Association between neurofibromatosis type 1 and cerebrovascular diseases in children: a systematic review

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Running head: NF-1 and cerebrovascular disease in children

ABSTRACT

Background: Neurofibromatosis type 1 (NF-1) is an autosomal dominant disease that affects one in every 3000 individuals. This disease can present a wide range of clinical manifestations, ranging from skin abnormalities to severe vascular changes. Although little recognized, cerebrovascular diseases (CVD), often present since childhood and diagnosed late, may have clinical manifestations ranging from headache and cognitive deficits to aneurysm rupture causing death. Thus, the CVD play an important role in the clinical manifestations, the severity of the condition and the prognosis of patients with NF-1. This systematic review aims to summarize the body of evidence linking NF-1 and CVD the in children.

Methods: Two independent reviewers performed a systematic review on the PubMed and EMBASE search platforms, using the following key terms: “neurofibromatosis type 1”, “recklinghausen disease”, "children", "adolescents", "stroke", "moyamoya disease", "vascular diseases", "cerebrovascular disorders", "aneurysm" and "congenital abnormalities". Studies focused on assessing the development of CVD in children with NF-1 were included.

Results: Seven studies met the inclusion criteria. Twelve different clinical manifestations have been associated with cerebrovascular changes in children with NF-1; 44,5% of diagnosed patients were asymptomatic.

Conclusion: The available evidence suggests that cerebrovascular diseases are related with the progression of NF-1, even in the absence of a clear clinical manifestation. In addition, better prognosis was observed when imaging tests were performed to screen for cerebrovascular changes. This generated early interventions and consequently more favorable outcomes.

Key words: Neurofibromatosis type 1; Cerebrovascular diseases; Children, Moyamoya.

INTRODUCTION

Neurofibromatosis type 1 (NF-1) is an autosomal dominant, chronic and progressive disease [1] with an incidence of approximately 1:3000 individuals and almost half of the cases of hereditary origin (familial NF) [2]. The alteration in the *NF1* gene, located at chromosome 17 q11.2, is responsible for the inability to synthesize the neurofibromin cytoplasmic protein, which acts as a modulator in cell growth and differentiation since uterine life, and which is expressed in the nervous system, endothelium and smooth muscle cells of blood vessels. The gold-standard diagnosis can be achieved through molecular genetic testing, which is related to high cost and low availability in the public health system [3] Frequently, diagnosis is based on the presence of two or more criteria that encompass the main clinical manifestations of the disease and that were established by the National Institutes of Health (NIH) Consensus Development Conference [4]. NF-1 is constantly associated with vasculopathy and cerebrovascular abnormalities of pathophysiology that is still not understood [5-7]. Several cases have been reported in children, but the incidence of cerebrovascular diseases (CVD) associated with complications and the long-term impacts on these individuals is still poorly recognized, which warrants more studies on the topic [8].

There are multiple case reports in the literature of individuals with NF-1 that developed cerebrovascular diseases (CVD) [9] and heterogeneous neurological manifestations and several complications are present in this association [10] , which generates great morbidity and mortality in patients with this genetic condition [11]. The association of NF-1 with CVD is described to result in a range of pathologies, such as cerebral ischemia,

aneurysms and *Moyamoya* Syndrome (MMS). The latter, in turn, is characterized by progressive stenosis or occlusion of the internal carotid artery and its branches. For this reason, although lack of full knowledge regarding the natural history, symptoms, etiology and management of such syndrome, it is already known that routine vascular screening/assessment in NF-1 patients is necessary for early identification of this condition [12] . Using such approach, CVD in patients with NF-1 can be diagnosed since childhood. However, this diagnosis is often delayed, as not all children with NF-1 undergo neuroimaging tests [13]. Furthermore, CVDs are still one of the major causes of death, with almost six million people annually [14], aside from being associated with significant morbidity worldwide, which makes them an important public health problem [15]. When CVD are detected early, proper clinical management is able to minimize its impact on adult life [11].

Therefore, detailed studies on the association between NF-1 and CVD are still needed [16]. In this present study, we performed a systematic review to summarize the body of evidence on the association between NF-1 and the development of CVD in children. Increasing knowledge in this field can drive development of more effective protocols to optimize diagnosis and therapy to reduce both mortality and the number of hospitalizations of these patients.

