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Title: Conversion and Neuro-inflammation Disorder Observational Study (CANDO). Study protocol of a feasibility study.

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Abstract

Background: Conversion disorder (CD) or functional neurological disorder (FND) affects at least 764,000 people in the UK per year. As its origin is unknown and treatment has limited effects the condition forms a high individual and societal burden and clinically-unmet need. Research aiming to improve the outlook for people with this condition is urgently required. Exploration of the role of stress response and systemic low-grade inflammation(SLI) in CD/FND is warranted. The first step is to establish the feasibility of identifying, recruiting and assessing a clinical cohort of CD/FND patients for biomarkers of SLI, in addition to objective and subjective measures of stress and related factors.

Methods: The settings are currently clinics and services within the Tees, Esk and Wear Valleys NHS Foundation Trust (TEWV). Phase 1 and phase 3 of our work are described in this paper, assessing the feasibility of assessing a cohort of CD/FND patients. Ethical approval has been granted for this study. The study will use observational measures including a blood sample for assessment of inflammation biomarkers; hair cortisol testing; self-report measures of stress, childhood trauma and health; targeted neurocognitive functioning and psychiatric examination. The findings will be used to inform future phases of our work.

Discussion: Study outcomes will be knowledge about levels of SLI, psychological and cognitive symptoms in patients with CD/FND that is so far largely unknown. Knowledge regarding the feasibility of conducting a study in this population will also be gained. This will enable a comprehensive testing and evaluation of the proposed processes of recruitment, retention and data collection. This is hoped to lay the groundwork for future work leading to the development of novel treatments for CD/FND patients.

Keywords: Conversion Disorder; Functional Neurological Disorder; Inflammation; Stress; Cognitive function; Adverse Childhood Experience; Feasibility; Protocol

Background

1.1 Background and Rationale

Conversion disorder (CD) or functional neurological disorder affects at least 764,000 people in the UK per year. It leads to long-term distress, disability, diminished quality of life and consequent demand on health care services (1). As its origin is unknown(2) and treatment has limited effects (3-5), this condition forms a high individual and societal burden and clinically-unmet need. Research aiming to improve the outlook for people with this condition is urgently needed.

The theoretical model implicating stress response and systemic low-grade inflammation (SLI) in the development of mental disorders is gaining ground(6-11), implying SLI activity resulting in sickness behaviour (fatigue, mood and cognitive symptoms) that, if prolonged, may provoke stress-related mental disorders (6) such as depression and Post Traumatic Stress Disorder (PTSD) (7-9).

CD is often stress-related (10) but associated with functional neurological and cognitive problems, not with mood symptoms(11). Recent functional neuroimaging (fMRI) studies suggest brain alterations in the emotion-motor processing in people with motor CD (12, 13) that result in functional neurological symptoms, not in depression or Post Traumatic Stress Disorder(PTSD). Focusing on CD with non-seizure motor symptoms will provide us with an excellent opportunity to understand the pathogenic mechanism as basis for motor function mental disorders instead of mood disorders in relation to SLI and sickness behaviour.

In a recent case study, treatment of subjective cognitive problems such as planning difficulties and mental slowness, resulted not only in improved cognitive functioning, but also improved motor symptoms (14). Both motor and planning functions are represented in the cerebellum where many inflammatory receptors are also found.

We want to explore the hypothesis that motor CD with neurocognitive symptoms such as planning problems is related to systemic low-grade inflammation (SLI) and that the cerebellum is involved in the pathogenic mechanism. We envisage five steps for addressing this hypothesis:

- Step 1: establish the feasibility of assessing a clinical cohort of up to 30 CD patients with motor symptoms for high sensitivity C-reactive protein (hsCRP), neurocognitive symptoms and biological (hair cortisol) and psychological signs of stress.
- Step 2: develop a rodent model for CD focusing on (in) voluntary control motor deficits in relation to SLI and cerebellar involvement.
- Step 3: if assessing a clinical cohort is feasible, and hsCRP scores compared to norm scores indicate SLI in CD, establish the role of cytokines and microRNA in the pathogenesis of CD.
- Step 4: should the rodent model confirm a link between cerebellar inflammation and (in) voluntary motor symptoms, assess cerebellar function in CD patients by fMRI.
- Step 5: depending on outcome of earlier steps, evaluate an anti-inflammatory intervention in CD with motor symptoms.

This Protocol is for step 1 and step 3, the feasibility study, the results of which will inform the further steps by providing us with knowledge about levels of SLI, psychological and cognitive symptoms in

patients with CD that so far is lacking and enable a comprehensive testing and evaluation of the proposed processes of recruitment, retention and data collection.

1.2 Objectives

This study will explore the feasibility of recruiting and retaining a cohort of participants with a disabling disorder and collecting data through psycho-diagnostic testing, clinical lab and neurocognitive testing.

