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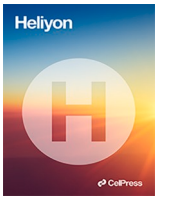

Research article

DRI Triton SS-OCT applied to detect choroidal nodules in paediatric patients affected by NF1

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ABSTRACT

Purpose: To examine whether image processing of non-mydriatic DRI Triton SS-OCT (Topcon Corporation, Tokyo, Japan) using the red free filter could assess the presence of choroidal nodules and thus include their detection as a diagnostic criterion in neurofibromatosis type 1 (NF1).
Material and methods: We included 417 eyes from 210 patients, 377 - from 190 patients diagnosed with NF1 according to the criteria established by the National Institutes of Health Consensus Development Conference (NIH) and 40 from 20 healthy patients as a control group. The mean age was 9.4 years (range 2 years–18 years). All patients had their visual acuity measured by a test according to age, were examined for the presence of lisch nodules and an Optical Coherence Tomography (OCT) of the macular area was performed. All the OCT images were analysed to check if visible nodules could be identified.
Results: Ages 14 (95% CI=(9.7,18.3)) and 12 years (95% CI=(9.1,14)) are the cut-off points that best separate those with choroidal nodules with Triton OCT and lisch with slit lamp, respectively, from those without. lisch nodules were detected in 50% of cases of NF1 patients. The presence of choroidal nodules did not present a statistically significant correlation with the occurrence of optic pathway glioma ($p = 0.96$) nor with the patient's visual worsening ($p = 0.072$). A statistically significant correlation was observed between the presence of choroidal nodules and the presence of lisch nodules ($p < 0.05$).

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Conclusion: The Topcon Triton OCT red free tool would not be a good tool to detect choroidal nodules in patients with NF1 because of its low sensitivity. If the presence of choroidal nodules were to be included in the diagnostic criteria for NF1, it would be convenient to use a device with red and infrared radiations.

1. Introduction

Neurofibromatosis type 1 (NF1) was first described by Von Recklinghausen [1]. It is an autosomal dominant disease and its incidence is 1 in 2500–3000 live new-borns [2–4]. According to The National Institutes of Health Consensus Development Conference (NIH), at least two of the following clinical criteria must be met for diagnosis: 6 or more café-au-lait spots, two or more cutaneous neurofibromas, one or more plexiform neurofibromas, axillary or inguinal freckles, optic glioma, two or more lisch nodules, bone lesions and a first degree relative with NF1 [5]. At the ocular level the most frequent alterations are lisch nodules, optic pathway glioma and orbital plexiform neurofibromas. In 2000 Yasunari et al. [6] observed that 100% of NF1 patients examined with an infrared ophthalmoscope had alterations in the choroid; this layer of the retina is altered in patients with NF1. The lesions seen in the choroid are hyperreflective patchy areas that cannot be detected by conventional autofluorescence ophthalmoscopy or fluorescein angiography. Indocyanine green angiography can help us to determine if there are such lesions in the choroid, but as it is an invasive test it is not recommended for paediatric patients [7]. These lesions tend to increase in number as the patient grows up and are usually located in the posterior pole of the retina, following the vascular arcades [8,9]. In histopathological studies the choroidal nodules that appear in this type of patients are ovoid in shape and are composed of hyperplastic Schwann cells, melanocytes and ganglion cells [10,11]. Viola et al. [9] found that the frequency of choroidal nodules in paediatric patients is 71%. Also Goktas et al. [12] observed a prevalence of 78.9% of nodules in these patients. Vagge et al. [13] found choroidal nodules in 69.2% of the patients examined and in the most extensive review published to date, Parrozzani et al. [14] found choroidal changes in 60.5% of paediatric patients with NF1. In all cases, the observation techniques used include IR.

However, many ophthalmological clinics are equipped with the non-mydriatic DRI Triton SS-OCT (Topcon Corporation, Tokyo, Japan), which includes a filter that removes IR and red colours from the image and there is no conclusive evidence on the effectiveness of this equipment in detecting the presence of choroidal nodules.