MATERIALS AND METHODS

Ethics statement

There were no patients directly involved in the research. The present study used publicly data from previously published studies to perform a systematic review. All information given to the research team was de-identified. Thus, the study was exempted from revision by the Institutional Review Board of the Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, Brazil, and did not require signed consent forms.

Search Strategy

A systematic review of NF-1 and its association with CVD in children aged between 0 to 18 years old was performed, in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) report. Two independent reviewers (BBD and FHAG) conducted the research in the following databases: PubMed and EMBASE

The keywords used in the research were: "neurofibromatosis type 1", "recklinghausen disease", "children", "adolescents", "stroke", "moyamoya disease", "vascular diseases", "cerebrovascular disorders", "aneurysm", "congenital abnormalities". The search strategy used in PubMed and EMBASE is presented in the supplementary file 1. All articles published in English were searched, without time or population restriction of the study. Initially, titles and abstracts were read by the reviewers (Fig 1) and systematic reviews, letters to the editor, case reports and comments were excluded. We did an additional manual search of the reference lists from selected articles to identify eligible publications

that may not have appeared in our electronic search strategy. The search was conducted on May 15, 2020. This review was registered in the PROSPERO International Registry (registration number: CRD42020180942).

Fig 1: Flowchart of the study selection process study characteristics. Abbreviations: CVD: cerebrovascular disease.

Data Extraction

Inclusion criteria were: (1) cross-sectional, cohort or case-control studies; (2) studies focusing on NF-1 cerebrovascular disorders; (3) studies carried out with children (from 0 to 18 years old) and (4) studies in which the diagnostic criteria for NF-1 recommended by the NIH were used. Articles in a language other than English, duplicated or not yet published, as well as studies that were not about CVD in patients with NF-1 or that presented cerebrovascular events associated with trauma, neoplasia, radiation treatment or use of medications were excluded. The selection of the studies was divided into 4 steps: 1 reading of the titles, (2) reading of the article abstracts, (3) evaluation of the full articles selected from the previous step and inclusion of other studies present in the reference lists of the selected articles, (4) selection of the studies to include in the systematic review. Data extraction was performed independently by two authors (BBD and FHAG) and the discrepancies between the reviewers were resolved by consensus after discussion with more experienced authors (MBAG, BBA). A table for data extraction was built by each reviewer before writing the manuscript. The table included information on all relevant variables in each retrieved study.

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150 **Data Analysis**

151 All studies addressed the following variables to assess the relationship between NF-1
152 and CVD in children: age at diagnosis of NF-1, age at the time of image examination to
153 identify CVD, cerebrovascular alteration found, affected vessels, method used for the
154 diagnosis of NF-1, type of image examination performed, associated clinical
155 manifestations and neurosurgery indication(Table 1).

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157 **Quality Assessment**

158 The methodological quality of the studies included in the meta-analysis was assessed
159 using the Newcastle-Ottawa Scale (NOS) (Table 2) [17]. NOS scores of 0–3, 4–6 and
160 7–9 were considered to be low, moderate and high quality, respectively. The overall
161 methodological quality was then summarized based on the observed quality trends.

162

163 **Table 1.** Summary and characteristics of the articles

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Study (author, year)	Country	Type of study	Sample size	Age of patients at NF1 diagnosis	Age of patients at image study	Cerebrovascular alteration	Afected vessel	Image study used	Diagnosis os NF1	Clinical manifestations	Neurosurgery
(Rosser et al., 2004)	United States of America	Case Series	Total (353); MRI (316); Vasculopathy (8)	Mean, 1.4 years	Mean, 7.3 years	Stenosis / occlusion, cerebral ischemia, ectasia, Moyamoya, aneurysm and hypoplasia	PCA, ICA and MCA	MRI, MRA and Conventional Angiography	NIH diagnostic criteria[a]	Hemiparesis (1), seizure (1) and asymptomatic (7)	3 patients (exploratory surgery, encephaloduroarteriosynangiosis and pial synangiosis)
(Cairns et al, 2008)	Australia	Case series	Total (698); MRI (144) ; Vasculopathy (7)	Ranged from 18 months to 5 years	Mean, 6.8 years	Hypoplasia, stenosis/occlusion, collateral vessels	ACA, MCA, PCoA, ICA and PCA	MRI, MRA and Conventional Angiography	NIH diagnostic criteria[a]	Asymptomatic (5), seizure (1), hemiparesis (1), paraesthesia (1) and TIA (1)	1 patient (pial synangiosis)
(Rea et al, 2009)	Canada	Retrospective Cohort	Total (419) ; MRI (266); Arteriopathy (17)	Median, 2 years	Median, 5.2 years (7 children) Median, 5.3 years (10 children)	Stenosis / occlusion, aneurysm, Moyamoya	ICA, MCA and ACA	MRI, MRA, CT, angio-CT and Conventional Angiography	NIH diagnostic criteria[a]	Seizure (3), hemiparesis (1), speech delay (2), Bell's palsy (1), learning disability (4), paraesthesia (1), weakness (2), hyperreflexia (2), ADD (1)), hyperphagia (1), episodic dysphasia (1), infantile spasms (1), hypertonia (1), clonus (1), ptosis (1), RAPD (1), hemibalism (1), dystonia (1), aphasia (1), AIT (1) and fine motor delay (1).	6 patients (pial synangiosis)