We will include an evaluation of the costs associated with recruitment, retention and analysis to inform the next steps of the research and to meet the following specific aims:

- To establish the feasibility of assessing a clinical cohort of CD patients for biomarkers of SLI such as complete blood counts and high sensitivity C-reactive protein (hsCRP), inflammation-associated microRNAs (miR-146a, miR-155, miR-223, miR-21, and miR-132), cytokines (TNF, IL1b, IL6, IFNg, VEGF and ANG2) and hair cortisol (15) as well as psychological signs of stress.
- To establish the feasibility of identifying, recruiting and retaining participants from this patient group and to determine the acceptability of the study processes.

A further objective of this study is to establish a Patient and Public Involvement (PPI) advisory group. All participants in the study will be invited to provide feedback on study procedures and patient materials as part of the study, but in addition we would like to recruit interested people with lived experience of the condition to advise on and contribute to dissemination of the study findings and the design and management of future research projects.

Methods

2.1 Study setting

It is anticipated that the majority of participants will be recruited through clinics and services within the Tees, Esk and Wear Valleys NHS Foundation Trust (TEWV). Other services that may be involved are Humberside Trust, the Neurology Dept. of York Teaching Hospital and GP practices in Yorkshire.

2.2 Inclusion criteria

Our target population will be adult patients, aged 18 and above with diagnosed or suspected functional neurological disorders/conversion disorders with motor symptoms. Both incident and prevalent cases will be included.

2.3 Exclusion criteria

The exclusion criteria includes patients with a diagnosis of Cushing's syndrome, any blood-clotting disorders (e.g. haemophilia) or transfusion transmissible infections (e.g. HIV); the use of steroidal medication; patients with non-motor conversion disorder, and patients with pseudo-seizures as well as epileptic seizures. We will also exclude patients with brain injury or neuro-degenerative conditions such as dementia or Parkinson's disease. Also, for this feasibility stage, patients who are not able to complete self-administered questionnaires in English will be excluded.

Patient eligibility is determined by a checklist completed by medics. This process is shown in the flowchart below.

- insert figure 1 here-

2.4 Recruitment

An information leaflet about the study will be circulated to clinicians and colleagues within the participating NHS trusts who may be providing care for this patient group and who may be interested in introducing the study to their patients. It will be made clear that there is no expectation that they participate in the study. Interested Health Care Professionals (HCPs) will be invited to contact the study team should they want further information about the study

Other recruitment options will also be explored including GP practices and the neurology and emergency departments of hospital trusts and mental health trusts as mentioned above. Should this be feasible, participating community mental health teams [CMHTs) and GP practices will, where possible, identify potential participants through electronic searches; in addition to which GPs and other health professionals will be able to introduce the study to suitable patients during a consultation.

2.5 Procedures

In any of the above settings the clinician, nurse, GP or other healthcare provider (HCP) can introduce the study, give or send the patient an invitation letter with a copy of the patient information sheet and invite the patient to complete a 'Permission for release of personal contact details' form which would be securely faxed or emailed to the research team. A nurse or suitably-qualified researcher will contact the patient by telephone to answer any questions and arrange a face-to-face appointment with the potential participant at his/her home or preferred suitable location, to confirm capacity and eligibility, and, if the patient is happy to go ahead and eligible, take informed consent.

Consenting participants will be invited to complete the baseline questionnaires. Researchers will invite feedback on the time taken to complete the questionnaires and whether the task presented any problems, to help the research team assess patient burden. Blood and hair samples, together with blood pressure and height, weight and waist measurements, will be taken either at the baseline visit or the follow-up appointment according to patient preference.

Study researchers will also arrange an appointment for the participant to attend the follow-up session for neuro-cognitive tests and psychiatric examination, in an NHS or University of York setting. This examination will provide participants with an expert opinion on their condition.

All participants will continue to receive their usual care throughout the study.

2.6 Participant Timeline

- Insert figure 2 here -

2.7 Outcomes

2.7.1 Primary outcomes

The feasibility of establishing the cohort and performing psycho-diagnostic assessment for description of the cohort indicating the relation between experienced stress and SLI will be assessed through the collection of the following data:

2.7.1.1 Definition of the cohort

Definition of the cohort will include a psychiatric examination using DSM-5 classification (11), Clinical Global Impression Scale (CGI) (16), Adverse Childhood Experiences (WHO-ACE-IQ) (17), Life Events Stress (LCU) (18). The perceived Stress Reactivity Scale (PSRS) (19) and Recent Perceived Stress Questionnaire (20) will also be completed and systolic and diastolic blood pressure and Body Mass Index (BMI) recorded.

2.7.1.2 Possible confounders

Possible confounder of SLI such as chronic medical conditions (21) will be recorded in addition to: number of physical symptoms using an English version of the LKV(PSQ)(22), anxiety using the GAD7 (23) and depression using the PHQ9 (23) as well as the self-reported use of anti-inflammatory medication at the point of recruitment to the study.

