ORIGINAL RESEARCH

Inter- and intrarater agreement of Computed Tomographic brain calcification scoring in Primary Familial Brain Calcification

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ABSTRACT

BACKGROUND AND PURPOSE: The Total Calcification Score (TCS) is a visual rating scale to measure Primary Familial Brain Calcification (PFBC) related calcification severity on Computed Tomography (CT). We investigated the inter- and intrarater agreement of a modified TCS.

MATERIALS AND METHODS: Patients aged ≥18 years with PFBC or Fahr's syndrome who visited the outpatient clinic of a Dutch academic hospital were included. The TCS was modified, for example by adding hippocampal calcification, and ranged from 0 to 95 points. Fifteen raters evaluated all CTs, of whom three evaluated the CTs twice. Their Entrustable Professional Activity (EPA) level ranged from II (medical student) to V (neuroradiologist). Agreement was assessed using the intraclass correlation coefficient (ICC) for the total score. Kendall's W and weighted Cohen's Kappa were used to determine the inter- and intrarater agreement for individual locations, respectively.

RESULTS: Forty patients were included (mean age 60 years, 53% female). The median modified TCS was 34 (range 4-76). For all EPA levels, the interrater agreement of the modified TCS was excellent (ICC=0.97 (95% CI 0.95-0.98)). Kendall's W's were good to excellent for commonly affected locations, but poor to moderate for less commonly affected locations for raters with lower levels of expertise. The intrarater agreement of the modified TCS was excellent. Kappa's of most locations were substantial to almost perfect.

CONCLUSIONS: The modified TCS can be used with excellent reproducibility of the overall amount of brain calcifications and with limited training, although for some individual calcification locations more expertise is needed.

ABBREVIATIONS: CI, Confidence Interval; CT, Computed Tomography; EPA, Entrustable Professional Activity; IBGC, Idiopathic Basal Ganglia Calcification; ICC, Intraclass Correlation Coefficient; IQR, Interquartile Range; PFBC, Primary Familial Brain Calcification; SD, Standard Deviation, TCS, Total Calcification Score; UMCU, University Medical Center Utrecht.

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SUMMARY SECTION

PREVIOUS LITERATURE: The Total Calcification Score (TCS) is a visual rating scale on CT scans that evaluates calcification severity in different locations of the brain. The TCS has been used in several studies in patients with Primary Familial Brain Calcification (PFBC) and Fahr's syndrome, which are rare neurological disorders characterized by basal ganglia calcification. The reproducibility of the TCS has not been evaluated in detail yet. This study evaluated the inter- and intrarater agreement of a modified TCS in a group of raters with different backgrounds and levels of expertise.

KEY FINDINGS: The modified TCS is an excellent reproducible score to quantify the overall amount of brain calcifications in patients with PFBC and Fahr's syndrome, whilst limited expertise of the rater is needed. For some individual locations more expertise is needed.

KNOWLEDGE ADVANCEMENT: The score can be used in clinical practice and research to evaluate the location, burden, and progression of intracranial calcifications in PFBC and Fahr's syndrome patients. This study is a next step in the improvement of the diagnostic process for this rare phenomenon.

INTRODUCTION

Primary Familial Brain Calcification (PFBC), also known as Fahr's disease or Idiopathic Basal Ganglia Calcification (IBGC), is a rare neurological disorder that is characterized by bilateral basal ganglia calcifications.(1) Calcifications often develop in other locations of the brain as well, for example in the thalami, cerebral subcortical white matter, or cerebellum.(2) These calcifications may cause symptoms like cognitive decline, movement disabilities, or neuropsychiatric disorders. The symptoms correlate with the calcification burden in PFBC patients.(2-4)

Accurate assessment of calcification location and burden is an important step in the diagnostic process of PFBC.(1) Assessment of the calcifications may also play a role in disease monitoring and evaluation of interventions. Objective methods to quantify these calcifications are limited. One method is the Total Calcification Score (TCS), which is a visual rating scale on computerized tomography (CT) scan that evaluates calcification severity in different locations of the brain.(5) The TCS was developed by a French IBGC Study group in 2013. Since then, several studies have used the TCS to quantify the amount of calcifications in PFBC patients.(2-4)

Before implementing the TCS in clinical practice or future studies, it is essential to evaluate its reproducibility. The French IBGC Study(5) group showed excellent interrater agreement between two members of the study group, but further data on inter- and intrarater agreement is lacking. The feasibility of using the TCS by raters with different levels of expertise is also unknown.

After working with the TCS in our PFBC patients at our specialized clinic, we gained several insights that led to revision of the original TCS. This study aimed to investigate the inter- and intrarater agreement of a modified TCS in patients with PFBC by a group of raters with different levels of expertise.

MATERIALS AND METHODS

Patient selection

This study was conducted in accordance to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Ethical approval was obtained from the local Dutch Medical Ethical Review Committee NedMec (registration numbers 21-170 and 22-1005). All patients gave written informed consent.

