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Original Article

Seizure in Neurodegeneration with Brain Iron Accumulation: A Systematic Review

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ABSTRACT: ***Background:*** Neurodegeneration with brain iron accumulation (NBIA) is a rare genetic disorder. Its clinical manifestations comprise a wide spectrum mainly movement disorders. Seizure as a clinical manifestation is known to occur in some NBIAs, but the exact prevalence of epilepsy in each individual disorder is not well elucidated. The aim of this review was to investigate the frequency of seizures in NBIA disorders as well as to determine the associated features of patients with seizures. ***Method:*** The electronic bibliographic databases PubMed, Scopus, Embase, and Google Scholar were systematically searched for all cases in any type of article from inception to December 16, 2019. All the reported cases of NBIA (with or without genetic confirmation) were identified. Case reports with an explicit diagnosis of any types of NBIA, which have reported occurrence (or absence) of any type of seizure or epilepsy, in the English language, were included. Seizure incidence rate, type, and age of onset were reported as frequencies and percentages. ***Result:*** 1698 articles were identified and 51 were included in this review. Of 305 reported cases, 150 (49.2%) had seizures (phospholipase A2-associated neurodegeneration (PLAN) = 64 (50.8%), beta-propeller protein-associated neurodegeneration (BPAN) = 57 (72.1%), pantothenate kinase-associated neurodegeneration (PKAN) = 11 (23.4%), and others = 18 (very variable proportions)). The most frequent seizure type in NBIA patients was generalized tonic-clonic seizure with the mean age of seizure onset between 2 and 36 years. However, most of these papers had been published before the new classification of epilepsy became accessible. Affected patients were more likely to be females. ***Conclusion:*** Seizures are common in NBIA, particularly in PLAN and BPAN. In PKAN, the most common type of NBIA, around 10% of patients are affected by seizures. BPAN is the most possible NBIA accompanying seizure. Most of the findings regarding the seizure characteristics in the NBIAs are biased due to the huge missing data. Therefore, any conclusions should be made with caution and need further investigations.

RÉSUMÉ : Crises convulsives associées à la neuro-dégénérescence avec accumulation de fer dans le cerveau : une revue systématique. ***Contexte :*** La neuro-dégénérescence avec accumulation intracérébrale de fer (« NBIA » en anglais) constitue un trouble génétique peu fréquent. Ses manifestations cliniques composent un large spectre, pour l'essentiel des troubles du mouvement. De plus, on sait désormais que des crises convulsives sont une manifestation clinique de certains cas de NBIA ; toutefois, la prévalence exacte de l'épilepsie pour chaque cas individuel n'a pas encore été bien élucidée. L'objectif de cet article est donc d'étudier la fréquence des crises convulsives associées à la NBIA et de déterminer les caractéristiques des patients présentant de telles crises. ***Méthodes :*** Nous avons ainsi interrogé de façon systématique les bases de données bibliographiques électroniques PubMed, Scopus, Embase et Google Scholar pour tous les cas de NBIA et dans tous les types d'articles, et ce, de la création de ces bases jusqu'au 16 décembre 2019. Tous les cas signalés de NBIA, avec ou sans confirmation génétique, ont été identifiés. Nous avons en outre inclus des rapports de cas rédigés en anglais qui incluaient à la fois un diagnostic explicite de NBIA (tout type) et qui avaient rapporté des crises convulsives de tout type ou l'absence de telles crises. Enfin, soulignons que le taux d'incidence, le type et l'âge d'apparition des crises convulsives ont été compilés sous forme de fréquences et de pourcentages. ***Résultats :*** Nous avons identifié un total de 1698 articles. De ce nombre, 51 ont été inclus dans notre étude. Sur un total de 305 cas de NBIA signalés, 150 patients (49,2 %) ont donné à voir des crises convulsives. Chez 64 patients, ces crises ont été associées à une neuro-dégénérescence liée à la phospholipase A2 (50,8 %) ; chez 57 patients, à une neuro-dégénérescence liée à la protéine bêta-propulseur (*β-propeller*) (72,1 %) ; chez 11 patients, à une neuro-dégénérescence associée à la pantothénate kinase (23,4 %) ; chez 18 autres, à une proportion très variable. Le type de crise convulsive le plus fréquent chez les patients atteints de NBIA était la crise tonico-clonique généralisée, l'âge moyen d'apparition des premières crises se situant entre 2 et 36 ans. Cependant, rappelons que la plupart de ces articles avaient été publiés

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avant que la nouvelle classification de l'épilepsie ne devienne accessible. Enfin, les patients affectés étaient le plus souvent de sexe féminin. ***Conclusion :*** Les crises convulsives sont fréquentes chez les patients atteints de NBIA, en particulier quand il est question de neuro-dégénérescence liée à la phospholipase A2 et de neuro-dégénérescence liée à la protéine bêta-propulseur. Dans le cas des neuro-dégénérescences associées à la pantothénate kinase, le type le plus courant de NBIA, environ 10 % des patients sont affectés par des crises convulsives. Les neuro-dégénérescences liées à la protéine bêta-propulseur sont par ailleurs celles qui sont les plus susceptibles de s'accompagner de crises convulsives. Cela dit, la plupart des résultats concernant les caractéristiques des crises convulsives liées aux NBIA sont biaisés en raison de l'importance de données manquantes. Par conséquent, toute conclusion devrait être tirée de façon prudente et s'appuyer sur des recherches supplémentaires.