2.7.1.3 Targeted neurocognitive functioning

Assessment of neurocognitive functioning will be conducted using tools that have been found to be discriminative and reliable markers of change with improvement in CD [15]. i.e. mental slowness (14), divided attention (24); working memory [WAIS-IV](25). Tests taken will be:

1. Digit span of the Wechsler Adult Intelligence Scale for working memory, forwards and backwards (25);
2. Trail Making Test A and B for information processing and divided attention (24) taken from the Delis Kaplan Executive Functioning Scales.
3. Color-Word Interference Test (Stroop) for information processing and inhibition/attention (26) as part of the Delis Kaplan Scales.
4. Symbol Substitution (Coding) of the Wechsler Adult Intelligence Scale for information processing (25).
5. Tower of London for executive functioning (27) as part of the Delis Kaplan Scales.

2.7.1.4 High sensitivity C-Reactive protein

Characteristics of the proposed outcome measure (hsCRP) including standard deviation will be taken for future power calculation.

2.7.1.5 Biomarkers of inflammation and stress

Other biomarkers will be assessed including venepuncture for assessing total blood counts and hsCRP, and cortisol hair test as biomarker for chronic accumulative stress assessed by Anglia Ruskin University Biomarker lab (15). Blood and hair samples will be sent for analysis at participating trusts and assessed for clinical lab findings indicating SLI: complete blood counts and hsCRP [blood samples) and cortisol (hair) the results compared with norm scores.

2.7.1.6 Inflammatory cytokines

Targeted assessment of circulating inflammatory cytokines will be conducted based on how SLI has been measured in contexts within and beyond neurology (e.g. obesity, type one diabetes, ageing). Cytokine (TNF, IL1b, IL6, IFNg, VEGF and ANG2) measurements combined with hsCRP results will give us a comprehensive view of our cohort to assess systemic inflammation.

2.7.1.7 Micro RNAs

Targeted assessment of circulating (cell-free) inflammation-associated microRNAs based on how SLI has been measured in contexts within and beyond neurology (e.g. obesity, type one diabetes, ageing), including miR-146a, miR-155, miR-21, miR-223, and miR-132.

2.5.2 Secondary outcomes

The processes associated with the study will be assessed for acceptability to participants and health care providers, canvassing views of both. The numbers of patients identified through each of the recruitment methods and the proportion of those who were willing and eligible to take part will be recorded. Willingness to complete assessment processes will be monitored including, attrition rates and reasons, to identify any barriers to completion. Finally, the time and cost of data collection and analysis will also be assessed.

Data Management and Ethics

3.1 Approval

This study has been reviewed and approved by the NHS North West 11 Research Ethics Committee, Preston. IRAS nr. 261252

3.1 Confidentiality

All data will be handled in accordance with the UK Data Protection Act 1998. The Case Report Forms (CRFs) will not bear participant names. This data will be pseudo-anonymised using study identification numbers for identification. Data management activities will be described in a trial-specific Data Management Plan. Blood samples will be collected and processed in accordance with TEWV NHS Foundation Trust policies and procedures. Hair samples with be collected, stored and shipped in accordance with the protocols of the Anglia Ruskin Biomarker Laboratory who will be analysing the anonymised samples.

3.2 Ethical Issues

We are aware that people with disabling conditions represent a vulnerable group. However we do not anticipate any major ethical issues with the proposed study since there are no novel interventions and every effort will be made to keep the burden for patients as low as possible.

The total assessment burden for patients will be one blood sample, taken at home or other suitable location by a nurse or other appropriately-qualified person and a selection of questionnaires that will take no more than 45 minutes to fill in. Researchers will be aware of the need for breaks.

The psychiatric examination of 45 minutes, and the neurocognitive tests of 45 minutes will be arranged in a NHS setting and all travel costs will be reimbursed.

3.3 Risks and anticipated benefits for study participants and society

All participants will receive usual care. No treatment will therefore be withheld by participating in this study. It is possible that in participating patients may benefit from the experts' appraisal and treatment recommendations that may arise from the assessments.

3.4 Informing potential participants of possible benefits and known risks

The patient information leaflet will provide potential participants with information about the possible benefits and any known risks of taking part in the study. Participants will be given the opportunity to discuss this issue with their clinician or study researcher prior to consenting to participate. The researcher will inform the participant if new information comes to light that may affect the participant's willingness to participate in the study.

3.5 Research Governance

The study will be conducted to protect the human rights and dignity of the participant as reflected in the 1996 version of the Helsinki Declaration. Patients will not receive any financial inducement to participate. In order to protect participants the following provisions will be made/upheld; the study has been designed to minimise pain, discomfort and fear and any foreseeable risk in relation to the treatments involved, the explicit wishes of the participant will be respected including the right to withdraw from the study at any time, the interest of the patient will prevail over those of science and society, provision will be made for indemnity by the investigator and sponsor. The University of York has agreed to act as sponsor for the study.