In this retrospective study, all patients aged ≥ 18 years who were diagnosed with PFBC or Fahr's syndrome and visited the outpatient clinic of the University Medical Center Utrecht (UMCU), the Netherlands, between September 1st, 2019, and July 1st, 2023, were eligible for inclusion. The UMCU is an academic hospital with expertise in PFBC and Fahr's syndrome. PFBC was diagnosed based on: 1) presence of bilateral basal ganglia calcifications as seen on CT, 2) TCS above the age-specific threshold (original TCS > 0 in age < 40 years, > 4 in age 40 to 60 years, and > 5 in > 60 years),(5) and 3) clinical symptoms consistent with the diagnosis. A genetic mutation associated with PFBC confirmed the diagnosis, but was not a mandatory criterium for inclusion. Patients were diagnosed with Fahr's syndrome if they met the aforementioned criteria for PFBC, but a secondary cause associated with bilateral basal ganglia calcification was identified, for example endocrine disorders like hypoparathyroidism.(1) All consecutive patients who were scanned in an outpatient setting according to the PFBC CT scanning protocol in the UMCU were included in this study. Patients were excluded if they were scanned according to a different CT scanning protocol or in another hospital.

Computed Tomography imaging

The CT scanning protocol was an unenhanced scan of the full brain at 120 kilo voltage peak (kVp) and 250 milli-amperage. All scans were acquired at dual layer detector scanners (Iqon, CT7500, Philips Healthcare, Cleveland, Ohio). The scan data were reconstructed at a slice thickness of 0.9 millimetres using iterative model based reconstruction. When a patient was scanned multiple times during the study period, the most recent scan was included.

Modified Total Calcification Score

The original TCS is a visual rating scale that quantifies the amount of calcification in eighteen different locations in the brain: left and right lenticular nucleus, left and right caudate nucleus, left and right thalamus, left and right cerebral subcortical white matter, cerebral cortex, left and right cerebellar hemisphere, vermis, left and right midbrain, pons, medulla, and left and right internal capsule only if independent of other calcifications. Each location gets attributed a score ranging from 0 to 5: 0 = no calcification; 1 = punctate; 2 = faint; 3 = moderate; 4 = severe; and 5 = severe and confluent. Examples of CT scans with different degrees of calcification in several locations

are included in the article that developed the TCS.(5) The TCS is the sum of score points of all locations and this overall score ranges from 0 to 90 points.(5)

After working with the original TCS in previous research, we updated the original TCS by modifying three aspects.(2) First, we removed the items 'independent internal capsule calcification left and right' from the score. Independent internal capsule calcifications have not been observed in patients with PFBC or Fahr's syndrome before on CT, neither in our study population (assessed by raters B.S. and P.d.J.), nor in literature.(2, 5) When the internal capsule is calcified, these calcifications are always confluent with calcifications in nearby locations and never independent.(2, 5) Second, we divided the item 'cerebral cortex calcification' into a left and right cerebral cortex, which is in accordance with the other locations that are already scored separately. Third, we added the items 'hippocampal calcification left and right' to the score. We commonly observed hippocampal calcification in PFBC in our clinical practice, but the hippocampus is not included in the original TCS. Hippocampal calcifications were scored bilaterally as: 0 = no calcification; 1 = punctate; 3 = moderate; or 5 = severe. We did not include score 2 and 4 since the hippocampus is too small to quantify the calcifications on a 5 point scale. Examples of the hippocampal calcification score are shown in the Online Supplemental Data FIG S1. An example of the modified TCS scoring form is shown in the Online Supplemental Data Table S1. The modified TCS ranges from 0 to 95 points.

CT scan assessment

Fifteen raters with different backgrounds and levels of expertise from the UMCU visually assessed 40 consecutive CT scans of the brain of 40 individual patients on 120 kVp reconstructions at least once, by using the modified TCS. Level of expertise for evaluating neurological CT scans was predetermined based on the Entrustable Professional Activity (EPA) level: I = has knowledge; II = may act under full supervision; III = may act under moderate supervision; IV = may act independently; and V = may act as supervisor and instructor.(6) EPA level V applied to residents or radiologists with extensive experience in neuroradiology. Among the raters were: three radiologists (D.R., P.d.J., W.M., EPA levels V, IV, IV, respectively), three radiology residents (M.B., S.d.L., S.U.V., EPA level IV, V, III), one geriatrician (N.G., EPA level II), one internist (M.P., EPA level II), five geriatric residents (B.S., M.v.B., M.R., R.P., T.K., all EPA level II), one internal medicine resident (W.V., EPA level II), and one final-year medical student (B.L., EPA level II). Each rater received an instruction manual including an overview of the anatomy of the brain and examples of calcification scores in different brain regions, the latter was adapted from the developmental study of the TCS.(5) Examples of hippocampal calcification were collected from a previous study that evaluated hippocampal calcification in a cohort of memory clinic patients.(7) Three raters (B.S., P.d.J., W.M.) scored the 40 scans twice with a minimum time interval of 3 months between the first and second assessment to determine the intrarater reproducibility. During the second assessment, raters were blinded for scores of the first assessment. The scores of the first assessment were used to determine the interrater agreement. Each scan was examined in axial, coronal and sagittal view. All raters were blinded for clinical variables.