The aim of this study is to examine whether by image processing of non-mydriatic DRI Triton SS-OCT (Topcon Corporation, Tokyo, Japan) using a filter that removes red colours, we could also assess the presence of choroidal nodules and thus be able to include their detection with this type of equipment, as a diagnostic criterion for NF1.

2. Material and methods

This is a case-control, prospective study conducted from October 2018 to May 2021 at the Hospital Sant Joan de Déu in Barcelona. During this period, a cross-sectional analysis was performed and the data of the patients included in the study was analysed.

All patients uncooperative for the performance of optical coherence tomography (OCT) in the macular area, patients with associated ocular pathology that may alter the visualization of the retinal layers and patients without a confirmed clinical diagnosis of NF1 were excluded.

The study is performed in accordance with the Declaration of Helsinki and received institutional approval from the Ethics Committee Fundació Sant Joan de Déu, Esplugues de Llobregat, Barcelona, with ethics approval reference (PIC-60-18) on October 3, 2018.

All patients and their families received information about the study and signed the informed consent form upon agreement.

All patients included in the study had their visual acuity (VA) measured on the LogMar scale with the test recommended for their age. For patients aged 6–36 months the Teller test was used, for patients aged 3–4 years the preverbal LEA test was used, for those aged 4–5 years the preverbal HOTV test was used and for those older than 5 years, the verbal HOTV test was used. An examination of the anterior pole by an ophthalmologist with experience in detecting lisch nodules was performed and, finally, an OCT of the macular area with the Triton OCT DRI Triton SS-OCT instrument (Topcon Corporation, Tokyo, Japan) records a colour retinography of the posterior pole. The same colour image is processed through the RED FREE filter, which is already installed in the equipment itself, to eliminate the reds of the non-mydriatic retinography.

All images were reviewed by two people with expertise in the detection of choroidal nodules in a blinded manner with respect to the diagnosis of NF1, and in the case of disparity in the presence or absence of nodules, a third examiner assessed the images. Image 1 shows the presence of choroidal nodules in one of the subjects.

R version 4.3.0.: R Core Team (2023). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, was used to perform the calculations. The Youden index maximization criterion was used to calculate the optimal cut-off point for age for the presence of choroidal nodules and for the presence of lisch nodules [15–17].

Sensitivity and specificity analysis for the diagnosis of NF1 based on the occurrence of choroidal nodules or lisch nodules was performed [18].

To assess the association between the presence of choroidal nodules and visual acuity, and the association between the presence of glioma and the presence of choroidal nodules, generalized linear mixed models were used to take into account the availability of repeated measurements in the same individual (one in each eye) [19].

The confidence level was stablished at 95%.

3. Results

417 eyes from 210 subjects were included. 3 patients had only one eye, because the other eye had been enucleated, 377 from 190 patients diagnosed with NF1, according to the National Institutes of Health Consensus Development Conference (NIH) criteria, and 40 eyes from 20 healthy subjects as a control group [5].The mean age was 9.4 years (range 2 years–18 years) and 109 were male. The sample and the control group were equivalent in age and sex distribution. The mean VA was LogMar 0.11 with a standard deviation of 0.24. Twelve and nine eyes were discarded due to poor image quality or incomplete data for the calculation of choroidal nodules and for lisch nodules respectively.

Of the total sample, we were finally able to analyse 405: 369 eyes belonged to patients diagnosed with NF1, of which 91 had choroidal nodules; the remaining 36 were eyes without the disease and without choroidal nodules or lisch nodules (Table 1).

14 years, 95% CI=(9.7,18.3) (Graph 1) and 12 years, 95% CI=(9.1,14) (Graph 2) were the ages for the best discrimination of patients with and without choroidal or lisch nodules, respectively.

Table 2 shows the sensitivity (25%) and specificity values (100%) for visible choroidal nodules when observing macular images obtained with the Triton OCT DRI Triton SS-OCT instrument (Topcon Corporation, Tokyo, Japan).

Regarding the lisch nodules, Table 3 shows that of the 408 eyes analysed, 368 belonged to patients diagnosed with NF1 and of these, 183 had lisch nodules and 185 did not.