3.6 Monitoring and reporting adverse events

This study will record details of any Serious Adverse Events [SAEs) that are required to be reported to the Research Ethics Committee [REC) under the terms of the Standard Operating Procedures for RECs. An SAE is defined as an untoward occurrence that: i) results in death; ii) is life threatening; iii) requires hospitalisation or prolongation of existing hospitalisation; iv) results in persistent or significant disability or incapacity; v) consists of a congenital anomaly or birth defect; or vi) is otherwise considered medically significant by the investigator.

Should a research participant experience a SAE we will report this to our main REC if in the opinion of the chief investigator the event was 'related' (i.e. it resulted from administration of any of the research procedures) and 'unexpected'. Reports of related and unexpected SAEs will be submitted within 15 days of the chief investigator becoming aware of the event, using the appropriate form.

Study Management

4.1 Governance

In order to attain the objectives described above, we will develop an interdisciplinary project management structure with the co-applicants as governance board to address any issues in terms of feasibility that might arise during the project, and to ensure the future developments aimed at as described above.

A steering group consisting of CFC, JR, and SG will meet regularly and oversee producing the deliverables to target and time. Further involvement of NHS would enable us to build a network of collaborators, both clinical and preclinical, and of different specialisms such as psychiatry, neurology, nurses, psychotherapy and basic scientists.

4.2 Deliverables

Findings of this study will be discussed with the research team, who will be involved in the follow up steps. Based on our discussion of the outcome of this feasibility study, we will then prepare grant proposals for follow up steps. A publication will also be prepared with regards to the feasibility outcomes.

4.3 Statement of Indemnity

NHS Indemnity procedures will apply. The University of York will also provide relevant cover.

4.4 Dissemination

A full dissemination plan will be drawn up in collaboration with the PPI group as it becomes established. It is anticipated that this will include publication of the protocol and results and dissemination through patient and carer groups as well as conference presentations. In addition the lead investigator will present the findings at the ICPM and EAPM conferences.

4.5 Study Status

The study is ongoing. Data collection commenced in August 2019 and is continuing. Data collection will be completed by mid-2020 and evaluation of the study processes will commence soon after.

Discussion

5.1 Relevance of expected findings

This study will be the first to our knowledge to i) assess stress-related SLI in CD/FND patients, and ii) establish the feasibility of the processes involved within this vulnerable population. It is therefore important for the development of work in CD/FND, and is the first step in an anticipated larger project aiming to develop new treatments for this population.

It is envisaged that this study will provide knowledge about levels of SLI, psychological and cognitive symptoms in patients with CD/FND that is so far largely unknown. Furthermore it will provide valuable knowledge regarding the feasibility of conducting a study in these patients, including issues with recruitment, retention, data collection, and proposed procedural processes. This knowledge will enable a comprehensive testing and evaluation of the proposed processes involved in the study and will inform future study phases.

More precisely, we would consider that creating a larger cohort is feasible if we would be able to recruit at least 60% of people approached for participation and if we can interest a variety of sites for participation, including sites outside mental health trusts, such as neurology, physiotherapy practices, and primary care sites. Also, there should be indications that the study procedures would be acceptable for patients, in terms of tolerance for the duration of interviews, the blood and hair

sampling and potentially distressing revisiting of past events, and willingness to attend psychiatric assessment. Data should be complete with an attrition rate not above 40%. Another aspect of feasibility would be that if we consider that inclusion or exclusion criteria might need to be refined, that these can be incorporated. Regarding the lab, feasibility would be expressed in if we succeed to get the required samples and to deliver them to the respective labs, with resulting valid lab outcomes.

An ongoing issue is the classification of conditions such as CD in the research literature as there is a tendency in the international literature to introduce new classifications for this condition, that are sometimes of rather short duration. In the WHO ICD-10,(28) conversion disorder was the classification for this condition, with similar criteria as in the DSM IV and DSM-5(11). The DSM-5 term is conversion disorder/functional neurological disorder. In the development phase of the ICD-11, the term functional neurological disorder (FND)(29) made it into the Beta version of the ICD-11.(30) However, in the final ICD-11 version, this was abandoned in favour of the classification Dissociative neurological symptom disorder.(31,32) Also, there has been a controversy about whether this condition should be in the psychiatry or in the neurology section of the ICD-11. As collaboration between neurologists and psychiatrists is of the utmost importance, both in research and in clinical terms, such changes of terminology and envisioned ICD sections should preferably be avoided to support conducting internationally generalisable research into this condition that should withstand the comparison over time, unless compelling reasons would exist to make such adaptations.