Keywords: Seizure; Neurodegeneration with brain iron accumulation

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Introduction

Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group of genetic disorders affecting both children and adults with the unifying feature of iron accumulation in specific brain structures, especially globus pallidus. Main defective proteins in different NBIAs have no known direct role in iron homeostasis, but similar pathologic changes in consistent brain areas, mostly basal ganglia, have led to this assumption that iron accumulation is a common pathophysiologic feature among NBIAs.

Different types of NBIA are recognized, labeled according to the molecular finding, replacing the historical term Hallervorden–Spatz disease. The most common subtype is pantothenate kinase-associated neurodegeneration (PKAN) designating the defective enzyme discovered to cause it. Soon after PKAN was described, other malfunctioning enzymes and their responsible genes were discovered and the NBIA group began to expand, today encompassing at least 10 distinct disorders (Table 1).[1–4] This category is expected to divide further into more subcategories, as still a substantial proportion of "sporadic disorders of uncertain origin" continue to exist as an unclassified heterogeneous subclass of NBIAs.[4]

NBIA disorders are rare with an overall estimated prevalence of 1 in 500,000. Their clinical manifestations comprise a wide range of the spectrum (Table 2) mainly movement disorders (especially

Table 1: The distinct disorders and their responsible proteins and genes comprising the neurodegeneration with brain iron accumulation group

Label	Acronym	New MDS designation[4]	OMIM	Full name	Protein	Gene	Chr.	Inher.	Notes
NBIA1	PKAN	NBIA/DYT-PANK2	234200	Pantothenate kinase-associated neurodegeneration	Pantothenate kinase 2	*PANK2*	20p13	AR	Some PKAN cases have been mentioned as Hallervorden–Spatz disease in the past
NBIA2	PLAN	NBIA/DYT/PARK-PLA2G686	612953	Phospholipase A2-associated neurodegeneration	phospholipase A2	*PLA2G6*	22q13.1	AR	Also known as PARK 14; includes INAD
NBIA3		NBIA/CHOREA-FTL	606159	Neuroferritinopathy	Ferritin light chain polypeptide	*FTL1*	19q13.33	AR	
NBIA4	MPAN	NBIA/HSP-C19orf12 (MPAN)	615043	Mitochondrial membrane protein-associated neurodegeneration	C19orf12 (mitochondrial protein)	*C19orf12*	19q12	AR	
NBIA5	BPAN	NBIA/PARK-WDR45	300894	Beta-propeller protein-associated neurodegeneration	WD40-repeat protein 45 (beta - propellar protein)	*WDR45*	Xp11.23 dominant	XLD	Previously named SENDA
NBIA6	CoPAN	–	609855	CoA synthase protein-associated neurodegeneration	Coenzyme A synthase	*CoASY*	17q21.2	AR	
–	FAHN	HSP/NBIA-FA2H	612319	Fatty acid-2 hydroxylase-associated neurodegeneration	Fatty acid 2 hydroxylase	*FA2H*	16q23.1	AR	Also known as SPG35
–	–	PARK-ATP13A2	606693	Kufor–Rakeb disease	Cation-transporting ATPase 13A2	*ATP13A2*	1p36.13	AR	Also known as PARK9
–	–	NBIA/DYT/PARK-CP	604290	Aceruloplasminemia	Ceruloplasmin	*CPL*	3q24-q25	AR	
–	–	NBIA/DYT-DCAF17	241080	Woodhouse–Sakati syndrome	Nucleolar transmembrane protein	*C2orf37 (CDAF17)*	2q31.1	AR	Also known as late-onset NBIA

AR = autosomal recessive; Chr = chromosome; HSP = hereditary spastic paraparesis; INAD = infantile neuroaxonal dystrophy; Inher = inheritance; MDS = Movement Disorder Society; NBIA = neurodegeneration with brain iron accumulation; OMIM = Online Mendelian Inheritance in Man; PARK = Parkinson's disease; SENDA = static encephalopathy of childhood with neurodegeneration in adulthood; SPG = spastic gait gene.