Table 4 shows the sensitivity (50%) and specificity values (100%) for lisch nodules when observing iris patient with the slit lamp by a paediatric ophthalmologist.

Graphic 3 compares the visual acuity values between patients presenting and non-presenting choroidal nodules detectable in the images obtained with the Triton OCT. As shown, there is no statistically significant difference ($p = 0.072$) in visual acuity between both groups.

Table 5 shows that of the 405 eyes analysed, 122 are from patients diagnosed with NF1 and optic pathway glioma, and of these, 29 had choroidal nodules with our OCT. No statistically significant relationship was found between choroidal nodules and optic pathway glioma ($p = 0.96$) [19] (see Table 6).

It has been shown that the presence of choroidal nodules is associated with having lisch nodules (Chi-square test, $p = 0.00016$) [20] as shown in Table 6.

4. Discussion

The presence of choroidal nodules in patients with NF1 is defined as a bright, patchy area appearing in the retinal layer of the choroid that can be visualized by fundus examination using infrared equipment. There is already a diagnostic criterion published by the National Institutes of Health Consensus Development Conference (NIH) [5] which does not include the presence of these choroidal nodules, but does include lisch nodules.

In our study lisch nodules were found in 49.7% of patients affected by NF1, results very similar to those previously published by Viola et al. [9] The youngest patient in whom we were able to detect these lisch nodules was 3 years old. Ragge et al. [20] already published that it is very difficult to detect them at an early age. It should also be taken into account that patients under 3 years of age are often non-cooperative, so in some cases we might not have detected them at this age.

In our study we identified the presence of choroidal nodules in 25% of patients diagnosed of NF1, a value that varies significantly from those previously published by Viola et al. (71%) [9], Goktas et al. (79%) [12] and Parrozzani et al. (60,2%) [14]. According to A. Vagge et al. [13] the presence of this choroidal nodules in NF1 patients is age dependant, appearing more often in older patients. The samples in the present study and the ones used by these previous ones are very similar in age, so we ruled out the possibility that our patients were younger and had not yet debuted with these nodules. Accordingly, we can conclude that the under detection of choroidal nodules in our sample of NF1 affected patients, when compared to previous publications, must be attributed to the fact that our OCT automatically removes red light information from the image, which is presented in grey tones to the observer.

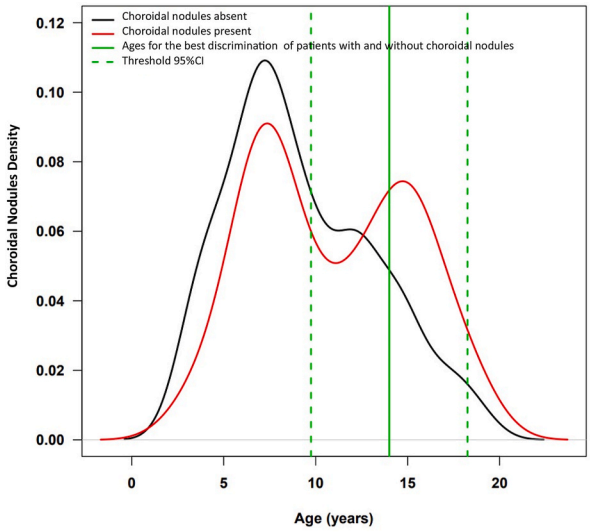
According to the study results, presenting choroidal nodules detectable with a red free OCT image is associated with having lisch nodules, but their detection is not directly related to presenting optic pathway glioma.

As far as the authors have been able to read, there is no published evidence on the possible relationship between the presence of choroidal nodules and VA. According to the obtained results, no relationship could be established in the study sample.