It has been suggested that somatoform disorders would gradually be classified otherwise pending their further understanding of pathogenic mechanism, or clear-cut treatment implications related to a new diagnostic classification.(33) However, for conversion disorder, as the literature stands now, there is no such rationale to change the classification, not in terms of pathogenic mechanisms, and not in terms of available treatment modes. Hence from a clinical epidemiological research perspective, it would be preferable to stick with existing classifications whilst we continue to try to understand this condition better, in, preferably, interdisciplinary research efforts. For future research, in view of this shift in classifications, a thorough phenomenological description of the symptoms experienced by the patients and observed by doctors and other health care professionals becomes of the utmost importance, in order to enable researchers and clinicians from different backgrounds to understand which patients and conditions we explore. For this purpose, we use the following table, which enables us to describe the phenomenology in a detailed manner, from the perspective of possible cerebellar involvement.

-Insert table 1 here -

5.2 Strengths and limitations

The key strengths of this study are the use of both objective and subjective observational methods to assess stress related SLI, psychological and cognitive symptoms in this sample population. This will ensure a more complete understanding of the primary outcomes. Another key strength is that the patients will receive an expert opinion on their condition, providing benefit and hopefully encouraging study completion.

There are however several limitations to the study. Firstly, the study is currently only based in a single NHS trust, limiting our knowledge of how the processes may work in other settings. However, it is anticipated that other NHS trusts will become involved as the study progresses.

Secondly, patients who are not able to complete self-administered questionnaires in English will be excluded as the questionnaires are only validated in English. In larger future studies, provisions for non-English speakers should be made.

Thirdly, the diagnosis of CD/FND can be complex and not always given on the basis of positive symptoms despite updated guidance (34), therefore our sample population may be particularly heterogeneous. Furthermore, given the potential various motor symptoms of the patients, it is anticipated that some patients may have difficulty with some procedures (e.g. hand tremors or vision problems may affect ability to complete questionnaires or certain cognitive tests). However, it is the purpose of the feasibility study to assess these issues.

5.3 Conclusion

This innovative, translational study explores stress-related SLI in CD/FND patients and the feasibility of an anticipated larger project aiming to develop new treatments for this vulnerable population.

Abbreviations

ACE Adverse Childhood Experience

ANG2 Angiopoietin-2

CD Conversion Disorder

CRF Case Report Form

fMRI functional Magnetic Resonance Imaging

FND Functional Neurological Disorder

HCP Health Care Professional

hsCRP high sensitivity C-Reactive Protein

ICD-11 International Classification of Disease 11th Edition

IL1b Interleukine1b

IL6 Interleukine 6

IFNg Interferon gamma

IRAS Integrated Research Application System

miR-146a, miR-155, miR-223, miR-21, and miR-132 micro RiboNucleic Acid (microRNA)

NHS National Health Service

PTSD Post Traumatic Stress Disorder

REC Research Ethics Committee

SAE Serious Adverse Event

SLI Systemic Low-grade Inflammation

TEWV Tees, Esk and Wear Valleys NHS Foundation Trust

TNF Tumor Necrosis Factor

VEGF Vascular Endothelial Growth Factor

Declarations section:

Ethics approval and consent to participate

The study has been designed and will be carried out in accordance with the principles laid down in the Helsinki declaration (2013). Participation in the study is voluntary. Written informed consent will be obtained from all patients and the patients will be explicitly informed about the fact that they can withdraw their consent to participate at any time, without any specific reason and with no negative consequences with regard to their future medical treatment. Patients who wish to withdraw from the study will continue to receive usual care. In addition, patients are informed which independent person is available in case of concerns. Patient names and other confidential information will be treated according to the medical confidentiality rules, and data will be separated from patient names. Each participant will be identified in the database by a number and a code, and these codes are only available to the participating investigators. Furthermore, data related to the study are stored on a protected server of the University of York, which can only be accessed by the members of the research team. This study has been reviewed and approved by the NHS North West 11 Research Ethics Committee, Preston. IRAS nr. 261252.

Competing interests: none reported

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Authors' contributions: CFC, DL, MW, SA and SB designed the study; SB, SA, CC and CFC were involved in study management and writing of protocol; SA was involved in writing draft paper; SA, LdV and CC contributed on protocol how to collect and interpret neurocognitive data; JR and CFC on how to undertake psychiatric examination; All authors approved the final draft of the paper.

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References

1. Gelauff J, Stone J, Edwards MJ, Carson A. The prognosis of functional (psychogenic) MOTOR symptoms: a systematic review. J Neurol Neurosurg Psychiatry. 2014;85(2):220-6

2. Van der Feltz-Cornelis CM. [The conversion disorder in the DSM-5: what's in a name?]. Dutch. TijdschrPsychiatr. 2015;57(8):577-8.

3. Kroenke K. Efficacy of treatment for somatoform disorders: a review of randomized controlled trials. Psychosomatic Medicine, 2007 Dec; Vol 69 (9), pp 881-8. 2007.

4. Mace CJ, Trimble MR. Ten-Year Prognosis of Conversion Disorder. British Journal of Psychiatry. 1996;169:282-8.

5. Ruddy R HA. Psychosocial interventions for conversion disorder. Review. Cochrane Database Syst Rev 2005;4:CD005331. .

6. Viljoen M, Panzer A. Non-termination of sickness behavior as precipitating factor for mental disorders. Med Hypotheses. 2005;65(2):316-29.

