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DRAFT

POST-STROKE ACQUIRED CHILDHOOD APHASIA. A SCOPING REVIEW

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ABSTRACT

Aphasia has a great impact on children's lives, with stroke being its most common and studied etiology. However, our knowledge about this disorder is limited, the studies on this topic are sparse, and a consensus regarding its definition is lacking. In particular, the interpretation of this condition varied over time: from the rigid description of the so-called "standard doctrine" (Lenneberg, 1967) to the adoption of adult models for post-stroke aphasia. Therefore, this review provides a critical overview of childhood aphasia after stroke, focusing on its epidemiology, definition, diagnosis, and clinical manifestation.

The scoping review approach was adopted, following PRISMA-ScR guidelines. Pubmed, Web of Science, and PsycInfo databases were searched for related peer-review papers in English.

Forty-six records were identified; the majority were single cases and case series, only a few were reviews and observational studies. Epidemiologic data are scarce; a few studies report that aphasia affects about one-third of children post-stroke. Despite terminological differences, there is an overall agreement on the definition of post-stroke aphasia in children as a language disorder acquired after the age of two. Approaches for the diagnosis and evaluation vary widely, including both assessments for developmental language disorders and tests for aphasia in adults. The clinical manifestations described in children are numerous and varied, similar to those found in adults, in contrast with the "standard doctrine". This review highlights the need for further studies to improve the knowledge of this condition, develop validated and specific assessment tools, and standardize clinical management.

Keywords: aphasia, post-stroke, children, pediatric, language

Non-standard Abbreviations and Acronyms

AAC = Acquired Aphasia in Children

ACA = Acquired Childhood Aphasia

AIS = Arterial Ischemic Stroke

AVM = Arteriovenous Malformation

CAD = Crossed Aphasia in Dextrals

fMRI = functional Magnetic Resonance Imaging

ICF = International Classification of Functioning, Disability and Health

MCA = Middle Cerebral Artery

MIT = Melodic Intonation Therapy

PACE = Promoting Aphasics' Communicative Effectiveness

rCBF = regional Cerebral Blood Flow

RR = Relative Risk

rTMS = repetitive Transcranial Magnetic Stimulation

TBI = Traumatic Brain Injury

1. INTRODUCTION

Acquired aphasia in childhood is a rarely explored and controversial topic; the scientific and clinical interest on this issue increased over the years. Language disorders have a great impact on children's lives, with important consequences for the individual's education, personality, and social development. However, our knowledge of childhood aphasia remains limited.

Besides "aphasia", other different expressions such as "dysphasia" or "acquired language disorder/impairment" have been used interchangeably in pediatric literature (Vargha-Khadem, O'gorman & Watters, 1985; Brookshire et al., 2000; Anderson et al., 2002; Catroppa & Anderson, 2004). Nowadays there is a good consensus among clinicians and researchers that a complete and/or partial loss of language abilities should be called "aphasia" while the use of other terms could lead to confusion regarding diagnosis (Worrall et al., 2016), but a universally recognized definition has not been established.

Difficulties in defining childhood aphasia are primarily due to the fact that language disorders in children occur when the central nervous system is not mature yet and the linguistic abilities are still evolving. A brain lesion could disrupt the aspects of language that are already developed, or interfere with the acquisition of those that have not fully emerged yet.

In addition, to our knowledge, no standardized language assessment for the diagnosis of acquired childhood aphasia is available.

Descriptions of its clinical presentation drastically changed over time. The first clinical descriptions of childhood aphasia date back to the second half of the nineteenth century and present the disorder as transient and extremely homogeneous in terms of symptomatology. In particular, the traditional description of childhood aphasia clinical profile, known as Lenneberg's "standard doctrine" (Lenneberg, 1967), included invariably non-fluent telegraphic speech, agrammatism, articulatory disorders, absence of positive symptoms (logorrhea, neologisms, jargon), and unimpaired auditory comprehension. This belief prevailed until 1978, when Woods and Teuber (1978) described the first case of jargon aphasia in a 5-year-old child with comprehension impairment. In the following years,

other examples of fluent aphasia were reported in children whose speech was characterized by the presence of neologisms, paraphasias, jargon, logorrhea, verbal stereotypes, perseverations, and circumlocutions or paragrammatical speech (Van Hout, Evrard & Lyon, 1985; Van Hout, 1991).

Aphasia in children follows damage to the neural language network and, similarly to the adult population, etiology can be various. The most commonly reported causes of childhood aphasia are cerebrovascular diseases, with a prevalence of ischemic strokes (Tsze & Valente, 2011). Traumatic (Basso & Scarpa, 1990), infectious (Van Hout & Lyon, 1986), hypoxic (Murdoch & Ozanne, 1990), epilepsy associated (Landau, & Kleffner, 1957), and neoplastic (Hudson, 1990) etiologies have also been described. Since stroke is the most common cause of childhood aphasia, the present review will be focused on this particular etiology to provide greater uniformity. In addition, aphasia as an outcome of cerebrovascular accidents is the clinical condition that historically has been most studied in adult aphasiology, leading to the classical interpretative theory (Goodglass and Kaplan, 1972). The great medical advances that occurred in the last decades and the increasing adherence to evidence-based guidelines for the management of acute neurological disorders reduced childhood mortality rates, with more and more children surviving and living with long-term impairments (Paediatric Stroke Working Group, 2004).