(Ghosh et al, 2012)	United States of America	Case Series	Total (398); MRI (312); MRA (143); Vasculopathy (15)	Mean, 4.3 ± 3.5 years	Mean, 11.7 SD ± 7.3 years	Stenosis/occlusion, cerebral ischemia, Moyamoya	ICA, MCA, PCA and VA	MRI, MRA, angio-CT and Conventional Angiography	NIH diagnostic criteria[a]	Headache (5), seizure (2) and asymptomatic (7)	1 patient (encephaloduroarteriomyosynangiosis procedure)
(Kaas et al, 2012)	United States of America	Cross Sectional	Total (181); Neuroimaging (77); cerebral vasculopathy (12)	Median 8 years (n=14)	Ranged from 3 to 13 years	Moyamoya, stenosis/occlusion, tortuosity, elongation, displacement, developmental venous anomaly	ACA, MCA, ICA, PCA and VA	MRI, MRA, Conventional Angiography	NIH diagnostic criteria[a]	Weakness (1), reduced responsiveness (1) and asymptomatic (10)	3 patients (2 - revascularization surgery)
(Han et al, 2014)	China	Case Series	Total (6)	Median, 2.7 ± 2.1 years	Mean, 11.4 SD ± 8.3 years	Moyamoya, stenosis / occlusion, intracerebral hemorrhage	ICA, MCA and ACA	MRI, MRA, DSA, SPECT (Conventional digital subtraction angiography, Brain perfusion single-photon emission computerised tomography	NIH diagnostic criteria[a]	TIA (3), headache (1), intracerebral hemorrhage (1) and cerebral ischemia (1)	5 patients (Revascularization surgery)
(Santoro et al, 2017)	Italy/France	Retrospective cohort	Total (18)	Mean, 2.93 SD± 3.03 years	Mean, 7.43 SD ± 4.27 years	Stenosis/occlusion	MCA, ACA and PCA	MRI, MRA and DSA	NIH diagnostic criteria[a]	Hemiparesis (2), seizure (2), headache (6) and asymptomatic (8)	11 patients (revascularization surgery)

Table Note: [a]National Institutes of Health (NIH) Consensus Development Conference diagnostic criteria: consists of the presence of two or more of the following characteristics - six or more cafe au lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in post pubertal individuals; two or more neurofibromas of any type or one plexiform neurofibroma; freckling in the axillary or inguinal regions; optic glioma; two or more Lisch nodules (iris

hamartomas); a distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis and a first-degree relative (parent, sibling, or offspring) with NF-1 by the above criteria.

Abbreviations: NF-1:Neurofibromatosis Type 1; PCA: posterior cerebral artery; MCA: middle cerebral artery; ACA: anterior cerebral artery; ICA: internal carotid artery; PCoA: posterior communicating artery; VA: vertebral artery; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; CA: conventional angiography; CT: computed tomography; angio-CT: computed tomography angiography; DSA: digital subtraction angiography; SPECT: Brain perfusion single-photon emission computerized tomography; TIA: transient ischemic attack; RAPD: DPAR: relative afferent pupillary defect; ADD: attention deficit disorder; SD: standard variation

Table 2: Quality Assessment of Studies Included in the Systematic Review by Newcastle Ottawa Scale.

