

Optic disc haemorrhages at baseline as a risk factor for poor outcome in the Idiopathic Intracranial Hypertension Treatment Trial

Michael Wall,¹ Matthew J Thurtell,² for the NORDIC Idiopathic Intracranial Hypertension Study Group

¹Departments of Neurology and Ophthalmology, University of Iowa College of Medicine, Iowa City, Iowa, USA

²Department of Ophthalmology, University of Iowa College of Medicine, Iowa City, Iowa, USA

Correspondence to

Dr Michael Wall, University of Iowa Hospitals and Clinics, Department of Neurology, 200 Hawkins Dr, PFP, Iowa City, IA 52242-1091, USA; michael-wall@uiowa.edu

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ABSTRACT

Background The risk of optic disc haemorrhages on visual outcome in idiopathic intracranial hypertension (IIH) is unknown. We report the type and frequency of optic disc haemorrhages and other fundoscopic abnormalities at baseline in the study eye of the 133 subjects enrolled in the Idiopathic Intracranial Hypertension Treatment Trial completing 6 months of follow-up.

Methods We reviewed optic disc photographs to tabulate the frequency and type of optic disc haemorrhages, other fundoscopic abnormalities and papilloedema grades of the study eye at baseline and analyse if their presence is associated with a poor visual outcome.

Results 27.2% of subjects had nerve fibre layer haemorrhages in at least one eye. Five of seven, 71% of subjects that met criteria for treatment failure, had nerve fibre layer haemorrhages in at least one eye (Fisher's exact test: $p=0.02$). There was a good correlation between presence of nerve fibre layer haemorrhages and Frisén grade (Spearman's correlation, $p=0.002$; $r=0.271$). Subjects with nerve fibre layer haemorrhages had a higher cerebrospinal fluid pressure (40.0 mm water, $p=0.04$). There was poor correlation between nerve fibre layer haemorrhages at baseline and the perimetric mean deviation change at 6 months. Cotton wool spots were present in 4% of subjects, exudates in 3% and pseudodrusen in 4%.

Conclusions Nerve fibre layer haemorrhages are common in patients with IIH with mild visual loss and correlate with the severity of the papilloedema. They occur more frequently in treatment failure subjects and therefore may be associated with poor visual outcomes.

Trial registration number NCT01003639, Post-results.

INTRODUCTION

Idiopathic intracranial hypertension (IIH) is a syndrome characterised by increased intracranial pressure with its associated signs and symptoms in an alert and oriented patient. Neuroimaging is normal except for findings known to occur with chronic raised intracranial pressure of any cause. Lumbar puncture and cerebrospinal fluid (CSF) analysis is normal except for increased intracranial pressure. In addition, no secondary cause of intracranial hypertension is apparent.

We have completed the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), a multicentre, double-blind, randomised, placebo-controlled study of 165 subjects with mild visual loss. All subjects received a lifestyle modification programme of weight-reduction

with a low sodium diet. Additionally, subjects were randomised to receive either acetazolamide or matching placebo. We found significant improvement in the acetazolamide group for visual field function (perimetric mean deviation (MD)), papilloedema grade, CSF pressure and quality of life measures.¹

There are few other series of cases that tabulate haemorrhages in cases of increased intracranial pressure. Binenbaum *et al*² studied 100 patients with raised intracranial pressure with 70% of the cases having IIH. Sixteen had retinal haemorrhages: 8 with superficial intraretinal peripapillary haemorrhages and 8 with splinter haemorrhages on the disc. All those with retinal haemorrhages had papilloedema described as moderate to severe.

Other than peripapillary wrinkles,³ retinal folds³ and retinal nerve fibre layer haemorrhages, other ancillary fundoscopic findings in the papilloedema of IIH are uncommon. Subretinal haemorrhages⁴⁻⁶ and pseudodrusen have been the subject of a few case reports.^{7,8} Cotton wool spots have been documented in association with papilloedema and anaemia with two of the five cases having these nerve fibre layer infarcts.⁹

In our report of baseline characteristics of fundus photos, only haemorrhages in the macula were categorised. Of the 165 subjects at study entry, only 3 (2%) had haemorrhages within one disc diameter of the macular region.¹⁰ Since retinal nerve fibre layer haemorrhages may represent acute and recent increase in increased intracranial pressure, we hypothesised that they may be a risk factor for poor outcome. Therefore, we analysed optic disc photos for the 133 subjects who had data at baseline and 6 months and reported our findings.