Statistical analysis

Data was collected based on the date of scanning and included: age, sex, diagnosis, and results of genetic testing (if available). Data were presented using number with percentage for categorical variables, mean with standard deviation (SD) for continuous non-skewed variables, and median with interquartile range (IQR) for skewed variables. Prevalence of calcified brain locations was calculated based on the scores of the rater with the highest level of expertise and most years of experience in neuroradiology (neuroradiologist D.R.). The interrater agreement for the overall score of the modified TCS and for the subscore of each individual item was assessed using the intraclass correlation coefficient (ICC) with its 95% confidence interval (CI) and Kendall's Concordance Coefficient W, respectively. The interrater agreement was determined for all raters and per level of expertise. The intrarater agreement was assessed using the ICC and weighted Cohen's Kappa, respectively, with their 95% CIs.(8) An ICC of < 0.5 can be interpreted as poor, of 0.5 - 0.75 as moderate, of 0.75 - 0.9 as good, and of > 0.90 as excellent agreement.(9) Similarly, a weighted Cohen's Kappa of <0.0 can be interpreted as poor, of 0.0 - 0.2 as slight, of 0.21 - 0.4 as fair, of 0.41 - 0.6 as moderate, of 0.61 - 0.8 as substantial, and of 0.81 - 1.0 as almost perfect.(10) There is no general agreement on cut-off values to interpret Kendall's W, which ranges from 0 (no agreement) to 1 (complete agreement). The higher the W score, the better the overall agreement.(8) For the purpose of this study, the W scores were interpreted in the same way as the ICC (which also ranges from 0 to 1 and is interpreted conform the same rule "the higher, the better"). Statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, N.Y., USA).

RESULTS

Forty patients were included in this study. Baseline characteristics are presented in Table 1. The mean age was 59.9 years (SD 14.7) and 52.5% was female. The majority of patients (95%) was diagnosed with PFBC. A genetic mutation was found in half of the patients who underwent genetic testing. The SLC20A2 gene was the most commonly affected gene.

According to the ratings of neuroradiologist D.R. (EPA level V), the modified TCS ranged from 4 to 76 points (median 34, IQR 15 – 54). The most common affected locations included: both lenticular nuclei (affected in 100% of patients), one or both cerebellar hemispheres (affected in 70%), one or both thalami (affected in 68%), left and right subcortical white matter (affected in 65%), and one or both caudate nuclei (affected in 63%). Hippocampal calcification was present in 24 patients (60%), of whom 19 (79%) had bilateral and 5 (21%) unilateral calcification. In the 80 hippocampi of 40 included patients, calcifications were absent in 37 (0 points, 46%), punctate in 15 (1 point, 19%), moderate in 11 (3 points, 14%), and severe in 17 (5 points, 21%) hippocampi. In patients aged < 60 years, 6 out of 17 patients (36%) had calcifications in one or both hippocampi, compared to 18 out of 23 patients (78%) aged ≥ 60 years. Cerebral cortex calcifications were observed in 18 patients (45%), of whom 15 (83%) had bilateral and 3 (17%) had unilateral calcifications. Calcifications in the left and/or right mesencephalon, pons, and medulla were scarce (present in 10%, 10%, and 3% of patients, respectively). Independent internal capsule calcifications were not observed. The prevalence of calcification per location is shown in Online Supplemental Data FIG S2.

Interrater agreement

The interrater agreement for the modified TCS and each individual location is shown in Table 2. The ICC of the overall score of the modified TCS was excellent for all raters (0.96; 95% CI 0.94-0.98), for raters within the same EPA level, and for all comparisons between two individual raters (Table 2 and Online Supplemental Data, Table S2). For the most commonly affected locations (lenticular nucleus, caudate nucleus, thalamus, cerebral subcortical white matter, cerebral cortex, and cerebellar hemisphere), the interrater agreement was good to excellent, although Kendall's W increased with the level of expertise in most locations. The interrater agreement in raters with lower levels of expertise was poor to moderate in areas that were less frequently affected (hippocampus, vermis, mesencephalon, medulla), whilst good to excellent in raters with a high level of expertise.

Intrarater agreement

The intrarater agreement of the overall score of the modified TCS was excellent for all three raters (ICC ranging from 0.96 to 0.99). The Kappa's of almost all locations were substantial to almost perfect. The intrarater agreement was only moderate for the hippocampus for rater W.M., poor for the mesencephalon for rater B.S., and poor for the medulla for rater W.M.. Table 3 presents the intrarater agreement for the modified TCS and each individual location.