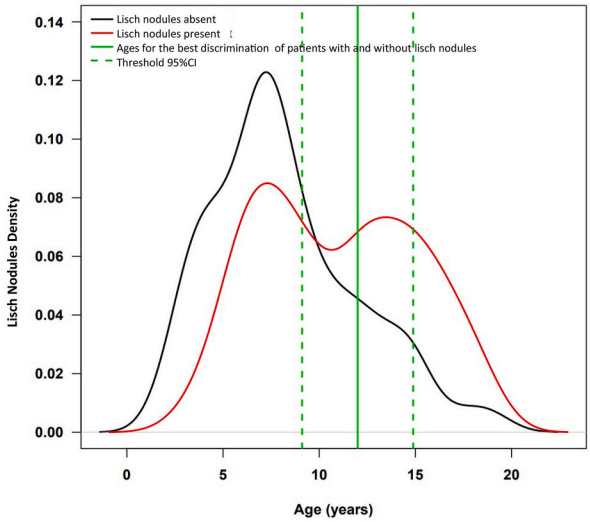
This study has certain limitations regarding the age of the sample. We believe that the data would have greatly improved if our sample had included a larger number of patients between 2 and 4 years old in order to improve the clinical diagnosis of these patients. Precisely this group of patients is the most complex to explore, since, on many occasions, they do not cooperate adequately.

Table 1
Choroidal nodules presence vs diagnosis of NF1.

Choroidal Nodules presence	Diagnosis of NF1		
	Yes	No	Total
Yes	91	0	91
No	278	36	314
Total	369	36	405



Graph 1. Graph of densities with cut point for choroidal nodules.



Graph 2. Graph densities with cut point for Lisch nodules.

Table 2
Accuracy measures for choroidal nodules as a diagnostic test for NF1.

Choroidal nodules presence as a diagnostic test for NF1			
	Estimate	95%	CI
Sensitivity	0.25	0.20	0.29
Specificity	1.00	0.90	1.00
Pos. Pred. Val.	1.00	0.96	1.00
Neg. Pred. Val.	0.11	0.08	0.16

5. Conclusion

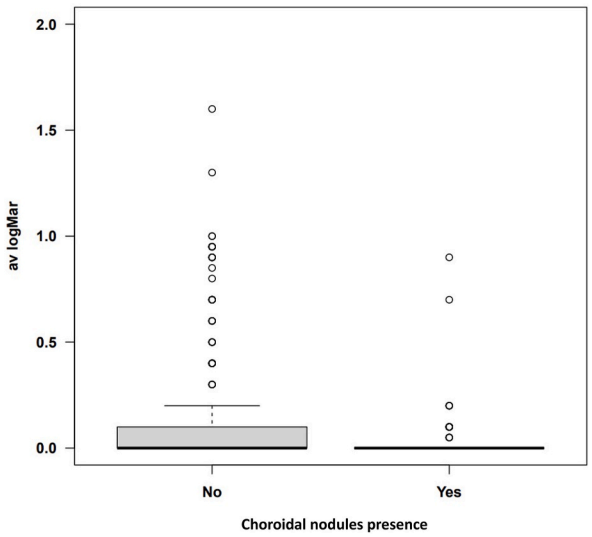
The authors conclude that the TOPCON TRITON OCT red free tool is not effective for the detection of choroidal nodules in paediatric NF1 patients because of its low sensitivity. If choroidal nodules are included as a diagnostic criterion for NF1 in the future, it should be taken into account that the equipment used provide images with IR and red light information.

Table 3
Lisch nodules presence vs diagnosis of NF1.

Lisch Nodules Presence	Diagnosis of NF1		
	Yes	No	Total
Yes	183	0	183
No	185	40	225
Total	348	40	408

Table 4
Accuracy measures for Lisch nodules as a diagnostic test for NF1.

Lisch nodules presence as a diagnostic test for NF1			
	Estimate	95%	CI
Sensitivity	0.50	0.45	0.55
Specificity	1.00	0.91	1.00
Pos. Pred. Val.	1.00	0.98	1.00
Neg. Pred. Val.	0.18	0.13	0.23



Graph 3. Boxplot: VA logMar according to choroidal nodules presence.

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki and received institutional approval from the Ethics Committee Fundació Sant Joan de Déu, Esplugues de Llobregat, Barcelona, with ethics approval reference (PIC-60-18) on October 3, 2018.

All participants/patients (or their proxies/legal guardians) provided informed consent to participate in the study.

Data availability statement

The data that has been used has been anonymized and published in UPC COMMONS [21]. https://doi.org/10.34810/data1054.