METHODS

The study was approved by each site's Institutional Review Board and individual written informed consent was obtained. The tenets of the Declaration of Helsinki were followed. One hundred and sixty-five patients with IIH with mild visual loss were enrolled at 38 Neuro-Ophthalmology Research Disease Investigator Consortium sites in the USA and Canada over a 3-year period. Subjects were included if they met the modified Dandy criteria for IIH and had perimetric MD between -2 and -7 dB on 24-2 Swedish Interactive Threshold Algorithm (SITA) Standard testing with reproducible findings on visual field examinations. Subjects were randomly assigned to receive a supervised low sodium diet either with acetazolamide or with matching placebo. Further study details can be found in other publications.^{1,11}

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Protocol defined treatment failure was when a subject with baseline MD up to -3.5 dB had visual function worsen by more than 2 dB MD from baseline in either eye, or when a subject with baseline MD between -3.5 and -7 dB had visual function worsen by more than 3 dB MD from baseline in either eye, confirmed by a second perimetric examination. An adjudication committee, using all available clinical information, needed to confirm that the worsening was most likely due to uncontrolled intracranial pressure and progression of IIH. Subjects who experienced treatment failure were withdrawn from further participation in the trial.

Sixty-nine of the 86 participants (80%) in the acetazolamide group completed follow-up compared with 57 of the 79 participants (72%) in the placebo group. There were seven participants who reached the end point of treatment failure in the trial, six in the placebo group and one in the acetazolamide group. Therefore, there were 133 subjects available for analysis of fundus haemorrhages who had 6 months of follow-up.

Outcome variables were assessed at baseline and at follow-up visits, with end of study assessments (6 months) being of primary interest. The primary outcome variable was the change from baseline to 6 months in the MD of the eye with the worst MD at baseline.

Fundus photography

The papilloedema grade (Frisén scale)^{12 13} was documented at each visit by three expert neuro-ophthalmologists. The presence of haemorrhages within one disc diameter of the optic disc was determined by the two authors. Any differences between the graders were adjudicated by them. If a haemorrhage was present, its type and location (by clock hour) was noted. The presence of cotton wool spots (focal nerve fibre layer infarcts) and pseudodrusen was also tabulated.

We defined a nerve fibre layer haemorrhage as a red radial often flame-shaped blood collection usually with feathery borders following the architecture of the retinal nerve fibre layer. They are thought to be due to rupture of precapillary arterioles or venules in the superficial nerve fibre layer. We defined subretinal haemorrhages as peripapillary blood collections circumferentially oriented around a portion of the optic disc. They are mostly located between the retinal pigment epithelium and the neurosensory retina.

Cotton wool spots are micro nerve fibre layer infarcts. Characteristically, they are small opacifications with white feathery edges. They are located in the retinal nerve fibre layer. Hard exudates are yellowish discrete bright focal collections thought to be due to lipid leakage from diseased vessels. They are usually located in the outer plexiform layer. Pseudodrusen are small discrete refractile bodies typically much smaller and less refractile than true optic disc drusen. They most often occur in long-standing chronic papilloedema.

Statistical analysis

Our preplanned study outcome measures were (1) a comparison of frequency of retinal nerve fibre layer haemorrhages in treatment failure eyes versus the frequency in non-treatment failure eyes and (2) correlations of nerve fibre layer haemorrhages with (a) Frisén papilloedema grade; (b) MD change over 6 months; (c) CSF pressure and (d) number of transient visual obscurations per day. No other statistical tests were done including any exploratory analyses. Associations between presence of nerve fibre layer haemorrhages and categorical or discrete variables are described using Spearman's rank correlation coefficients.