Table 1: Baseline characteristics of patients with Primary Familial Brain Calcification or Fahr's syndrome.

Characteristic	n = 40
Age	59.9 ± 14.7
Female	21 (52.5%)
Diagnosis	
PFBC	38 (95.0%)
Fahr's syndrome	2 (5.0%)
Genetic testing performed	32 (80.0%)
No genetic mutation	14 (43.8%)[a]
Results not known yet	2 (6.3%)[a]
Known genetic mutation	16 (50.0%)[a]
SLC20A2	10 (62.5%)[b]
MYORG	2 (12.5%)[b]
PDGFB	2 (12.5%)[b]
XPR1	2 (12.5%)[b]
JAM2	0 (0%)[b]
PDGFRB	0 (0%)[b]

Abbreviations: n = number, PFBC = Primary Familial Brain Calcification, SLC20A2 = Solute Carrier Family 20 member 2, MYORG = Myogenesis Regulating Glycosidase, PDGFB = Platelet Derived Growth Factor Subunit B, XPR1 = Xenotropic and Polytropic Retrovirus Receptor 1, JAM2 = Junctional Adhesion Molecule 2, PDGFRB = Platelet Derived Growth Factor Receptor Beta.
Data are presented as number (percentage) or mean (standard deviation).
a. As a percentage of the patients who underwent genetic testing.
b. As a percentage of the patients with a genetic mutation.

Table 2: Interrater agreement of the modified Total Calcification Score, for all raters and by level of expertise.

	All raters (n = 15)	Raters with EPA level II (n = 9)	Raters with EPA level III (n = 1)	Raters with EPA level IV (n = 3)	Raters with EPA level V (n = 2)
Intraclass correlation coefficient (95% CI)					
Modified Total Calcification Score	0.96 (0.94-0.98)	0.96 (0.93-0.97)	NA	0.95 (0.93-0.97)	0.98 (0.97-0.99)
Kendall's Concordance Coefficient W					
Left lenticular nucleus	0.82	0.83	NA	0.80	0.96
Right lenticular nucleus	0.83	0.85	NA	0.85	0.95
Left caudate nucleus	0.81	0.79	NA	0.83	0.98
Right caudate nucleus	0.81	0.80	NA	0.80	0.97
Left thalamus	0.93	0.94	NA	0.98	0.98
Right thalamus	0.91	0.92	NA	0.94	0.98
Left hippocampus	0.71	0.74	NA	0.68	0.95
Right hippocampus	0.70	0.72	NA	0.68	0.95
Left cerebral subcortical white matter	0.82	0.81	NA	0.89	0.91
Right cerebral subcortical white matter	0.81	0.79	NA	0.89	0.91
Left cerebral cortex	0.84	0.83	NA	0.90	0.95
Right cerebral cortex	0.84	0.83	NA	0.90	0.98
Left cerebellar hemisphere	0.95	0.95	NA	0.98	0.96
Right cerebellar hemisphere	0.94	0.95	NA	0.97	0.96
Vermis	0.77	0.69	NA	0.93	0.97
Left mesencephalon	0.58	0.48	NA	0.92	0.83
Right mesencephalon	0.54	0.41	NA	0.95	0.88
Pons	0.79	0.77	NA	0.94	0.91
Medulla	0.50	0.54	NA	0.67	0.84

Abbreviations: n = number, CI = Confidence Interval, NA = not applicable. EPA = Entrustable Professional Activity: level: I = has knowledge; II = may act under full supervision; III = may act under moderate supervision; IV = may act independently; and V = may act as supervisor and instructor.(6)
Values < 0.5 can be interpreted as poor (orange), of 0.5 - 0.75 as moderate (yellow), of 0.75 - 0.9 as good (light green), and of > 0.90 as excellent agreement (green).

Table 3: Intrarater agreement of the modified Total Calcification Score.