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Table 2: Clinical and brain MRI characteristics of NBIAs

Acronym	Clinical manifestation	MRI	Proportion of NBIAs (%)[3]
PKAN	Dystonia, parkinsonism, spasticity, pigmentary retinopathy, acanthocytosis, and neuropsychiatric features	T2 hyperintense signal surrounded by hypointense signal in globus pallidus, less involvement of substantia nigra (the "eye of the tiger" sign)	30–50
PLAN	Psychomotor regression, ataxia, autism, dystonia, parkinsonism, and optic atrophy	Iron seen later in disease, affecting globus pallidus and/or substantia nigra (<50% patients), cerebellar atrophy and gliosis, less often cerebral atrophy	20
Neuroferritinopathy	Adult-onset chorea or dystonia with subtle cognitive defects	Cavitary lesions plus T2 hypointense signal in: globus pallidus, substantia nigra, putamen, caudate, thalamus, red nucleus, or/and dentate	Rare
MPAN	Spasticity, dystonia, dementia, and peripheral nerve involvement	Iron affecting globus pallidus and substantia nigra equally, prominent medial medullary lamina streak on T2 sequences	6–10
BPAN	Intellectual disability, little to no language, mixed seizure types, juvenile parkinsonism, and autism	T2 hypointense signal in substantia nigra even greater than globus pallidus, T1 bright "halo" in substantia nigra/cerebellar peduncles, changes may be seen in early childhood	1–2
CoPAN	Intellectual disability, dystonia, spasticity, and behavioral problems	T2 hypointense signal in globus pallidus, less involvement of substantia nigra, putamen, thalamus, and tiger eye	Rare
FAHN	Spasticity, ataxia, dystonia, optic atrophy, dementia, and seizures	T2 hypointense signal in globus pallidus (in some patients), diffuse cerebral atrophy, white matter changes	Rare
Kufor–Rakeb disease	Juvenile parkinsonism and dementia	Few have evidence of iron accumulation, but when present, T2 hypointense signal in striatum, with global atrophy	Rare
Aceruloplasminemia	Adult-onset retinal degeneration, diabetes mellitus, and chorea or dystonia or ataxia	T2 hypointense signal usually in all of the following: dentate nucleus, substantia nigra, globus pallidus, putamen, caudate, thalamus, and cortex without cavitary lesions	Rare
Woodhouse–Sakati syndrome	Mixed neurologic and endocrine features (deafness, alopecia, progressive dystonia, dysarthria, dysphagia, cognitive impairment, hypogonadism, and diabetes mellitus)	Iron deposition in the globus pallidus and substantia nigra and white matter changes (in some patients)	Rare

MRI = magnetic resonance imaging.

dystonia and Parkinsonism) but also neuropathy, retinopathy, optic neuropathy, oculomotor abnormalities, mental disability, behavioral, and systemic disorders.[1–4] Seizure as a clinical manifestation is known to occur in some NBIAs such as phospholipase A2-associated neurodegeneration (PLAN) and beta-propeller protein-associated neurodegeneration (BPAN), but the exact prevalence of epilepsy in each individual disorder is not well elucidated.[2]

We reviewed the literature with a systematic method to establish the frequency of seizures reported in NBIA disorders as well as to determine the associated features of patients with seizure.

Method

Search Strategy

All details about search methodology regarding databases, keywords, time and language limits, and inclusion criteria were considered.[5] The electronic bibliographic databases Pubmed, Scopus, Embase, and Google Scholar were searched for all cases in any type of article from inception to December 16, 2019. The medical subject headings words "seizures" and "epilepsy" and keywords "neurodegeneration with brain iron accumulation," "Idiopathic NBIA," "Seitelberger disease," "infantile neuroaxonal dystrophy" (INAD), "Woodhouse–Sakati syndrome" (WSS), "Kufor–Rakeb syndrome" (KRS), "beta-propeller protein-associated neurodegeneration" (BPAN), "PLA2G6-associated neurodegeneration" (PLAN), "hereditary aceruloplasminemia" (HA), "fatty acid hydroxylase-associated neurodegeneration" (FAHN), "fatty acid 2-hydroxylase" (FA2H), "pantothenate kinase-associated neurodegeneration" (PKAN), "mitochondrial membrane-associated neurodegeneration" (MPAN), and "static encephalopathy of childhood with neurodegeneration in adulthood" (SENDA) were used for the search.

Endnote software X8 was used for the review and inclusion of studies.

Eligibility Criteria

Title and abstract screening and full-text screening were conducted independently by two reviewers. Case reports with an explicit diagnosis of any types of NBIA which were assessed for the incidence of any type of seizure or epilepsy were included. Further cases were identified via cross-referencing between papers. The articles, which were not available in full text or have not been written in English, were excluded. Detailed reasons for the exclusion of papers in each step are provided in the PRISMA diagram (Figure 1).