Table 1 Percentages of haemorrhages, exudates, cotton wool spots and pseudodrusen in IIHTT subjects at baseline

	Either eye	Study eyes	Non-study eyes	Both eyes
Haemorrhages (all)	31.6	24.1	19	7.3
Nerve fibre layer haemorrhages	27.2	22.1	16.9	7.3
Subretinal haemorrhage	4.4	2.2	2.2	0
Pseudodrusen	4.4	4.4	1.5	1.5
Cotton wool spots	3.7	2.9	2.9	0.7
Exudates	2.9	1.5	2.2	0.7

RESULTS

The frequency of haemorrhages and other fundoscopic findings is found in [table 1](#). About one-thirds of IIHTT subjects with mild visual loss had haemorrhages. Most were nerve fibre layer haemorrhages. Subretinal haemorrhages (4.4%) were less common ([table 1](#)). Retinal nerve fibre layer haemorrhages were present in 22.1% of study eyes and 16.9% of non-study eyes. Cotton wool spots were present in 3% of study eyes and 3% of non-study eyes. Pseudodrusen were present in 1.5% of subjects. [Figure 1](#) shows the locations of nerve fibre layer haemorrhages. Note they are most frequent where the nerve fibre layer is thickest at the superior and inferior poles. There were no cases of subhyaloid haemorrhages. Examples of retinal findings in IIHTT subjects are shown in [figures 2](#) and [3](#).

There was a significant correlation between presence of nerve fibre layer haemorrhages and high baseline Frisén grade (Spearman's correlation, $p=0.002$; $r=0.27$). IIHTT subjects with nerve fibre layer haemorrhages had a significantly higher CSF pressure (median 370 vs 330 mm water, $p=0.04$ Mann-Whitney U test). There was no significant correlation between nerve fibre layer haemorrhages at baseline and the perimetric MD change over the study intervention period of 6 months ($r=0.01$). There was a significant correlation between number of transient visual obscurations and presence of nerve

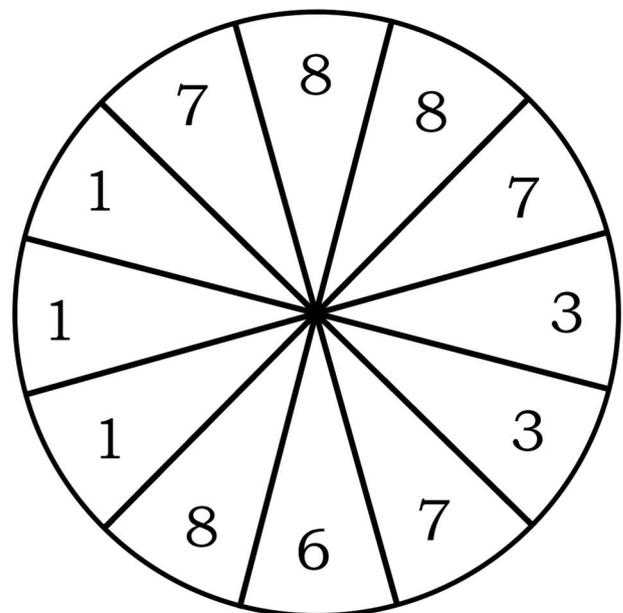


Figure 1 Locations of nerve fibre layer haemorrhages by clock hour. Note they are most frequent where the nerve fibre layer is thickest.



Figure 2 A subject with Frisén grade 3 papilloedema and retinal nerve fibre layer haemorrhages at 6 o'clock; this subject later met criteria for treatment failure.

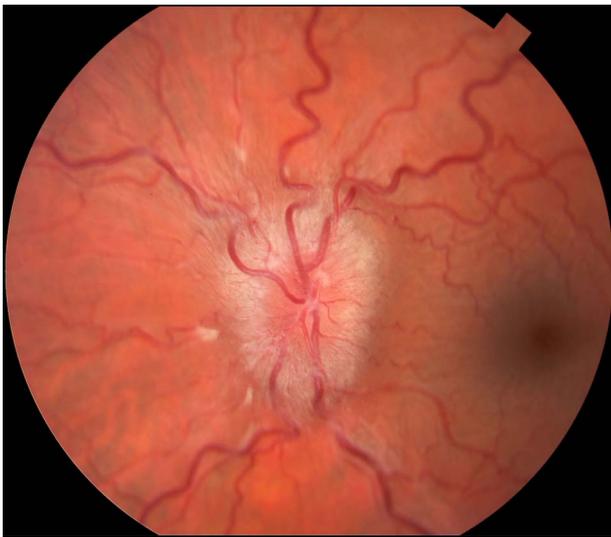


Figure 3 Exudates on the disc and peripapillary retina are present. Note also the choroidal folds involving the posterior pole.

fibre layer haemorrhages ($p=0.04$; $r=0.22$). Five of seven (71%) subjects who met criteria for treatment failure had nerve fibre layer haemorrhages in at least one eye (Fisher's exact test: $p=0.02$).