	Rater B.S. (EPA level II)	Rater P.d.J. (EPA level IV)	Rater W.M. (EPA level IV)
Intraclass correlation coefficient (95% CI)			
Modified Total Calcification Score	0.99 (0.99-1.00)	0.98 (0.97-0.99)	0.96 (0.93-0.98)
Weighted Cohen's Kappa (95% CI)			
Left lenticular nucleus	0.92 (0.84-1.00)	0.74 (0.57-0.92)	0.76 (0.64-0.88)
Right lenticular nucleus	0.91 (0.81-1.02)	0.69 (0.54-0.85)	0.71 (0.58-0.85)
Left caudate nucleus	0.90 (0.80-0.99)	0.79 (0.65-0.92)	0.85 (0.70-1.00)
Right caudate nucleus	0.92 (0.85-0.98)	0.70 (0.55-0.86)	0.80 (0.65-0.96)
Left thalamus	0.99 (0.96-1.01)	0.92 (0.85-0.99)	0.85 (0.73-0.98)
Right thalamus	0.96 (0.90-1.01)	0.88 (0.76-0.99)	0.84 (0.71-0.97)
Left hippocampus	0.87 (0.78-0.96)	0.84 (0.73-0.96)	0.53 (0.27-0.79)
Right hippocampus	0.85 (0.75-0.96)	0.87 (0.74-1.01)	0.47 (0.22-0.72)
Left cerebral subcortical white matter	0.87 (0.78-0.95)	0.79 (0.68-0.91)	0.83 (0.73-0.92)
Right cerebral subcortical white matter	0.81 (0.69-0.92)	0.80 (0.68-0.91)	0.78 (0.66-0.91)
Left cerebral cortex	0.90 (0.82-0.98)	0.91 (0.83-0.99)	0.75 (0.59-0.91)
Right cerebral cortex	0.87 (0.77-0.97)	0.86 (0.74-0.98)	0.77 (0.62-0.92)
Left cerebellar hemisphere	0.95 (0.91-1.00)	0.91 (0.84-0.98)	0.85 (0.75-0.95)
Right cerebellar hemisphere	0.97 (0.93-1.00)	0.93 (0.87-0.99)	0.88 (0.80-0.96)
Vermis	0.92 (0.81-1.02)	0.84 (0.74-0.94)	0.87 (0.76-0.98)
Left mesencephalon	0.00 (0.00-0.00)	0.90 (0.78-1.02)	0.82 (0.48-1.16)
Right mesencephalon	0.00 (0.00-0.00)	0.93 (0.84-1.03)	0.82 (0.48-1.16)
Pons	0.88 (0.75-1.01)	0.85 (0.64-1.06)	0.73 (0.48-0.99)
Medulla	0.66 (0.03-1.28)	1.00 (1.00-1.00)	0.00 (0.00-0.00)

Abbreviations: n = number, CI = Confidence Interval. EPA = Entrustable Professional Activity: level: I = has knowledge; II = may act under full supervision; III = may act under moderate supervision; IV = may act independently; and V = may act as supervisor and instructor.(6)

For the intraclass correlation coefficient: values < 0.5 can be interpreted as poor (orange), of 0.5 - 0.75 as moderate (yellow), of 0.75 - 0.9 as good (light green), and of > 0.90 as excellent agreement (green).

For the weighted Cohen's Kappa: values of <0.0 can be interpreted as poor (dark red), of 0.0 - 0.2 as slight, of 0.21 - 0.4 as fair, of 0.41 - 0.6 as moderate (yellow), of 0.61 - 0.8 as substantial (light green), and of 0.81 - 1.0 as almost perfect (green).

DISCUSSION

In this study, we updated the TCS by removing the items 'independent internal capsule calcification left and right', by dividing the item 'cerebral cortex calcification' into left and right, and by adding the items 'hippocampal calcification left and right'. We assessed the inter- and intrarater agreement of the modified score in patients with PFBC and Fahr's syndrome. The interrater agreement of the overall score was excellent and it could be accurately established by raters with both lower and higher levels of expertise. There was a high level of agreement between raters regarding frequently affected brain locations like the lenticular nucleus or thalamus. Variability between raters with limited expertise increased for locations that were less often affected. The intrarater agreement was excellent for the overall score and substantial to almost perfect for most brain regions, indicating a good reproducibility.

Our findings are re-assuring for the use of the TCS and modified TCS, which is in line with results of the French IBGC Study group(5) that brain calcifications can be scored with high interrater agreement. They reported a weighted Cohen's Kappa of 0.97 for the original TCS.(5) In addition to the previous study, we evaluated the agreement for all locations separately and tested raters with various expertise levels. Our findings are a valuable addition to the limited knowledge of the measurement of intracranial calcifications in PFBC.

To our knowledge, this is the first time the prevalence of hippocampal calcification has been described in PFBC and Fahr's syndrome patients. The prevalence of calcification in the other intracranial locations in PFBC has been described before.(2, 4) Hippocampal calcification can also be seen as incidental finding on CT scans in the general population. For example, in an Australian hospital study which randomly included 300 patients who underwent nonenhanced brain CT scans, hippocampal calcifications were present in 22% of patients aged over 50 years. No hippocampal calcifications were observed in patients below 50 years of age.(11) Another study, which examined brain CT scans of 1130 patients with (suspected) acute ischemic stroke, reported a prevalence of hippocampal calcification of 8% in patients < 40 years. This prevalence gradually increased with age up to 45% in patients > 80 years.(12) In a cohort including 1991 patients visiting a memory clinic (mean age 78 years), 19% had calcifications in the hippocampus on brain CT scan.(13) The prevalence in our study population (36% in < 60 years, 78% in ≥ 60 years) is considerably higher compared to these studies, suggesting that patients with PFBC or Fahr's syndrome have a higher risk of developing hippocampal calcification. However, we do not know whether this higher prevalence of hippocampal calcification in PFBC and Fahr's syndrome patients is primarily due to the pathophysiology of the disease or due to the presence of other risk factors. Given this higher prevalence of hippocampal calcification, we decided to add the hippocampus to the modified TCS to increase awareness for this frequently affected brain location.