CRediT authorship contribution statement

Carlos Fresno Cañada: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Joan Gispets Parcerisas:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Cristina Del Prado Sánchez:** Writing – original draft, Methodology, Investigation. **Enric Puigventós Rosanas:** Writing – original draft, Investigation. **Sara Perez-Jaume:** Data curation. **Héctor Salvador:** Investigation. **Ana Llorca Cardeñosa:** Writing – review & editing. **Joan Prat Bartomeu:** Investigation.

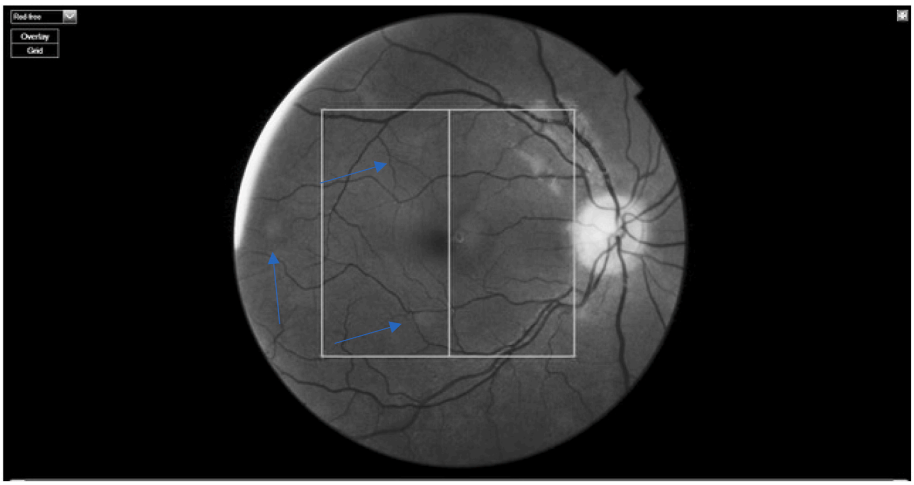


Image 1. Triton OCT DRI Triton SS-OCT with RED FREE filter on a patient presenting choroidal nodules. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 5
Optic pathway glioma according to choroidal nodules.

	Optic Pathway Glioma	
	No N = 283	Yes N = 122
Choroidal nodules		
No	221 (78.1%)	93 (76.2%)
Yes	62 (21.9%)	29 (23.8%)

Table 6
Association between choroidal and Lisch nodules.

	Lisch nodules		Total	p-value
	No	Yes		
Choroidal nodules				0.00016
No	82 (85.4%)	63 (60.6%)	145 (72.5%)	
Yes	14 (14.6%)	41 (39.4%)	55 (27.5%)	
Total	96 (48%)	104 (52%)	200	

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Joan Gispets Parcerisas reports financial support and article publishing charges were provided by Polytechnic University of Catalonia. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] v. Recklinghausen F, Uber Die Multiplen Fibrome Der Haut Und Ihre Beziehung Zu Multiplen Neuromen, 1882.
[2] S.M. Huson, P.S. Harper, D.A.S. Compston, Von recklinghausen neurofibromatosis: a clinical and population study in south-east Wales, Brain 111 (6) (1988) 1355–1381, https://doi.org/10.1093/brain/111.6.1355.
[3] D.H. Gutmann, A. Aylsworth, J.C. Carey, et al., The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2, JAMA 278 (1) (1997) 51–57, https://doi.org/10.1001/JAMA.1997.03550010065042.
[4] V.C. Williams, J. Lucas, M.A. Babcock, D.H. Gutmann, B. Bruce, B.L. Maria, Neurofibromatosis type 1 revisited, Pediatrics 123 (1) (2009) 124–133, https://doi.org/10.1542/peds.2007-3204.
[5] National Institutes of Health Consensus, Development conference statement: neurofibromatosis. Bethesda, Md., USA, july 13-15, 1987, Neurofibromatosis 1 (1988) 172–178.
[6] T. Yasunari, K. Shiraki, H. Hattori, T. Miki, Frequency of choroidal abnormalities in neurofibromatosis type 1, Lancet 356 (9234) (2000) 988–992, https://doi.org/10.1016/S0140-6736(00)02716-1.
[7] Y.S. Byun, Y.H. Park, Indocyanine green angiographic findings of obscure choroidal abnormalities in neurofibromatosis, Kor. J. Ophthalmol. 26 (3) (2012) 230–234, https://doi.org/10.3341/kjo.2012.26.3.230.