DISCUSSION

We found that IIHTT patients with mild visual loss had nerve fibre layer haemorrhages at presentation about one-third of the time. Nerve fibre layer haemorrhages are a manifestation of the severity of optic disc swelling for the following reasons. Radial retinal peripapillary capillaries are long with their arterial feeding end away from the optic disc; their venous drainage end feeds into veins on the optic disc. Therefore, the greater the severity of disc swelling, the more compression of the venous ends, and the greater the capillary dilation the more likely they

will rupture resulting in nerve fibre layer haemorrhages. We found a strong correlation between the presence of nerve fibre layer haemorrhages and grade of papilloedema. Since these haemorrhages are correlated with high-grade papilloedema and high-grade papilloedema is a risk factor for poor visual outcome,^{1 14} this finding suggests haemorrhages may be a marker for poor visual outcome. This is in concert with our finding that nerve fibre layer haemorrhages are significantly associated with higher baseline CSF pressures. Also, in a retrospective study, Orcutt *et al*¹⁵ reported that patients with high-grade papilloedema, or peripapillary subretinal haemorrhage, were significantly more likely to have substantial visual loss.

We have evaluated potential risk factors for IIHTT protocol-defined treatment failure in the seven IIHTT participants who met criteria for treatment failure. Six of the seven subjects were in the placebo-plus-diet arm of the study. We found male patients, those with high-grade papilloedema, daily transient visual obscurations and those with decreased visual acuity at baseline were more likely to experience treatment failure.¹⁴

To test the hypothesis that haemorrhages were correlated with treatment failure, we compared the frequency of nerve fibre layer haemorrhages in subjects meeting IIHTT criteria for treatment failure against those not meeting these criteria. We found a significantly higher frequency of nerve fibre layer haemorrhages in the treatment failure group adding suggesting there may be a relationship of the presence of these haemorrhages and poor visual outcome. Also, since we found frequent transient visual obscurations to be a risk factor for poor outcome, we investigated the association of the presence of nerve fibre layer haemorrhages with transient visual obscurations and found a significant correlation. This is not surprising as transient visual obscurations are related to the presence of high optic nerve tissue pressure, which is related to the degree of papilloedema.^{16–18}

Our findings need to be interpreted in the context of the entry criteria for the IIHTT. We required subjects to have an MD on automated perimetry of -2 to -7 dB, which qualifies as mild visual loss. Therefore, the frequencies reported are those for this grade of visual loss. Mild visual loss does not imply 'mild' IIH since some subjects developed severe visual loss; it also does not imply 'early' IIH as some subjects had been symptomatic for many months. We suspect that patients with IIH with more severe loss would have a higher frequency of these findings and those with less visual loss would likely have fewer findings. Also, since the fundus photo analysis was of baseline photos taken at the time of diagnosis, findings that occur with chronic or resolved papilloedema, such as pseudodrusen might be less frequent in this group.

In summary, retinal nerve fibre layer haemorrhages are common in patients with IIH with mild visual loss at the time of diagnosis. They are significantly associated with higher grades of papilloedema, higher baseline CSF pressures and IIHTT protocol-defined treatment failure. They may be a marker suggesting poorer visual outcomes. When retinal nerve fibre layer haemorrhages are present, one should consider more aggressive therapy to reduce intracranial pressure and the related optic disc oedema; initial follow-up examinations should occur in a timely way and often in the initial stages to be sure that preventable visual loss is not occurring and opportunities for treatment are not missed despite aggressive medical therapy.