A strength of our study is that we included a large group of raters with different backgrounds and levels of expertise. We evaluated the reproducibility and feasibility of the score in a relatively large group of patients with intracranial calcifications. We provided the raters with written instructions only, which appeared to be sufficient enough to adequately assess the calcification scores. Further, we enhanced an existing brain calcification score by adding several relevant items (bilateral cortex and hippocampus calcification) and removing a less relevant item (independent internal capsule calcification). The modified TCS obtains a more complete overview of all calcified brain locations compared to the original score. This is a next step in the improvement of the diagnostic process for this rare disease. However, the clinical relevance of calcification per specific brain location is still largely unknown. One recent study has demonstrated that calcifications in the lentiform nucleus and subcortical white matter are associated with motor and cognitive decline, respectively.(14) More research is needed in larger populations to evaluate the clinical relevance of other calcified brain locations.

Our study must be interpreted in the light of some limitations. First, we had a small number of raters with higher levels of expertise, yet this might have led to an underestimation of the reproducibility. One of our raters with EPA level II (N.G.) had previous experience with administering the original TCS.(2) Yet, none of the other readers had previous experience with the TCS. Therefore, reproducibility of calcification scoring with the (modified) TCS at another institution is likely achievable with the methodology of training and scoring as applied in the current study. Next, we modified the TCS without validating the cut-off values for pathological calcification.(4) The French IBGC Study group, which developed the original TCS, proposed age-dependent cut-off values for the original TCS to distinguish patients with normal amounts of intracranial calcification due to the natural ageing process from patients with pathological calcification.(5) These cut-off values need to be validated for our modified score. Since hippocampal calcification is prevalent in the general population, especially among older adults, cut-off values for the modified TCS will likely need to be raised. Therefore, caution is needed with applying the existing cut-off values to the modified TCS. These values might not be able to adequately differentiate between physiological and pathological brain calcification when the modified score is used. However, our modified TCS can be used to assess the calcification location, burden and progression in a more detailed and complete way in known PFBC and Fahr's syndrome patients. Further research is needed to re-establish cut-off values of the modified TCS, before it can be used to differentiate between physiological and pathological calcification load. Lastly, we used a single scanning protocol for this study. Reproducibility of the score may suffer when thicker slices are obtained or when contrast enhanced scans are used.

CONCLUSIONS

In conclusion, the modified TCS is an excellent reproducible score to quantify the overall amount of brain calcifications in patients with PFBC and Fahr's syndrome, whilst limited expertise of the rater is needed. For some individual locations more expertise is needed. The score can be used in clinical practice and research to evaluate the location, burden, and progression of intracranial calcifications in PFBC and Fahr's syndrome patients.

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SUPPLEMENTAL FILES

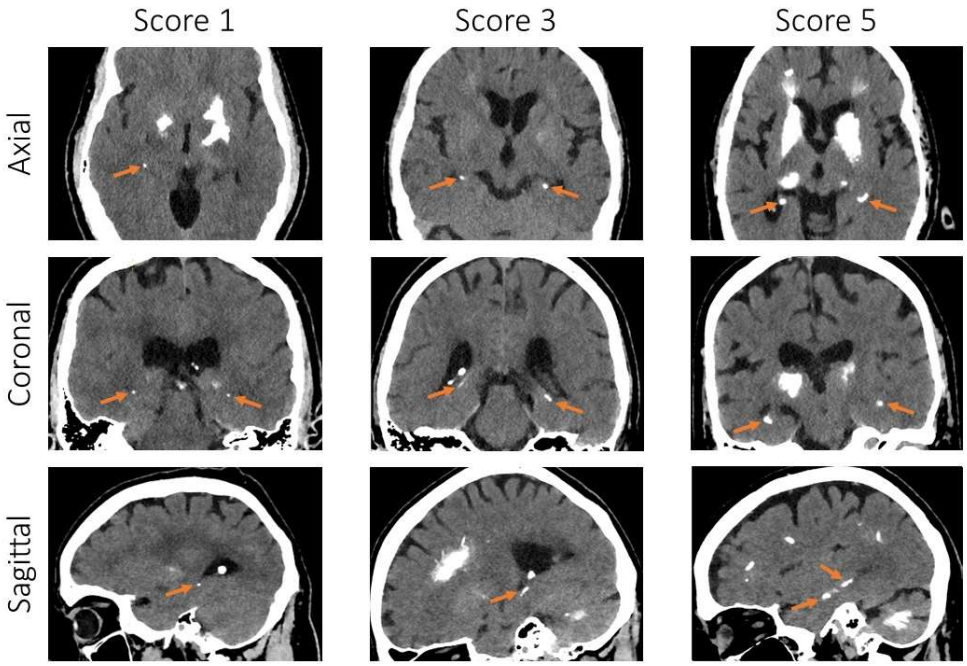

FIG S1. Example of hippocampal calcification score.