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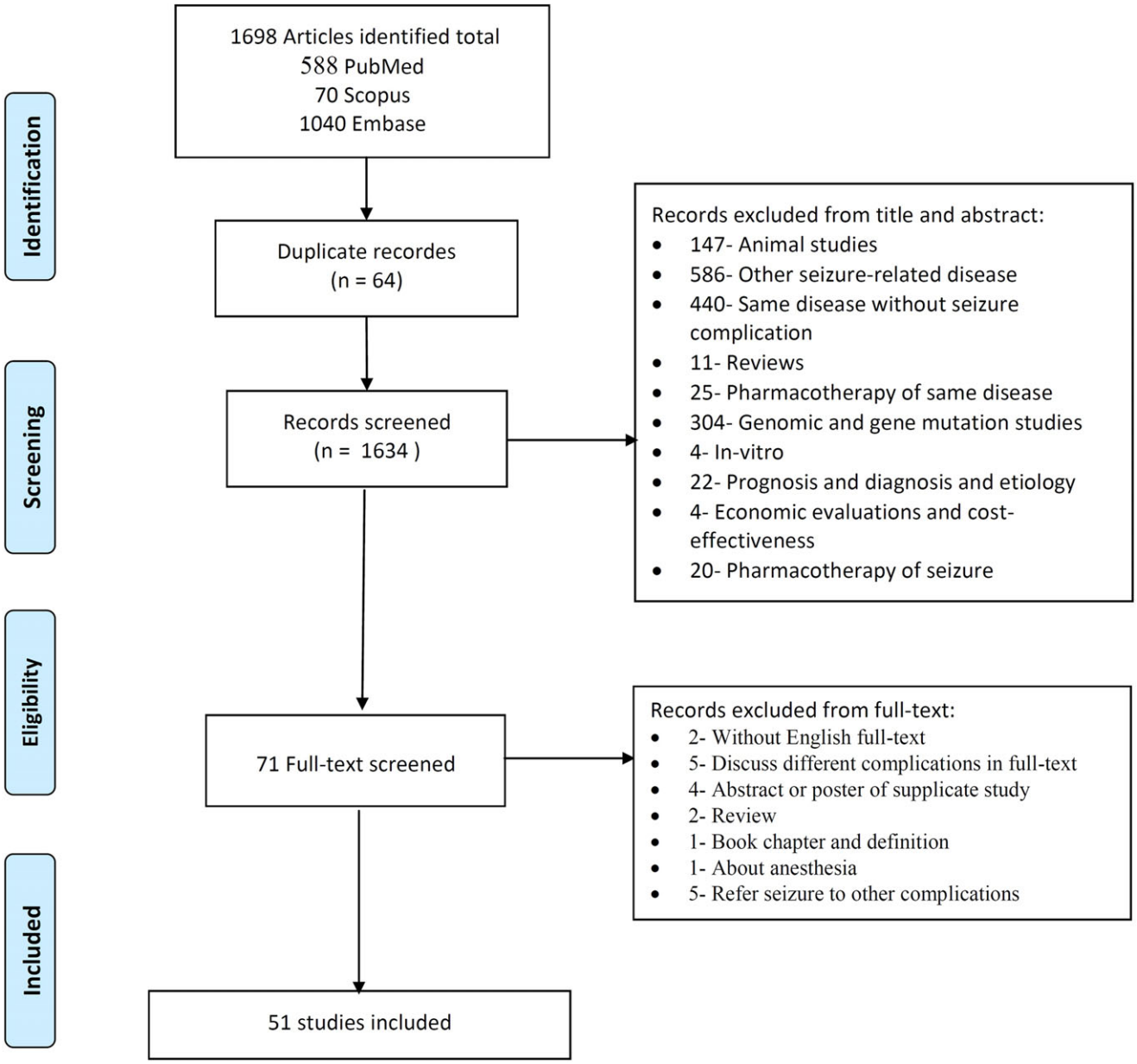

Figure 1: PRISMA diagram.

Quality Assessment

Two reviewers assessed the quality of the reports using the methodological quality of case reports/series tool.[6] This tool proposes an approach to evaluate the quality based on the domains of selection, ascertainment, causality, and reporting. Any disagreements were settled through discussion with a third reviewer.

Data Extraction

Two reviewers independently screened the titles and abstracts of all records. Then, the selection of full texts was accomplished based on the eligibility criteria. The reviewers independently extracted data on study characteristics, type of NBIA and demographic information, clinical characteristics, in particular seizure data including incidence rate, type of seizure, and age of seizure onset. Afterward, a third reviewer cross-checked the extracted data. In order not to miss any cases, we also reviewed cases in the references of all papers, including reviews, but during cross-checking, we ensured to omit the duplicate cases.

Statistical Analysis

All results presented as frequencies and percentages of reported data using Excel® 2016.

Results

A total of 1698 articles was retrieved from the electronic database search. Through the process of duplicate record elimination, title and abstract screening, and eligibility assessments, 71 articles fulfilled the inclusion criteria. After the full-text screening, 51 studies comprising of 305 cases were included (Figure 1, Table 3).