		Selection				Comparability		Outcome/Exposure			Overall
Source	Newcastle Ottawa Scale	1	2	3	4	5A	5B	6	7	8	Score[a]
(Kaas et al, 2012)	Cross-Sectional	0	*	*	**	N/A	N/A	**	0	N/A	6
(Santoro et al, 2017)	Retrospective Cohort	*	0	*	*	*	N/A	*	*	*	7
(Rea et al, 2009)	Retrospective Cohort	*	0	*	*	N/A	N/A	*	*	N/A	6

Table Note: *Indicates the score given to the study according to the NOS quality assessment scale.

Abbreviations: NA, not applicable;

[a] Determined by the total number of stars assigned to the study: 0–3 stars = poor; 4–5 stars = fair; 6–7 stars = good; 8–9/10 stars = excellent.

RESULTS

Study characteristics and quality evaluation

Initially, 243 studies were selected from the main database search. After detailed review, 70 duplicates were removed and 166 articles were excluded: 83 did not address CVD, 5 addressed CVD triggered by other factors, such as a particular medicine or neoplasms, 18 were case reports, 4 were letters to the editor and 2 were brief communications (Figure 1). Subsequently, 6 other studies were excluded for not being performed in humans, 9 for not being performed in children, 27 were not found or published and 2 were in a language other than English (Polish and German) (Fig 1). Finally, 10 studies that did not provide sufficient clinical data on the pediatric population were still excluded. The remaining studies (7), which describe NF-1 associated with CVD in children, were included in this review. Fig 1 summarizes the article selection process.

Among the seven selected studies, 2 had a medical record review project (retrospective cohort) 1 was a cross-sectional study and 4 were series of cases. In all of them, the NF-1 diagnostic criterion used was that developed by the NIH. Moreover, the eligible studies (cohort and cross-sectional) for the evaluation of the Newcastle-Ottawa Scale (NOS) were of good quality presenting between 6-7 stars (Table 2). Such studies were performed out in six different countries: one in Australia, one in Canada, one in China, one in Italy and France and three of them in different cities in the United States of America (Washington DC, Cleveland and Baltimore) (Fig 2).

Fig. 2: Distribution of studies used around the world.

Cerebrovascular alterations presented higher frequency at Willis polygon

In this review, we detected 12 types of cerebrovascular changes significantly associated with NF-1 and / or disease progression in children (Table 1). In six of the seven studies the internal carotid artery was the most affected vessel among patients: 75% in the study by Rosser et al., 80% in the study by Ghosh et al., and 100% in the studies by Read et al., Kaas et al., Han et al. and Santoro et al. In the study by Cairns et al. the most affected vessels were those of the Willis polygon (85,7% of patients) (Table 1 and Fig 3).

Fig. 3: **Flow diagram summarizing the main results of the systematic review.** Abbreviations: NF-1:Neurofibromatosis Type 1; MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; CA: conventional angiography; CT: computed tomography; angio-CT: computed tomography angiography; SPECT: Brain perfusion single-photon emission computerized tomography.

Radiologic investigation

The diagnosis of NF-1 was performed prior to brain imaging exams in all studies, showing that many CVDs could have been previously diagnosed, which possibly would prevent complications or more invasive treatments. The most frequently performed imaging tests were Magnetic Resonance Angiography (MRA) and Magnetic Resonance Imaging (MRI) performed in 100% of the studies evaluated followed by Conventional Angiography (CA) - 71.4%, Computed Tomography Angiography (Angio-CT) and Digital Substraction Angiography DSA - 28.5% each and finally Brain Perfusion Single-photon Emission Computerized Tomography (SPECT) and Computed Tomography (CT) - 14.2% each. (Table 1 and Fig 3).

The heterogeneous spectrum of clinical manifestations and delays in diagnosis of CVD

NF-1 has been closely associated with *MMS* vasculopathy in five studies and its presentation is related to worse outcomes and more evident clinical manifestations. In the study by Rea et al., It was possible to correlate NF-1 with the difficulty of developing cognitive functions such as reading, speaking and the ability to maintain attention. Furthermore, in the study by Ghosh et al, five of the fifteen patients evaluated presented headache as the only clinical manifestation that could indicate CVD. Thus, headache is possibly an important warning sign in this population.