[8] S. Nakakura, K. Shiraki, T. Yasunari, Y. Hayashi, S. Ataka, T. Kohno, Quantification and anatomic distribution of choroidal abnormalities in patients with type I neurofibromatosis, Graefes Arch. Clin. Exp. Ophthalmol. 243 (10) (2005) 980–984, https://doi.org/10.1007/S00417-005-1184-Z.
[9] F. Viola, E. Villani, F. Natacci, et al., Choroidal abnormalities detected by near-infrared reflectance imaging as a new diagnostic criterion for neurofibromatosis 1, Ophthalmology 119 (2) (2012) 369–375, https://doi.org/10.1016/j.ophtha.2011.07.046.
[10] T. Ueda-Consolvo, A. Miyakoshi, H. Ozaki, S. Houki, A. Hayashi, Near-infrared fundus autofluorescence-visualized melanin in the choroidal abnormalities of neurofibromatosis type 1, Clin. Ophthalmol. 6 (1) (2012) 1191–1194, https://doi.org/10.2147/OPTH.S35321.
[11] J.R. Wolter, Nerve fibrils in ovoid bodies: with neurofibromatosis of the choroid, Arch. Ophthalmol. 73 (5) (1965) 696–699, https://doi.org/10.1001/archopht.1965.00970030698019.
[12] S. Goktas, Y. Sakarya, M. Ozcimen, et al., Frequency of choroidal abnormalities in pediatric patients with neurofibromatosis type 1, J. Pediatr. Ophthalmol. Strabismus 51 (4) (2014) 204–208, https://doi.org/10.3928/01913913-20140513-02.
[13] A. Vagge, P. Camicione, C. Capris, et al., Choroidal abnormalities in neurofibromatosis type 1 detected by near-infrared reflectance imaging in paediatric population, Acta Ophthalmol. 93 (8) (2015) e667–e671, https://doi.org/10.1111/aos.12750.
[14] R. Parrozzani, M. Clementi, L. Frizziero, et al., In vivo detection of Choroidal abnormalities related to NF1: feasibility and comparison with standard NIH diagnostic criteria in pediatric patients, Investig. Ophthalmol. Vis. Sci. 56 (10) (2015) 6036–6042, https://doi.org/10.1167/iovs.14-16053.
[15] K. Skaltsa, L. Jover, J.L. Carrasco, Estimation of the diagnostic threshold accounting for decision costs and sampling uncertainty, Biom. J. 52 (5) (2010) 676–697, https://doi.org/10.1002/BIMJ.200900294.
[16] S. Perez-Jaume, N. Pallarès, K. Skaltsa, J.L. Carrasco, ThresholdROC: optimum threshold estimation tools for continuous diagnostic tests in R, J. Stat. Software 82 (2017), https://doi.org/10.18637/JSS.V082.I04.
[17] Youden WJ. INDEX FOR RATING DIAGNOSTIC TESTS. doi:10.1002/1097-0142.
[18] X.-H. Zhou, N.A. Obuchowski, D.K. McClish, Statistical Methods in Diagnostic Medicine, second ed., Wiley Ser Probab Stat, 2011, p. 592.
[19] Linear and Generalized Linear Mixed Models and Their Applications, Springer, New York, 2007, https://doi.org/10.1007/978-0-387-47946-0.
[20] N.K. Ragge, R.E. Frank, W.E. Cohen, A.L. Murphree, Images of Lisch nodules across the spectrum, Eye (Lond). 7 (1) (1993) 95–101, https://doi.org/10.1038/EYE.1993.20. Pt 1.
[21] Fresno Cañada C, Gispets Parcerisas J, Prado Sánchez C del, et al. Nódulos coroideos en edad pediátrica. Catalunya UP de, ed. doi:10.34810/data1054.