2.4	10/422	13.9	37/267	<0.001
Eye musclesurgery	5.7	24/419	5.2	14/267	0.787
Selenium	28.5	122/428	21.0	56/267	0.027
Botulinum toxin	2.3	10/427	1.5	4/267	0.442
Decision to treat with steroids if activity	58.4	97/166	69.1	67/97	0.086
Decision for surgical decompression if DON	63.2	12/19	77.8	7/9	0.439

*Three cases of oral steroid indication: two patients were already on oral steroid therapy at referral, which was continued in a gradual tapering manner. One patient refused intravenous steroids due to religious reasons and was therefore treated with oral steroids.
DON, dysthyroid optic neuropathy; EUGOGO, European Group On Graves' Orbitopathy.

vs 35.1%; p 0.040), even in active cases (57.1% vs 74.1%; p 0.013) and fewer indications for surgical decompression (8.9% vs 16.1%; p 0.021) in 2019 vs 2012 in OC.

DISCUSSION

Number of patients, centres and referral time

The number of participating centres increased from 2012 to 2019. Furthermore, the total number of included patients and the number of patients seen by each centre per month was higher in 2019 compared with 2012. Especially OC included more patients. The time from first diagnosis of GO to patients attending EUGOGO centres was shorter in 2019. Already in 2012, the referral time to a tertiary centre was reduced compared with 2000.[23] These changes might reflect a general increased awareness of EUGOGO centres and activity among general physicians/endocrinologists and patient organisations and the understanding to entrust GO patients to multidisciplinary specialised teams.

Demographic characteristics

The demographic data of the included patients were largely the same as reported in the previous study of 2012. The older age of the 2019 cohort could be explained by the general ageing of the population in Europe,[31] however, the difference of 3 years is probably not clinically relevant. The similar number of smokers was observed among the referred GO patients in 2012 and 2019. This supports the existing hypothesis that smoking is an important risk factor for GO.[32 33] More emphatic antismoking campaigns seem to be necessary. The investigation on the intensity of smoking, which could not be assessed in PREGO II (this information was not collected in 2000), showed that there was no difference in pack/years or cigarettes per day from 2012 to 2019.

Medical history

Many more patients in 2019 compared with 2012 were already under ATD and/or selenium treatment when referred to a EUGOGO centre, likely reflecting the improved awareness of the importance of a prompt control of thyroid dysfunction for GO of all degrees, as well as of treatment/prevention of progression of mild GO to more severe form. Selenium is the antioxidant agent with the most promising results in the therapy of mild and active GO.[18] The preventive effect of selenium, observed in a multicentre clinical trial published in 2011 by Marcocci *et al*,[34] was not yet widespread among physicians in 2012.

Methimazole was the most common ATD used at the time of first visit at an EUGOGO centre. This reflects a common worldwide trend,[35] as well the fact that carbimazole is not available in all European countries.[36] The daily doses of all ATD were lower

in 2019. A possible explanation is that there was a switch from the block-and-replace to the titration regimen,[37] as well as by a secular trend to a milder phenotype of Graves' hyperthyroidism, requiring lower doses of ATD.[38]

Glucocorticoid treatment was also more frequently initiated before the first visit at a EUGOGO centre in 2019, compared with 2012, and mostly administered intravenously. Intravenous glucocorticoids are, for the time being and especially in Europe, the first-line treatment, alone or in combination with mycophenolate, in patients with active moderate-to-severe GO.[39 40] The above changes (prereferral use of ATD, selenium, glucocorticoids) support the idea of an improved knowledge of therapeutic options of GO and up-to-date application of treatment among non-specialised physicians.

Contrary to the previous 2012 survey, there was an apparent increase in dermopathy. Dermopathy is usually associated with severe Graves' disease,[41] but there was a decline in severe GO cases in 2019. This apparent discrepancy might be related to an improved awareness among the investigators regarding dermopathy, even in its mild expression.

At variance with the previous 2000[22] to 2012 trend,[23] there was a higher prevalence of glaucoma in the medical history of patients referred to tertiary centres in 2019. The 2012 prevalence of 5.6% is similar to the known glaucoma prevalence in GO.[23 42] The trend to less frequent diagnosis of glaucoma at referral in 2012 was interpreted as a better understanding that GO patients may have elevated intraocular pressure (IOP not meaning glaucoma).[23] Glaucoma prevalence of 13.1% recorded in 2019 is similar to the one of 2000 (14%)[22] and it is greater than that reported in other GO studies and of the reported prevalence of ocular hypertension in GO.[42 43] The diagnosis of glaucoma made by the referring physicians was not reevaluated at the EUGOGO centres. It is likely that patients with elevated IOP are included in these 13.1%.Additional information for the diagnosis of a true glaucoma, for example, familiarity, optical coherence tomography diagnostic, visual field analysis, were not collected. Therefore, we cannot report on the actual rate of glaucoma in the referred patient collective, which may be lower. Further studies are needed to investigate possible changes in the prevalence of glaucoma in GO.

Ophthalmic symptoms and findings

Nearly all ophthalmic symptoms were similar in both groups except grittiness, which was less frequent in 2019. This might be explained by a general better understanding of dry eye. In 2019, 52.6% of the patients were using artificial tears at the first visit at an EUGOGO centre. Because data about the use of artificial tears is missing in 2012, we can only postulate, but not prove that there was an increased use of lubricants in 2019.

There was no difference in clinical signs of GO between 2012 and 2019. The trend of a reduced activity reported in 2012[23] was not found in 2019. Around 40% of the patients were referred in the active phase of the disease according to CAS and the overall clinical impression of the examiner. There was no statistical difference to our cohort from 2012. However, the distribution in severity changed. In 2019, the main number of patients were moderate cases. Milder cases were observed less frequently in tertiary centres, probably due to a broader knowledge of GO treatment among non-specialised physicians. Due to prompt diagnosis and treatment severe cases were declining in 2019; an important improvement which was already observed in 2012.[23]

Therapeutic decisions

A reduction of imaging, less indication for lid surgery, and, only comparing OC, even less indication for surgical decompression and steroid therapy (even in active cases) was observed in 2019 compared with 2012. This can be explained by the reduced number of severe cases and the experience in treating GO patients and the clinical experience that some clinical signs regress spontaneously over time, for example, upper eyelid retraction.[44]

Limitations

Weaknesses of the study include the fact that 3 of the original 13 centres that participated in the 2012 survey did not participate in 2019, and 6 new centres that did not participate in 2012 were included in 2019. The subgroup analysis for the 10 centres that participated in both surveys, however, showed similar trends to the entire 2019 groups.

Conclusion

In 2019, compared with 2012, there was a 23% increase in participating EUGOGO centres and a 62% increase in the total number of patients included in the study. The referral time to a tertiary centre was shorter in 2019. At the first visit at an EUGOGO centre, more patients were already under treatment with ATD and selenium. Once again, as it occurred in 2012 as compared with 2000, there was a decline in cases with severe GO. We speculate that this result might be linked to a broader awareness of the disease both among ophthalmologists, physicians and patients and earlier and adequate delivered treatment. The observed positive developments of GO in Europe could be linked to EUGOGO's mission, which includes educational commitments.

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Ethics approval The study protocol was first reviewed and approved by theInstitutional Review Board of the lead centre the Ludwig-Maximilians-University Munich (reference number 18–668) and confirmed to be in accordance with the Institutional Review Boards of each participating centre. The tenets of the Declaration of Helsinki were followed throughout the study. All patients participated in the study voluntarily and were informed of their right to abandon it at any chosen time without having to provide a reason. Informed consent was obtained in written form.

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