In general, the clinical manifestations found were very heterogeneous (Fig 3). Patients with a history of paresthesia, seizures, and even severe strokes were observed, among other manifestations. However, it is important to note that until the time of diagnosis of CVD, 44,5% of the patients were asymptomatic, which shows the importance of screening in childhood. Furthermore, the type of surgery most reported in the studies evaluated was *pial synangiosis* surgery (five of seven studies) followed by revascularization surgery (three of seven studies) (Fig 3). In the study by Santoro *et al*. patients who underwent surgical treatment (50%) exhibited global clinical stability.

DISCUSSION

NF-1 is a rare, autosomal dominant disease [18], which has a strong relationship with vascular malformations [19] and whose first symptoms commonly appear in childhood [20]. Such vascular alterations, although they can occur in any part of the child body [8], have a greater severity when presented in the central nervous system (CNS) [10]. For this reason, knowledge of the association between NF-1 and cerebrovascular diseases triggered by this disease can contribute to a better understanding of the pathophysiology of NF-1 manifestations in the CNS, as well as guide development of novel approaches to prevent cerebrovascular events in children with NF-1. This systematic review demonstrated that the use of early imaging methods is associated with early interventions and, consequently, more favorable outcomes, even in previously asymptomatic children.

Our search identified that all studies selected for systematic analysis reported that some artery of the Willis polygon was affected [9, 11-13, 21, 22] , of which the internal carotid artery is shown as the main site of alteration among all evaluated patients. Importantly, the branches generated by the internal carotid artery are the middle cerebral artery and anterior cerebral artery [23] , responsible for predominantly motor and somatosensory deficits [24]. Thus, the manifestations presented can vary from a focal motor deficit to an aphasia [13] , which makes early diagnosis difficult [25] since depending on the age of the child communication is still not effective and motor skills has not well-developed. Therefore, it is crucial that more studies are developed to assess the need for periodic screening in this group through brain imaging.

Of note, approximately 44.5% of the patients were asymptomatic at the time of the imaging exam, which showed vascular changes and rises the need of early screening. At first glance, this fact counts against the NIH NF-1 management manuals since brain imaging is only indicated in the presence of symptoms. In addition, in the study by Ghosh et al, 33.4% of the patients evaluated presented headache as the only symptom, which can be justified by the fact that the most common vascular alteration reported in all studies was arterial stenosis / occlusion. Moreover, the comparison between the selected studies about children with NF-1 and cerebrovascular diseases revealed that the earlier the imaging tests are performed, even when the children are asymptomatic at the time of the examination could contribute to better interventions. This corroborates the hypothesis that the performance of periodic and early examinations can impact on morbidity and mortality and on the quality of life of children with NF-1.

The available evidence allowed us to conclude that neurological manifestations of NF-1 in the pediatric group are heterogeneous and difficult to diagnose clinically, and in most cases, it is necessary to perform a complementary imaging test. In addition, when these manifestations are associated with MMS the children have a worse prognosis [22]. Notably, *MMS* is described with the severity of symptoms presented by children [12], what can be seen in six of the seven studies evaluated. Moreover, the neurosurgery most performed by the studies was pial synangiosis surgery, widely used for the treatment of *MMS* and reduction of its clinical manifestations. An important observation is that the surgical interventions performed were also more successful when associated with early imaging tests, which corroborates the idea of early screening for recognition of vascular

malformations on the CNS. The tests most used by the studies evaluated were MRA and MRI, although there is no consensus on which is best test to be performed or the periodicity established for that execution.

Our study has important limitations. Some studies did not contain sufficient information about the pediatric group, not allowing an adequate assessment. In addition, most studies are only descriptive, not performing statistical analysis of the data presented, which made it impossible to perform a meta-analysis. It is also important to highlight the low availability and quality of the studies carried out about this theme, which present a very variable number of patients and a little detailed analysis of each individual patient, which made comparisons between groups difficult. Besides, due to the small amount of evidence available, it was necessary to use the series of cases, which brings an important limitation since we were unable to apply an adequate quality scale to the studies. In addition, the available data on the chronology of the imaging exams and the reason for the indication of one method within the other is very scarce, which makes it difficult to interpret these parameters. Despite this, as it is a rare disease that affects 1 in every 3000 live births [26]and has major complications[10], we believe that this systematic review reaches the proposed ideas.