7. Del Grande da Silva G, Wiener CD, Barbosa LP, Gonçalves Araujo JM, Molina ML, San Martin P, et al. Pro-inflammatory cytokines and psychotherapy in depression: Results from a randomized clinical trial. J Psychiatr Res. 2016;75:57-64.

8. Vogelzangs N, de Jonge P, Smit JH, Bahn S, Penninx BWP. Cytokine production capacity in depression and anxiety. Translational Psychiatry. 2016;6:e825.

9. Kovacs D, Eszlari N, Petschner P, Pap D, Vas S, Kovacs P, et al. Interleukin-6 promoter polymorphism interacts with pain and life stress influencing depression phenotypes. J Neural Transm (Vienna). 2016;123(5):541-8.

10. Lea Ludwig JAP, Timothy Nicholson, Selma Aybek, Anthony S David, Sharon Tuck, Richard A Kanaan, Karin Roelofs,, Alan Carson JS. Stressful life events and maltreatment in conversion (functional neurological) disorder: systematic review and meta-analysis of case-control studies. Lancet Psychiatry.5:: 307–20.

11. Association AP. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. ed. Arlington, VA: American Psychiatric Publishing; 2013 2013.

12. Hassa T, De Jel E, Tuescher O, Schmidt R, Schoenfeld MA. Functional networks of MOTOR inhibition in conversion disorder patients and feigning subjects. Neuroimage Clin. 2016;11:719-27.

13. Ejareh Dar M, Kanaan RA. Uncovering the etiology of conversion disorder: insights from functional neuroimaging.Review. Neuropsychiatr Dis Treat. 2016;12:143-53.

14. de Vroege LK, D; Foruz,A.; van der Feltz-Cornelis,C.M.; . Cognitive rehabilitation treatment for mental slowness in conversion disorder: A case report. . Cogent Pychology. 2017;4(1).

15. Staufenbiel SM PB, Spijker AT, Elzinga BM, van Rossum EF. Hair cortisol, stress exposure, and mental health in humans: a systematic review. Psychoneuroendocrinology 2013;38 (8):1220-35.

16. Busner JT, SD;. Clinical Global Impressions Scale. Applying a Research Tool in Clinical Practice. Psychiatry (Edgmont) 2007;4 (7):28–37.

17. WHO. Adverse Childhood Experiences International Questionnaire (ACE-IQ) 2018 [updated 2018. Available from: http://www.who.int/violence_injury_prevention/violence/activities/adverse_childhood_experiences/en/.

18. Holmes TH, Rahe RH. The social readjustment rating scale. Journal of Psychosomatic Research. 1967;11:213-8.

19. Schlotz W YI, Zoccola PM, Jansen L, Schulz P. . The perceived stress reactivity scale: Measurement invariance, stability, and validity in three countries. . Psychol Assessment. 2011;23 (1):80. .

20. Levenstein S PC, Varvo V, Scribano ML, Berto E, Luzi C, Andreoli A. . Development of the Perceived Stress Questionnaire: a new tool for psychosomatic research. J Psychosom Res 1993;37(1):19-32.

21. (CBS). CBoS. Netherlands Central Bureau of Statistics (CBS) list. CBS vademecum. Den Haag:: CBS; 2005 2005.

22. Hemert AM, de Waal MW, Van Rood YR. Meetinstrumenten bij somatoforme stoornissen. Tijdschrift voor Psychiatrie. 2004;46(10):693-6.

23. Kroenke K, Spitzer RL, Williams JBW, Löwe B. The Patient Health Questionnaire somatic, anxiety, and depressive symptom scales: A systematic review. General Hospital Psychiatry. 2010;32:345-59.

24. Wechsler D. Wechsler adult intelligence scale – Fourth edition (WAIS-IV). . San Antonio, TX.: NCS Pearson.; 2008.

25. Reitan RM. Trail making test: Manual for administration and scoring.Tucson, AZ: Reitan Neuropsychology Laboratory.; 1992.

26. Stroop, J.R. Factors affecting speed in serial verbal reactions. Psychological monographs. 1938.50(5),38.

27. Shallice, T. Specific impairments of planning. Philosophical Transactions of the Royal Society of London. 1982. 298, 199-209.

28. Organization WH. The ICD-10 classification of mental health and behavioural disorders: clinical descriptions and diagnostic guidelines. Second edition ed. Geneva: World Health Organization; 1993 1/1/1993.

29. Jon Stone MH, Alan Carson, Donna Bergen, Raad Shakir. Functional disorders in the Neurology section of ICD-11. A landmark opportunity. Neurology. 2014;83(24):2299–301.

30.Luciano M. The ICD-11 beta draft is available online. World Psychiatry. 2015;14(3):375-6.

31.WHO. WHO releases new international classification of diseases (ICD-11): WHO; 2018 [updated 18/06/2018.