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Clinical science

Flora Levin, MD (investigator), Jonathan Feistmann, MD investigator), Katy Tai, MA (coordinator), Alex Yang, BA (co-coordinator), Karen Tobias, BA (coordinator), Melissa Rivas, BA (co-coordinator), Lorena Dominguez, BA (coordinator), Violete Perez, BA (coordinator); University of Iowa and Department of Veterans Affairs: Reid Longmuir, MD (principal investigator), Matthew Thurtell, MBBS, MSc (subinvestigator), Trina Eden (coordinator), Randy Kardon, MD, PhD (subinvestigator); The Eye Care Group: Robert Lesser, MD (principal investigator), Yanina O'Neil, MD (subinvestigator), Sue Heaton, BS, CCRC (coordinator), Nathalie Gintowt (co-coordinator) Danielle Rudich (co-coordinator); University of Utah: Kathleen Digre, MD (principal investigator), Judith Warner, MD (subinvestigator), Barbara Hart, BS (coordinator), Kimberley Wegner, BS (co-coordinator), Bonnie Carlstrom, COA (coordinator), Susan Allman (coordinator), Bradley Katz, MD, PhD (subinvestigator), Anne Haroldsen (regulatory); Bascom Palmer Eye Institute, University of Miami: Byron L. Lam MD (principal investigator), Joshua Pasol MD (subinvestigator), Potyra R Rosa MD (coordinator), Alexis Morante MS (co-coordinator), Jennifer Verriotto MS (coordinator); Bethesda Neurology: David Katz, MD (principal investigator), Tracy Asbury (coordinator), Robert Gerwin, MD (subinvestigator), Mary Barnett (data entry); Swedish Medical Center: Steven Hamilton, MD (principal investigator), Caryl Tongco (coordinator), Beena Gangadharan (co-coordinator), Eugene May, MD (sub-investigator); Dean A McGee Eye Institute: Anil Patel, MD (principal investigator), Bradley Farris, MD (subinvestigator), R Michael Siatkowsk, MD (subinvestigator), Heather Miller, LPN (coordinator), Vanessa Bergman (co-coordinator), Kammerin White (coordinator), Steven O'Dell (lumbar puncture), Joseph Andrezik (lumbar puncture), Timothy Tyle (lumbar puncture); University of Pennsylvania: Kenneth Shindler MD, PhD (principal investigator), Joan Dupont (coordinator), Rebecca Salvo (coordinator), Sheri Drossner (co-coordinator), Susan Ward (coordinator), Jonathan Lo (coordinator), Stephanie Engelhard (coordinator), Elizabeth Windsor (coordinator), Sami Khella (lumbar puncture), Madhura Tamhankar, MD (subinvestigator); Washington University in St Louis School of Medicine: Gregory Van Stavern, MD (principal investigator), Jamie Kambarian (coordinator), Renee Van Stavern, MD (subinvestigator), Karen Civitelli (regulatory), J Banks Shepherd, MD (subinvestigator); Emory University: Beau B Bruce, MD (principal investigator), MS; Valérie Biousse (subinvestigator), MD; Nancy J Newman, MD (investigator); Judy Brower, MMSc, COMT (coordinator); Linda Curtis, BSM (co-coordinator); University of Alabama Birmingham: Michael Vaphiades, DO (principal investigator), Karen Searcey (coordinator), Lanning Kline, MD (subinvestigator), Roy McDonald (coordinator); Raleigh Neurology Associates, PA: Syndee J Givre, MD, PhD (principal investigator), Tippi Hales (coordinator), Penni Bye (coordinator), Keisha Fuller (coordinator), Kenneth M Carnes, MD, (subinvestigator), Kimberly James (regulatory), Marisol Ragland (data entry); Saint Louis University: Sophia M Chung, MD (principal investigator), Dawn M Govreau, COT (coordinator), John T Lind, MD, MS (subinvestigator); David and Ilene Flaum Eye Institute, University of Rochester School of Medicine and Dentistry: Zoe Williams, MD (principal investigator), George O'Gara (coordinator), Kari Steinmetz (coordinator), Mare Perevich (coordinator), Karen Skrine (coordinator), Elisabeth Carter (coordinator), Rajeev Ramchandran, MD (subinvestigator); Ohio State University: Steven Katz, MD (principal investigator), Marc Criden, MD (investigator), Gina Coman, RMA, CPC, OCS (co-coordinator), John McGregor, FACS, MD (subinvestigator), Andrea Inman (regulatory); Johns Hopkins University: Prem S Subramanian, MD, PhD (principal investigator), Paul N Hoffman, MD, PhD (investigator), Marianne Medura (coordinator), M Michael Hartnett (coordinator), Madiha Siddiqui (coordinator), Diane Brown (coordinator), Ellen Arnold (coordinator), Jeff Boring, MD (subinvestigator), Neil R Miller, MD (subinvestigator); University of Southern California: Peter Quiros, MD (principal investigator), Sylvia Ramos (coordinator), Margaret Padilla (coordinator), Lupe Cisneros (coordinator), Anne Kao, MD (subinvestigator), Carlos Filipe Chicani, MD (subinvestigator), Kevin Na (regulatory); University of Houston: Rosa Tang, MD, MPH, MBA (principal investigator), Laura Frishman, PhD (coordinator), Priscilla Cajavilca, MD (coordinator), Sheree Newland, LVN (coordinator), Liat Gantz, OD, PhD (coordinator), Maria Guillermo Prieto, MD (coordinator), Anastas Pass, OD, JD (coordinator), Nicky R Holdeman, OD, MD (subinvestigator); University of Minnesota: Michael S Lee, MD (principal investigator), Helen Roemhild (coordinator), Wendy Elasky (coordinator), Anne Holleschau (coordinator), Jody Fissgus (coordinator), Jamie Walski (coordinator), Andrew Harrison, MD (subinvestigator); Oregon Health and Science University: Julie Falardeau MD (principal investigator), William Hills MD (subinvestigator), Cristi Bryant (coordinator), Donna Kim MD (investigator), Rebecca Armour MD (investigator), Lori Higginbotham (coordinator); University of Virginia: Steven A Newman, MD (principal investigator), Kristina Holbrook (coordinator), Laura D Cook, MD (subinvestigator), Holly Bacon (data entry), Janis Beall, COT (technician), Thomas Goddard, COA (technician), William Hall (technician), Debbie Hamilton (photographer), Alan Lyon (photographer); University of Calgary: William Fletcher, MD, FRCPC (principal investigator), Suresh Subramaniam, MSc, MD, FRCPC (investigator), Jeannie Reimer (coordinator), Jeri Nickerson (coordinator), Fiona Costello, MD, FRCPC (subinvestigator); The Greater Baltimore Medical Center: Vivian Rismondo-Stankovich, MD (principal investigator), Maureen Flanagan, CO, COA (coordinator), Allison Jensen, MD (subinvestigator); Stony Brook University: Patrick Sibony, MD (principal investigator), Ann Marie Lavorna, RN (coordinator), Mary Mladek, COT (coordinator), Ruth Tenzler, RN (coordinator), Robert Honkanen, MD