The results of this systematic review show that the possible implementation of screening measures using imaging methods has the potential to improve the early diagnosis of cerebrovascular alterations in children with NF-1 as well as early intervention. This could potentially reduce the number of deaths and sequelae caused by the diagnosis of

vascular change only when an injury is already installed. Even so, more robust and better-quality studies are needed to clarify the frequency and which exams should be recommended within each age group. An evaluation of imaging methods in isolation and in conjunction with clinical parameters is necessary in order to draw a better line of care for these children since birth.

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Availability of data and materials: The datasets used and/or analyzed during the current study are all publicly available.

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Figure 2

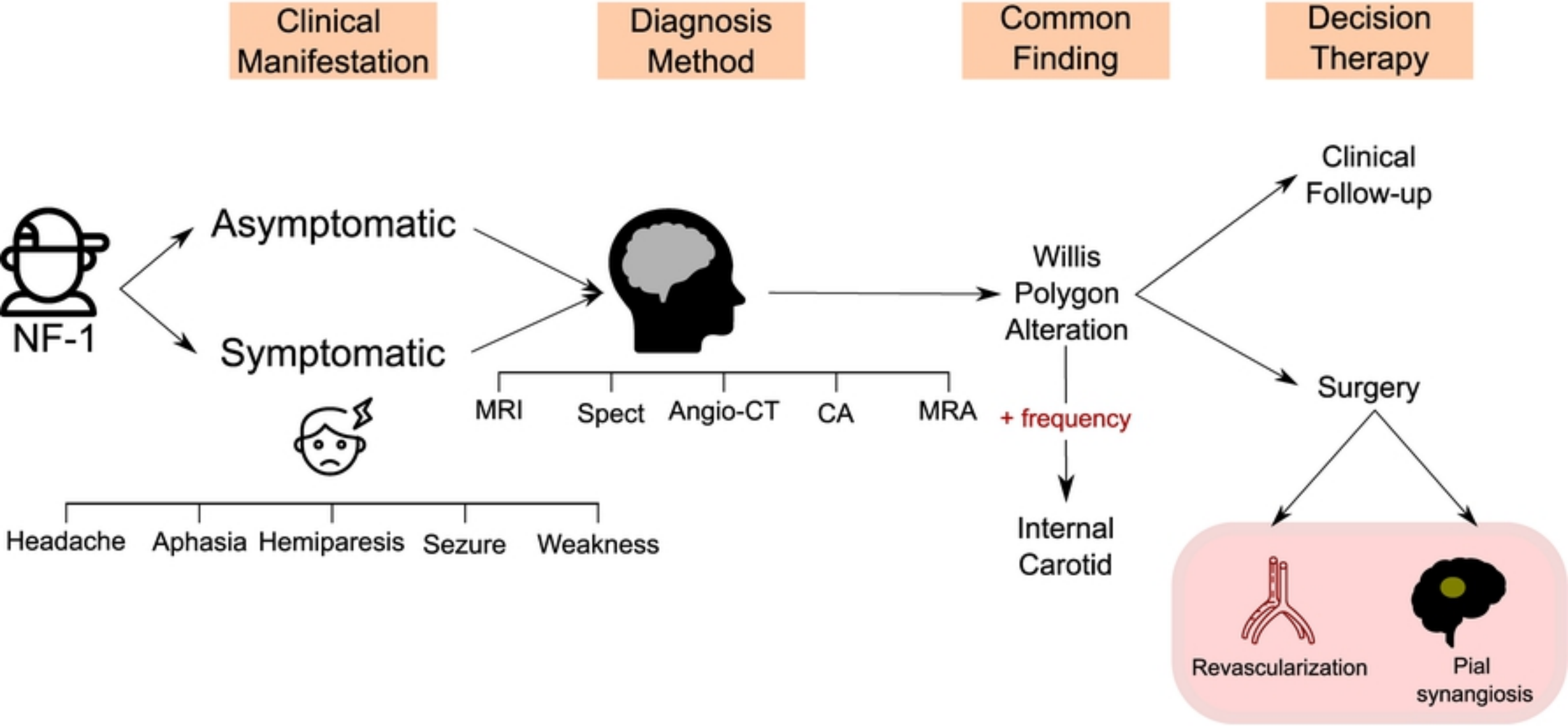
Clinical Manifestation
Diagnosis Method
Common Finding
Decision Therapy
NF-1
Asymptomatic
Symptomatic
Headache
Aphasia
Hemiparesis
Sezure
Weakness
MRI
Spect
Angio-CT
CA
MRA
Willis Polygon Alteration
+ frequency
Internal Carotid
Clinical Follow-up
Surgery
Revascularization
Pial synangiosis