Among these 305 cases in whom the seizure was mentioned as an investigated symptom, 150 (49.2%) had seizures. The incidence

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Table 3: Studies' characteristics, sorted alphabetically by author

Study	NBIA	N of cases	Sex	Age (mean)	Type of seizure	N of seizure patients (%)	Sex of seizure patients	Seizure onset age	Age of every seizure case at report time	Reference
Abusrair et al. (2018)	WSS	26	12 M 14 F	26.6 16<age<45	NA	3 (11.5%)	2 M 1 F	NA	19 21 35	[14]
Behrens et al. (2010)	KRS	5	4 M 1 F	10<Age<13	End-stage epileptic seizures	3 (60%)	3 M	NA	NA	[15]
Bischoff (1963)	Undetermined NBIA (probably PKAN)	1	M	–	–	0 (0%)	–	–	–	[16]
Chard et al. (2019)	BPAN	5	F	10.4	Family seizure-like episodes upon awakening and in sleep transition. Myoclonic and rare GTC GTC, absence, and atonic seizures.	3 (60%)	F	3 4 1	16 10 5	[17]
Cowen and Olmstead (1963)	INAD	2	1 M 1 F	NA	–	0 (0%)	–	–	NA	[18]
Crome and Weller (1965)	INAD	2	1 M 1 F	9	Grand mal seizure	2 (100%)	1 M 1 F	6 months 10 months	14 4	[19]
Darling et al. (2019)	Infantile onset PLAN (n = 10) childhood onset PLAN (n = 6)	16	11 M 5 F	3<Age<33 (10.2)	NA	8 (50%): 5 infantile onset PLAN 3 childhood onset PLAN	NA	Median = 5.9	NA	[20]
De Buitléir and Lynch (2016)	BPAN	1	F	17	NA	1 (100%)	F	1<age<3	17	[21]
Dezfouli et al. (2013)	PKAN and MPAN	12: PKAN(7) MPAN(5)	9M 3F	PKAN (7.4 years) MPAN (17.5 years)	GTC	4 (33.3%): 2 PKAN (28.5%) 2 MPAN (40%)	2M (PKAN) 2F (MPAN)	NA	15, 16, 8, 16, 16, 14, 13, 27, 24, 27, 28, 29	[22]
Dufke et al. (2014)	BPAN with WDR-45 mutation	3	M	NA	Epileptic seizures	1 (33%)	M	Childhood	NA	[23]
Eicke (1940)	Undetermined NBIA (probably PKAN)	1	F	NA	–	0 (0%)	–	–	NA	[16]
Eroglu-Ertugrul and Topaloğlu (2019)	Not specified	2	M	6.7	NA	100% (2)	M	3.5	6.5 7	[24]
Fasano et al. (2008)	HA	2	1 M 1 F (siblings)	54.5	Partial motor seizures	50% (1)	F	36	56 53	[25]
Fiinfgeld (1929)	Undetermined NBIA (probably PKAN)	1	M	–	–	0 (0%)	M	–	–	[16]

Garone et al. (2011)	Mutations in the gene for FA2H	2	M (siblings)	24	Generalized tonic seizures	1 (50%)	M	16	16	[26]
Gilman (1973)	Infantile Hallervorden–Spatz disease and INAD	2	F	NA	Grand mal seizure	50% (1): INAD case	F	6	NA	[16]
Gregory et al. (2008)	INAD (51 mutation positive) Idiopathic NBIA (28 mutation negative)	79 (51 with genetic confirmation)	NA	3<age<18	Mostly generalized seizure	38/51 (74.5%): generalized seizure ?/28	NA	Mean= 7	NA	[27]
Gross et al. (1957)	Undetermined NBIA (probably INAD)	1	F	–	–	0 (0%)	–	–	–	[16]
Hattingen et al. (2017)	BPAN with a hitherto unknown missense variant in *WDR45*	1	F	–	Seizures with loss of consciousness and absences	1 (100%)	F	3	33	[28]
Hayflick et al. (2013)	BPAN	23	3 M 20 F	33.5	Staring, absence or atonic seizures = 7/13 (53.8%) Febrile seizures 4/13 (30.7%) Myoclonic seizures 1/13 (7.7%) absence or atonic seizures along with febrile seizures 1/13 (7.7%)	13 (56%)	1 M 12 F	NA childhood	23, 30, 29, 22, 39, 49, 31, 24, 17, 31, 43, 31, 16	[29]
Haberland (1972)	INAD	1	F	–	NA	1 (100%)	F	1.5	3.5	
Hornemann et al. (2019)	BPAN	1	F	–	Started at the age of 4 months with infantile spasms then focal epileptic seizures at 2.5 years	1 (100%)	F	0.3 2.5	11	[30]
Huttenlocher and Gilles (1967)	INAD	3	F	–	–	0 (0%)	–	–	–	[31]
Illingworth et al. (2012)	PLAN Atypical-childhood PLAN	3 1	2 M/1 F 1 F	13 months <age<18 months	–	0	–	–	NA	[32]
Indravasu and Dexter (1968)	Undetermined NBIA (probably INAD)	4	1 M 3 F	NA	Generalized seizure	3 (75%)	1 M 2 F	5.5 months Birth 3 months Mean = 2.8 months	NA	[33]
Jellinger (1968)		1	M	–	–	0 (0%)	–	–	–	[16]
Kamoshita et al. (1968)	INAD	1	F	–	Generalized seizure	1 (100%)	F	4 months	5	[34]

Table 3: (*Continued*)