32. Organisation WH. International Classification of Diseases -11 (ICD-11) 2019.

33. Van der Feltz-Cornelis CM, van Dyck R. The notion of somatization: an artefact of the conceptualization of Body and Mind. Psychother Psychosom. 1997;66(3):117-27.

34. Daum C, Gheorghita F, Spatola M, Stojanova V, Medlin F, Vingerhoets F, Berney A, Gholam-Rezaee M, Maccaferri GE, Hubschmid M, Aybek S. Interobserver agreement and validity of bedside 'positive signs' for functional weakness, sensory and gait disorders in conversion disorder: a pilot study. J Neurol Neurosurg Psychiatry. 2015;86(4):425-30.

Table 1. Table used by clinicians to enable the detailed description of the phenomenology from the perspective of possible cerebellar involvement in CD patients

Please specify:	
No movement possible	Yes/NO
Abnormal Movement	Yes/NO
Tremor	Yes/NO Type
Body Part: …	
Left / right	
Speech disorder	YES/NO
Presenting complaint When How long Acute/insidious After Panic attack After pain After injury	 … … … YES/NO YES/NO YES/NO
History presenting complaint + history psychiatric history medical history + medication family history family psychiatric history premorbid personality	
Cerebellar ataxia equivalents	
Balance **Numbness** **Paralysis** **Tremor**	YES/NO YES/NO YES/NO YES/NO
Ataxic dysartria	**Speech** YES/NO **Swallowing** YES/NO
Oculocerebellar dysfunction	**Visual disturbances** YES/NO **Nystagmus** YES/NO
Cerebellum – LIPT (Arteria Inferior Cerebellar Artery)	**Sudden deafness** YES/NO **Vertigo** YES/NO
Cerebellar cognitive/affective syndrome (CCAS)	**Concentration** YES/NO **Memory** YES/NO
MMSE	Score and interpretation