Example of three patients with bilateral symmetrical hippocampal calcifications (severity score 1, 3, or 5) viewed in axial, coronal and sagittal planes. The orange arrows indicate the hippocampal calcification.

Table S1: Example of modified Total Calcification Score scoring sheet.

Location	Score					
Left lenticular nucleus	0	1	2	3	4	5
Right lenticular nucleus	0	1	2	3	4	5
Left caudate nucleus	0	1	2	3	4	5
Right caudate nucleus	0	1	2	3	4	5
Left thalamus	0	1	2	3	4	5
Right thalamus	0	1	2	3	4	5
Left hippocampus	0		1		3	5
Right hippocampus	0		1		3	5
Left cerebral subcortical white matter	0	1	2	3	4	5
Right cerebral subcortical white matter	0	1	2	3	4	5
Left cerebral cortex	0	1	2	3	4	5
Right cerebral cortex	0	1	2	3	4	5
Left cerebellar hemisphere	0	1	2	3	4	5
Right cerebellar hemisphere	0	1	2	3	4	5
Vermis	0	1	2	3	4	5
Left midbrain	0	1	2	3	4	5
Right midbrain	0	1	2	3	4	5
Pons	0	1	2	3	4	5
Medulla	0	1	2	3	4	5

The original Total Calcification Score was modified by removing the items 'independent internal capsule calcification left and right', by dividing the item 'cerebral cortex calcification' into left and right, and by adding the items 'hippocampal calcification left and right'.

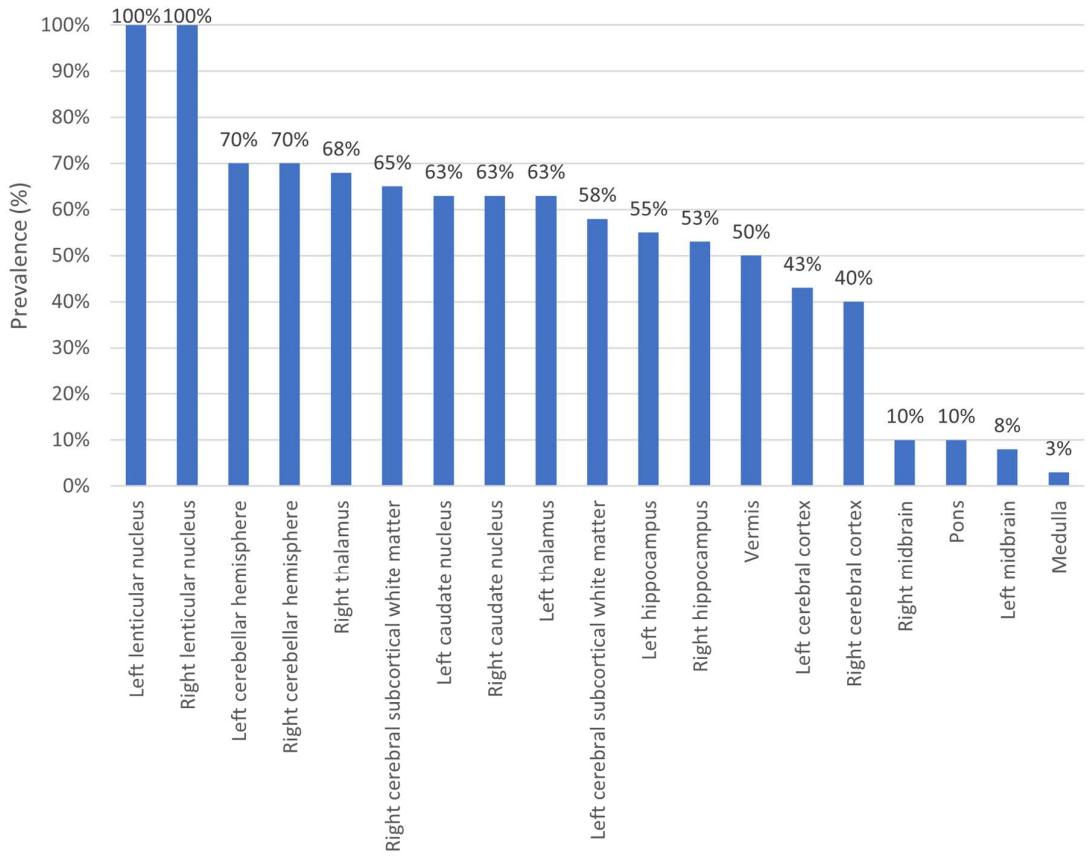

FIG S2. Prevalence of brain calcification per location in patients with PFBC and Fahr's syndrome.

Table S2: Interrater agreement of the modified Total Calcification Score.