Study	NBIA	N of cases	Sex	Age (mean)	Type of seizure	N of seizure patients (%)	Sex of seizure patients	Seizure onset age	Age of every seizure case at report time	Reference
Lange et al. (2017)	BPAN	1	F	–	Started at the age of 2 years with fever-associated atonic seizures. Since the age of 4 years typical absences occur daily. EEG shows generalized 3/sec spike-wave complexes	1 (100%)	F	2<age<4	9	35
Li et al. (2019)	BPAN	17	4 M 13 F	1.1-8.8	Spasm (37.5%), focal (31.2%), absence, myoclonic, and generalized tonic-clonic seizures	16 (94.1%) (13 moderate to severe)	4 M 12 F	Median 14.5 months (3–24 months) M cases had earlier seizure onset (3, 4, 5, and 18 months	NA	36
Lyon (1963)	Undetermined NBIA (probably INAD)	2	1 M 1 F	NA	NA	1 (50%)	F	2	NA	16
Martin (1972)	Undetermined NBIA (probably INAD)	3	2 M 1 F	NA	–	0 (0%)	–	–	NA	16
Methling et al. (2016)	NBIA not specified	1	NA	–	NA	1 (100%)	NA	NA	6	37
Mikati et al. (2009)	PKAN	1	F	11	Generalized tonic-clonic seizure	1 (100%)	F	8	11	38
Nakashima et al. (2016)	BPAN with WDR-45 mutation	3	M	3.6	Spasms (66.6%), Spasms→tonic seizure (33.4%)	3 (100%)	M	5.4 months	21 months 2 7	39
Nunez et al. (2018)	BPAN	1	F	–	–	0 (0%)	–	–	18	40
Osman (1935)	Undetermined NBIA (probably PKAN)	1	M	–	–	0 (0%)	–	–	NA	16
Parmar et al. (2012)	PKAN	1	M	18	NA	1 (100%)	M	NA	18	41
Pérez-Torre et al. (2017)	PKAN	2	F	26	Tonic-clonic seizure	2 (100%)	F	9 19	32 20	42
Rabinowicz (1957)	Undetermined NBIA (probably INAD)	1	F	–	–	0 (0%)	F	–	–	16
Ramdas et al. (2017)	BPAN	2	1 M 1 F	NA	Infantile spasm	1 (50%)	M	4 months	NA	43
Rathore et al. (2014)	BPAN	1	F	–	NA	1 (100%)	F	2	15	44
Riku et al. (2011)	NBIA with Lewy pathology and cerebellar degeneration	1	M	NA	Generalized seizures	1 (100%)	M	6	NA	45

Rohani et al. (2019)	BPAN	3	F	28.3	GTC	2 (66%)	F	9 months 12 months	24 22 39	[46]
Rohani et al. (2018)	KRS	5	1 m 4 F	31.8	GTC	2 (40%)	F	10 12	33 31	[47]
Rohani et al. (2014)	PKAN PANK2 mutations	24	18 M 6 F	17.9	NA	2 (8.3%)	NA	NA	NA	[48]
Rozdilsky et al. (1963)	Undetermined NBIA (probably INAD)	2	M	26.5	Grand mal seizures	2 (100%)	M	3 11	11 42	[49]
Russo et al. (2019)	BPAN de novo WDR45 mutations	4	F	7.25	Focal seizures and spasms 2/3 (66.6%) proximal myoclonic spasms and tonic seizures	3 (75%)	F	18 months 17 months 2 years	6 13 8 2	[50]
Saitsu et al. (2013)	SENDA with a WDR45 mutation	5	F	37	Epileptic seizure in 4 patients which one of them had a febrile seizure in 1/4 (25%)	4 (80%)	F	NA	33 28 40 51 33	[51]
Sandbank (1965)	INAD	1	M	–	–	0 (0%)	–	–	3	[52]
Seitelberger (1963)	Undetermined NBIA (probably INAD)	1	F	–	–	0 (0%)	–	–	–	[16]
Seitelberger (1953)	Undetermined NBIA (probably INAD)	1	F	–	–	0 (0%)	–	–	–	[16]
Scharenberg (1952)	Undetermined NBIA (probably INAD)	1	M	–	NA	1 (100%)	–	–	Birth	[16]
Schneider and Bhatia (2008)	WSS	2	1 M 1 F	29	NA	1 (50%)	F	2	36 22	[53]
Sozer Topcular et al. (2016)	Homozygous missense point mutation in PANK2 gene MPAN	2	M	26	GTC	1 (50%)	M	28	24 28	[54]
Szczechowski et al. (2014)	NBIA, Not specified	1	M	–	Idiopathic epilepsy	1 (100%)	M	2	6	[55]
Takei (1965)	INAD	1	M	–	NA	1 (100%)	M	1	4 years and 8 months	[16]
Tofaris et al. (2007)	Mutations in *PANK2*	1	F	–	Single generalized convulsion	1 (100%)	F	26	27	[56]
Toga (1970)	INAD	2	NA	NA	–	0 (0%)	–	–	–	[16]
Urechia (1950)	Undetermined NBIA (probably PKAN)	2	1 M 1 F	NA	–	0 (0%)	–	–	–	[16]
Veeravigrom et al. (2014)	NBIA, Not specified	1	F	–	Tonic seizures	1 (100%)	F	10	15	[57]