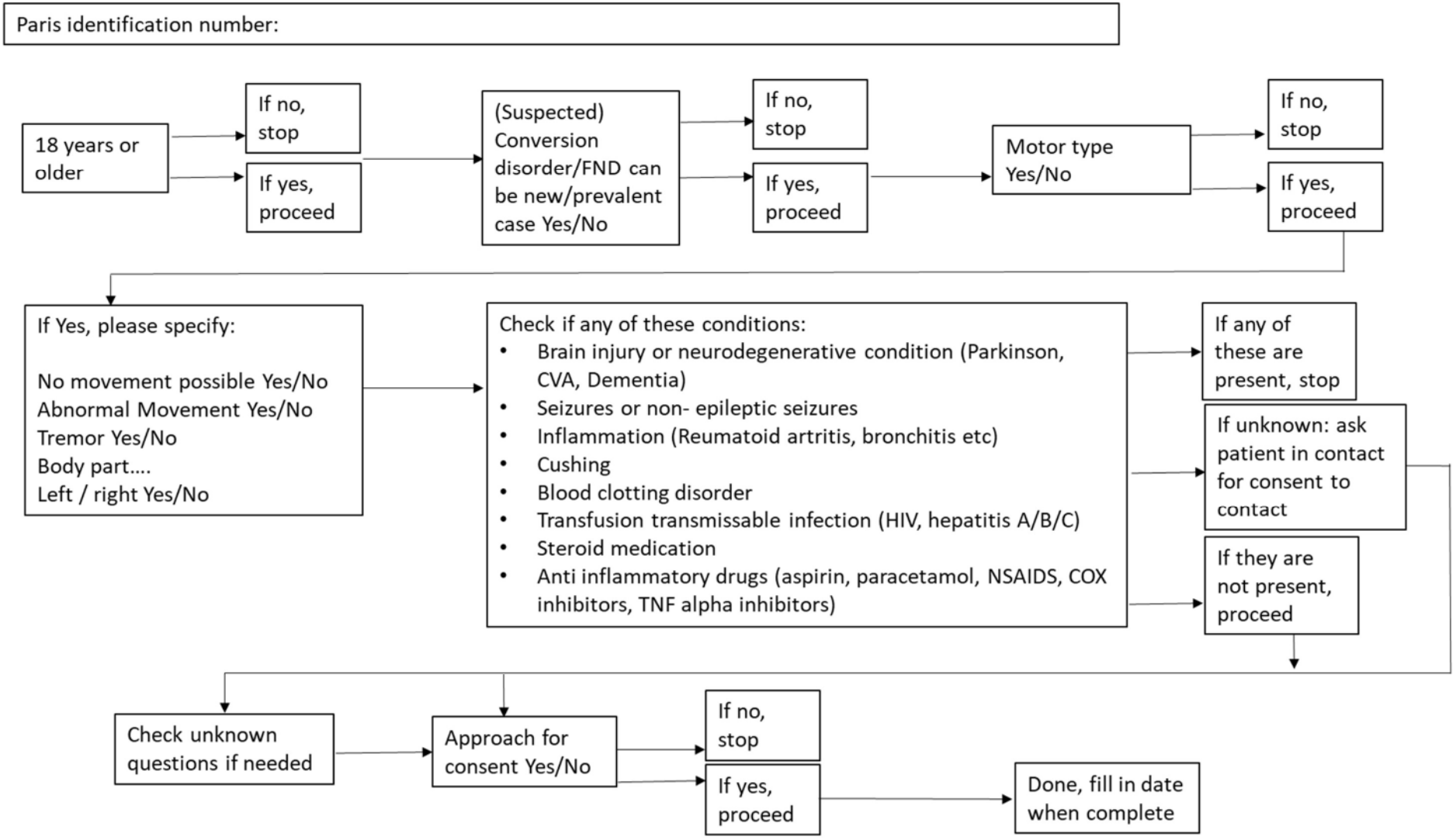

Figure 1. Patient Eligibility Flowchart

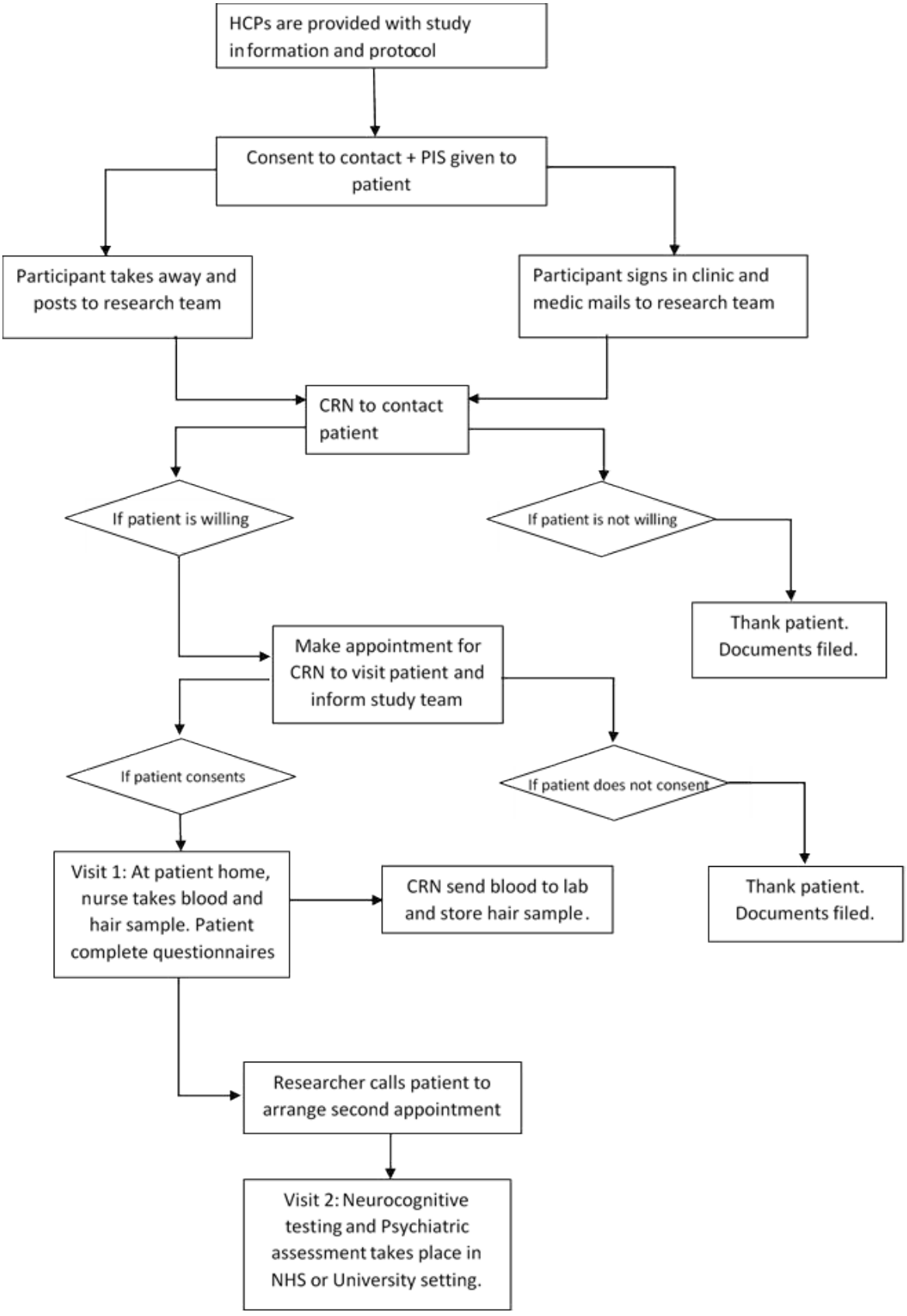

Figure 2. Patient Timeline Flowchart