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Data Coordination and Biostatistics Center: Jan Bausch, BS, Shan Gao, MS, Xin Tu, PhD, Hua He, PhD, Arthur Watts, BS (Biostatistics); Debbie Baker, Radu Constantinescu, MD, Karen Helles, Nichole McMullen, Bev Olsen, Larry Preston, Victoria Snively, Ann Stoutenburg (CHET/CTCC) (David and Ilene Flaum Eye Institute, University of Rochester School of Medicine and Dentistry); Deborah Friedman, MD (UT Southwestern Medical Center). NORDIC headquarters: O lyore Ayanru, Elizabeth-Ann Moss, Pravin Patel (Roosevelt Hospital). Consultant: Richard Mills, MD (Glaucoma Consultants Northwest). Data Safety Monitoring Board Members: Maureen Maguire, PhD (Chair) (University of Pennsylvania), William Hart, Jr, MD, PhD, Joanne Katz, ScD, MS (Johns Hopkins), David Kaufman, DO (Michigan State University), Cynthia McCarthy, DHCE MA, John Selhorst, MD (Saint Louis University School of Medicine). Adjudication Committee: Kathleen Digre, MD (University of Utah); James Corbett, MD, FAAN (University of Mississippi Medical Center); Neil R Miller, MD (Johns Hopkins University); Richard Mills, MD (Glaucoma Consultants Northwest).

Contributors MW was the Study Director for the IIHTT conducted the study, analysed the data and wrote the manuscript. MJT analysed the data and assisted in writing the manuscript.

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