Table 3: (*Continued*)

Study	NBIA	N of cases	Sex	Age (mean)	Type of seizure	N of seizure patients (%)	Sex of seizure patients	Seizure onset age	Age of every seizure case at report time	Reference
Verhoeven et al. (2013)	BPAN	3	F	42.3	-Focal 1/2(50%) -Absence in childhood, a mixture of absence, tonic-clonic, and tonic in adulthood (multiple spikes in EEG) 1/2(50%)	2 (66.6%)	F	2.5 13	33 52 42	58
Wigboldus (1968)	Undetermined NBIA (probably PKAN)	1	F	–	NA	1 (100%)	F	1	NA	16
Willoughby et al. (2018)	BPAN	1	F	–	Multi-focal frequent myoclonic seizures	1 (100%)	F	4 months	6	59
Xixis and Mikati (2015)	BPAN	1	F	–	Cluster of focal, febrile seizures consisting of right-sided, tonic-clonic activity She also developed tonic seizures during sleep	1 (100%)	F	3 months	6	60
Yamashita et al. (2004)	PKAN	1	F	–	–	0 (0%)	F	3 months	24	61
Yoganathan et al. (2016)	BPAN	1	F	–	Polymorphic seizures including febrile seizures and myoclonic seizures and generalized tonic seizures	1 (100%)	F	1	5 years and 11 months	62
Zarate et al. (2016)	BPAN	2	1 M 1 F	17	NA	1 (50%)	M	3	20 14	63
Zhang et al. (2013)	PLAN	24	16 M 8 F	5	Epileptic seizures	4 (16.7%)	3 M 1 F	1 year and 7 months	–	64

BPAN = beta-propeller protein-associated neurodegeneration; EEG = electroencephalography; FA2H = fatty acid 2-hydroxylase; GTC = generalized tonic-clonic; HA = hereditary aceruloplasminemia; INAD = infantile neuroaxonal dystrophy; KRS = Kufor–Rakeb syndrome; MPAN = mitochondrial membrane-associated neurodegeneration; NBIA = neurodegeneration with brain iron accumulation; PKAN = pantothenate kinase-associated neurodegeneration; PLAN = PLA2G6-associated neurodegeneration; SENDA = static encephalopathy of childhood with neurodegeneration in adulthood; WSS = Woodhouse–Sakati syndrome.

Table 4: The prevalence of epilepsy in each NBIA disorder and the available features related to these patients

Type of NBIA	N of reported case	Seizure prevalence (%)	Sex (%)	Mean age of onset (year)	Type of seizure
PLAN	126	64 (50.8%)	NA	5.4	Generalized seizure
BPAN	79	57 (72.1%)	73.2% F	2.3	Infantile spasms, absence, atonic, febrile, myoclonic, focal, and generalized tonic clonic, proximal myoclonic spasms, and tonic seizures
PKAN	47	11 (23.4%)	62.5% F	NA	NA
WSS	28	4 (14.3%)	50% F	2	NA
KRS	10	5 (50%)	40% F	NA	GTC
MPAN	5	2 (40 %)	66.6% F	NA	GTC
HA	2	1 (50%)	100% F	36	Partial motor seizures
FAHN	2	1 (50%)	100% M	16	Generalized tonic seizures
Not specified	6	5 (83.3%)	33.3% F	4.6	NA
Neuroferitinopathy	NA	NA	NA	NA	NA
CoPAN	NA	NA	NA	NA	NA
All NBIAs	305	150 (49.2%)	NA	NA	NA

BPAN = beta-propeller protein-associated neurodegeneration; FA2H = fatty acid 2-hydroxylase; GTC = generalized tonic-clonic; HA = hereditary aceruloplasminemia; INAD = infantile neuroaxonal dystrophy; KRS = Kufor–Rakeb syndrome; MPAN = mitochondrial membrane-associated neurodegeneration; NBIA = neurodegeneration with brain iron accumulation; PKAN = pantothenate kinase-associated neurodegeneration; PLAN = PLA2G6-associated neurodegeneration; SENDA = static encephalopathy of childhood with neurodegeneration in adulthood; WSS = Woodhouse–Sakati syndrome.

of seizure depending on the subtype of NBIA and the demographic characteristics of patients with seizures are presented in Table 4. To summarize, among all NBIA syndromes, seizures were most frequently reported in PLAN (64/126, 50.8%) followed by BPAN (57/79, 72.1%), PKAN (11/47, 23.4%), WSS (4/28, 14.3%), KRS (5/10, 50%), MPAN (2/5, 40%), HA (1/2, 50%), and FAHN (1/2, 50%).