Figure 3

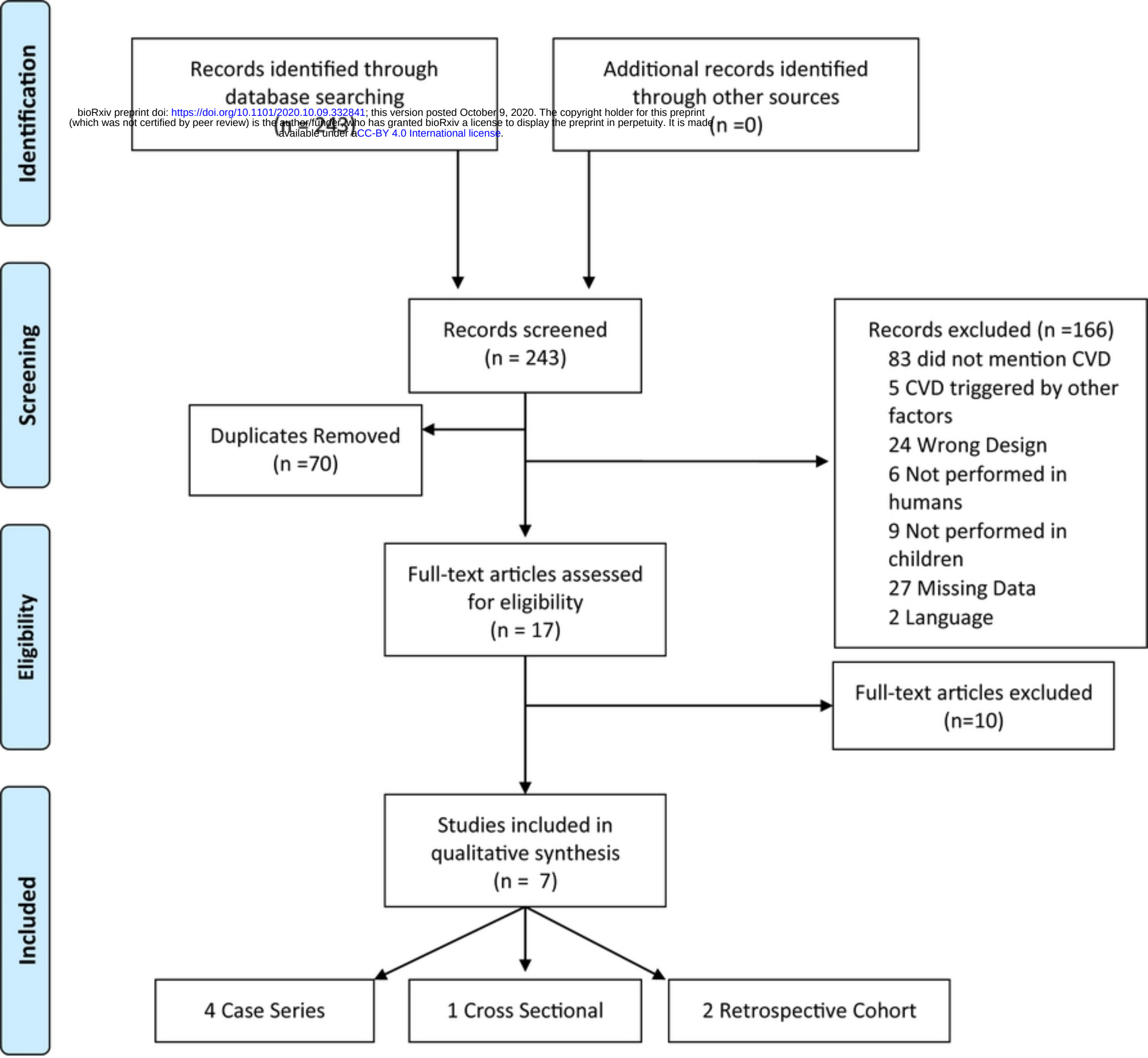

Figure 1