Rater	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1															
2	0.93 (0.88-0.96)														
3	0.97 (0.94-0.98)	0.96 (0.93-0.98)													
4	0.95 (0.91-0.97)	0.96 (0.92-0.98)	0.97 (0.95-0.99)												
5	0.96 (0.93-0.98)	0.94 (0.89-0.97)	0.97 (0.94-0.98)	0.94 (0.89-0.97)											
6	0.95 (0.91-0.98)	0.96 (0.92-0.98)	0.96 (0.93-0.98)	0.94 (0.89-0.97)	0.94 (0.89-0.97)										
7	0.96 (0.92-0.98)	0.96 (0.92-0.98)	0.96 (0.95-0.99)	0.95 (0.91-0.97)	0.96 (0.93-0.98)	0.98 (0.96-0.99)									
8	0.96 (0.92-0.98)	0.95 (0.91-0.98)	0.96 (0.92-0.98)	0.94 (0.88-0.97)	0.96 (0.92-0.98)	0.96 (0.93-0.98)	0.96 (0.92-0.98)								
9	0.95 (0.91-0.98)	0.94 (0.89-0.97)	0.98 (0.96-0.99)	0.97 (0.93-0.98)	0.95 (0.92-0.98)	0.94 (0.89-0.97)	0.96 (0.93-0.98)	0.96 (0.92-0.98)							
10	0.95 (0.91-0.97)	0.96 (0.93-0.98)	0.96 (0.93-0.98)	0.96 (0.92-0.98)	0.96 (0.92-0.98)	0.95 (0.91-0.97)	0.95 (0.91-0.97)	0.95 (0.90-0.97)	0.96 (0.92-0.98)						
11	0.98 (0.96-0.99)	0.95 (0.90-0.97)	0.97 (0.95-0.99)	0.96 (0.92-0.98)	0.97 (0.94-0.98)	0.96 (0.93-0.98)	0.97 (0.94-0.98)	0.97 (0.94-0.98)	0.97 (0.95-0.99)	0.96 (0.92-0.98)					
12	0.96 (0.93-0.98)	0.95 (0.91-0.97)	0.98 (0.95-0.99)	0.97 (0.95-0.99)	0.97 (0.94-0.98)	0.94 (0.89-0.97)	0.95 (0.91-0.97)	0.95 (0.92-0.98)	0.96 (0.93-0.98)	0.97 (0.95-0.99)	0.96 (0.93-0.98)				
13	0.95 (0.91-0.97)	0.95 (0.91-0.98)	0.95 (0.91-0.98)	0.93 (0.87-0.96)	0.95 (0.90-0.97)	0.96 (0.93-0.98)	0.96 (0.92-0.98)	0.96 (0.93-0.98)	0.96 (0.88-0.96)	0.95 (0.91-0.97)	0.94 (0.89-0.97)	0.96 (0.92-0.98)			
14	0.97 (0.94-0.98)	0.97 (0.94-0.98)	0.98 (0.97-0.99)	0.98 (0.96-0.99)	0.96 (0.93-0.98)	0.97 (0.94-0.98)	0.97 (0.95-0.99)	0.96 (0.93-0.98)	0.96 (0.93-0.98)	0.98 (0.96-0.99)	0.97 (0.94-0.98)	0.98 (0.97-0.99)	0.96 (0.93-0.98)		

15	0.97 (0.94-0.98)	0.96 (0.92-0.98)	0.98 (0.96-0.99)	0.98 (0.96-0.99)	0.95 (0.91-0.97)	0.96 (0.92-0.98)	0.96 (0.93-0.98)	0.95 (0.91-0.97)	0.97 (0.95-0.99)	0.97 (0.95-0.99)	0.97 (0.95-0.98)	0.98 (0.96-0.99)	0.96 (0.92-0.98)	0.98 (0.97-0.99)

Data given are intraclass correlation coefficients with 95% confidence intervals. For the intraclass correlation coefficient: values < 0.5 can be interpreted as poor (orange), of 0.5 - 0.75 as moderate (yellow), of 0.75 - 0.9 as good (light green), and of > 0.90 as excellent agreement (green).

Rater 1: final-year medical student B.L., Entrustable Professional Activity (EPA) level II; rater 2: internal medicine resident W.V., EPA level II; rater 3: geriatric resident B.S., EPA level II; rater 4: geriatric resident M.v.B., EPA level II; rater 5: geriatric resident M.R., EPA level II; rater 6: geriatric resident R.P., EPA level II; rater 7: geriatric resident T.K., EPA level II; rater 8: internist M.P., EPA level II; rater 9: geriatrician N.G., EPA level II; rater 10: radiology resident S.U.V., EPA level III; rater 11: radiology resident M.B., EPA level IV; rater 12: radiologist P.d.J., EPA level IV; rater 13: radiologist W.M., EPA level IV; rater 14: radiology resident S.d.L., EPA level V; rater 15: radiologist D.R., EPA level V.