Patients with seizures were more likely to be females and the mean age of seizure onset ranged from 2 to 36 years. The most frequent seizure type in NBIA patients was generalized tonic-clonic seizure, although in BPAN a variety of other seizure types (including infantile spasms, absence, atonic, febrile, myoclonic, focal, proximal myoclonic spasms, and tonic seizures) and in HA focal motor seizure had been reported. However, we should emphasize that most of these papers had been published before the new classification of epilepsy became accessible. So, the type of seizure is based on the previous version of the classification of epilepsy when these papers were released. In most instances, except in some cases of BPAN, seizure was not an early symptom of NBIA. The data regarding the natural history of seizures per se is scarce in the literature. Most of these patients were controlled with one or two antiepileptic drugs.

Discussion

Epilepsy is a frequent neurological disorder, affecting 0.7% of the general population (lifetime prevalence per person is 7/1000[7]). Causes of seizure in childhood and young patients in order of frequency are genetic (including hereditary neurodegenerative disorders), structural lesions, metabolic disorders, and infections.[8] In the late-onset sporadic neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease, seizures are reported to occur in about 4.1% and 2.6% of cases, respectively.[9,10] In early-onset neurodegenerative disease, seizures occur more frequently and further complicate the nature of these disorders. One example is NBIA, a group of syndromes clinically characterized by the combination of dystonia, parkinsonism, retinal or optic nerve pathology, and other neurological signs including seizure. Given the lack of systematic data about seizure frequency and characteristics,[2,11] we systematically reviewed the literature. Our systematic review revealed that NBIAs as a subcategory of hereditary neurodegenerative disorders are an important cause of epilepsy in children and young adults. Seizure in NBIAs is generally more frequent compared to Wilson's disease, another metal storage disease, where seizures have been reported in 6.2% of cases.[11,12]

Among the NBIA disorders, the ones most frequently reported to have epilepsy as a consistent manifestation are PLAN (especially the INAD subtype), BPAN, FAHN, and WSS.[2,4] By contrast, PKAN – the most common NBIA – is thought to be an infrequent cause of epilepsy.[2]

In the present study, in each NBIA disorder, the proportion of patients with seizures was reported to be between 14% (for WSS) and 72% (for BPAN). However, these numbers are biased due to exclusion of papers in which the occurrence of seizure has not been reported and also due to the limited number of case reports for some NBIAs, such as FAHN and HA. These considerations make the estimation of the proportion of patients presenting with seizure very fragile and highlight the importance of complete clinical descriptions, for example, the total number of reported cases of FAHN in papers which alluded to the presence or absence of seizure was two, one of them had seizures, resulting in 50% seizure prevalence in this disorder. Obviously, these percentages cannot be compared to the percentages of more frequent NBIAs such as PLAN with 126 reported cases with seizure annotation in the papers, 64 of them having seizures, resulting in a prevalence of 50% in this disorder. The obvious fact, however, is that PLAN is the most reported NBIA (considering crude numbers) with seizures and this is less biased by the low prevalence, as this disease accounts for nearly 20% of all NBIAs. The other interesting finding of this review is that seizure is not an infrequent finding in PKAN, as 23% of 47 reported PKAN patients happened to be suffering from epilepsy. The other salient result from the current review is that seizure occurrence is more frequent in BPAN (72%) than

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in any other NBIA and this seems to be a solid result. In spite of the lower prevalence of BPAN compared to PLAN (2% vs. 20% of all NBIAs), the crude number of BPAN patients with seizures stand just next to PLAN (57 and 64 cases, respectively). We estimate based on the present study that BPAN is the most probable NBIA with seizure included in the clinical picture (nearly 72%) followed by PLAN (50%) and PKAN (23%). The other NBIAs, which may be commonly accompanied by seizures, would be WSS, KRS, MPAN, FAHN, and HA, but the exact proportion of patients with seizures and the order of frequency among these disorders cannot be judged with available data.

As already outlined, the findings of our systematic need to be interpreted with caution as no study were specifically addressed to screen the NBIA population for the occurrence of seizures. Our assumptions are indeed based on individual case reports and case series. In addition, the data regarding the natural history of seizures and treatment response were scarce in the literature, thus making it hard to draw conclusions also in terms of the relationship with the natural history of these progressive disorders. Likewise, the data regarding seizure onset age, sex, seizure type, and phenomenology was insufficient, and the results might be distorted by excessive missing data. On the other hand, one cannot be sure that all the reported seizures in the previous reports have been epileptic in nature, for example, the possibility of including provoked seizures should be considered as a bias which cannot be sorted out retrospectively. In addition, the papers were from a diverse time period and almost all of them were published before the new classification of epilepsy. Therefore, the new classification could not be applied to the cases.[13] For instance, based on these data, we were not able to differentiate between generalized tonic-clonic seizures and bilateral tonic-clonic ones which is a new concept. Another problem regarding the classification was that the seizure type, which was not the goal of most reports, was not mentioned or clearly understandable from the reports (see Table 3). So, the readers are advised to consider this issue as a major limitation. Another limitation to our review that readers should be aware of is that this study solely reviewed the English literature on NBIAs which can make the conclusion more biased.

Nevertheless, our study is the first study in this regard, and future studies with more precise information will be needed to clarify this issue.

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