We believe that what is currently known about post-stroke aphasia in adults cannot be trivially applied for children. On the one hand, there is no consensus on the clinical manifestation of post-stroke aphasia in children (Lenneberg standard doctrine vs. Goodglass and Kaplan aphasia models). On the other hand, since language is still developing, the characterization of aphasia in this population should take into account a developmental model of language and literacy. From a preliminary search of the published literature, sparse information about this condition emerged, potentially leading to uncertainty in its clinical management. Therefore, we undertook a scoping review to categorize and highlight what is known and identify gaps for further research. The review adopted an exploratory approach and the aim was to analyze the terminology, definition, and specific criteria used by the authors to diagnose and describe aphasia in the post-stroke pediatric population. Only children with

congenital and/or neonatal stroke were excluded to limit the research field to acquired language disorders in children who were already exposed to environmental language stimuli.

2. METHODS

This paper aims to identify all relevant studies published on acquired childhood aphasia following stroke, and discuss them to provide a clinically relevant overview of the literature to date. The scoping review approach was adopted to map the existing literature in a complex field of interest that has not been comprehensively reviewed before (Arksey & O'Malley, 2005) and the PRISMA ScR guidelines (see Supplementary Material) were adopted (Moher et al., 2015). Four research questions guided the review:

- a) How is post-stroke childhood aphasia defined in the peer-reviewed scientific literature?
- b) What is the epidemiology of post-stroke childhood aphasia?
- c) Which assessment tools are employed for its diagnosis?
- d) Which clinical manifestations are associated with post-stroke aphasia in children?

2.1. Data sources and search strategy

PubMed, Web of Science, and PsycInfo electronic databases were searched (see **Appendix 1** for detailed search queries). Wildcard symbols were adopted to consider all possible variations of words while Boolean operators were used to narrow, widen and combine literature searches. Specific keywords and search strategies were identified (GG, IC, MS). Additionally, a hand-search of the reference lists of relevant articles was conducted in order to avoid missing relevant works.

2.2. Studies selection

Citations were imported into a web-based bibliographic manager (Mendeley Desktop 1.17.11), in order to remove all duplicates. A two-stage screening process was used to identify pertinent studies, through the web-based systematic review software Covidence (<https://www.covidence.org>) for the title and abstract screening. The title and abstract of each citation were independently screened by two reviewers (GG, MV), and disagreements were discussed and resolved through consensus rounds

(GG, MV, MG, MC). Publications that satisfied eligibility criteria were obtained and a full-text screening was performed by four independent reviewers (DC, FF, GG, MV). Conflicts were solved by discussion with all other co-authors.

2.3. Eligibility criteria

We selected only articles written in English. Studies were retrieved up to August 2021, without any other temporal restrictions. We focused on children and youth with acquired aphasia following a stroke that occurred between 30 days and 18 years of age. We excluded diffuse axonal injuries, hypoxic/anoxic brain injuries, traumatic brain injuries, tumors, primary epileptic syndromes (e.g., Landau-Kleffner syndrome), and neurotoxic complications. Moreover, we excluded children with syndromes or developmental language disorders. Articles where aphasia was only cited and that did not answer any of the review questions were also excluded.

2.4. Data charting process

Included articles were independently analyzed by four reviewers (DC, FF, GG, MV). The team developed a Microsoft Excel (Microsoft Corporation, Redmond, WA) data charting form to extract study characteristics (publication year, study design, population features). Information about the above-listed research questions was independently collected from each paper, in accordance with the objectives of this work. Data were then integrated and discrepancies were addressed through discussion.

3. RESULTS

As shown in **Figure 1**, reporting the paper selection process, 1271 studies were identified in PubMed, 1276 in Web of Sciences, and 671 in PsycInfo databases. After excluding duplicates, 2413 potential records were identified. 2223 records were excluded after examining titles and abstracts (e.g., non-English language, developmental language disorders, adult population, etc.). 190 full-texts were obtained and further screened: 145 of them did not meet eligibility criteria and were excluded. 46 records were included in this scoping review. Among these, six were narrative reviews, eight were

observational studies, and 32 were single cases or case series. Publication dates of the peer-reviewed papers ranged from 1982 to 2021.

Among the six narrative reviews, published between 1996 and 2015, two focused on clinical manifestations of acquired childhood aphasia (Paquier & Van Dongen, 1996; Van Hout, 1997), two examined the specific clinical condition of crossed aphasia (Marien et al., 2001; Marien et al., 2002), one considered childhood language disorders following central nervous system injuries, including aphasia (Dennis, 2010), while the last one analyzed acquired speech and language disorders, in particular dysarthria and aphasia (O'Hare, 2015).

The eight identified retrospective observational studies were published between 2000 and 2021 and were heterogeneous in terms of purpose, methodology and recruited population.

Finally, the present review included nine case series (Aram et al., 1983; VanDongen, Loonen & VanDongen, 1985; Cranberg et al., 1987; Martins & Ferro, 1993; Garg & DeMyer, 1995; Patel, Smith & Garg, 1995; Bottari et al., 2001; Gout et al., 2005; Kozuka et al., 2017) and 23 single cases (see Table 1). Among these, nine cases were also considered and cited in the above-mentioned narrative reviews (Van Dongen et al., 1985; Cranberg et al., 1987; Tanabe et al., 1989; Burd et al., 1990, Martins et al., 1993; Ikeda et al., 1993; Hynd et al., 1995; Marien et al., 2001; Hetherington et al., 2004). Overall, 56 case descriptions (30 males and 26 females) were analyzed. Papers were published between 1982 and 2021.

3.1. Definition of post-stroke childhood aphasia

All authors referred to the acquired linguistic disorder in children using the term “aphasia”, with the exception of O'Hare (2015), who adopted the terms “aphasia” and “dysphasia” interchangeably, and Danelli et al., (2013), in which “dysphasia” was used referring to “the partial loss of the ability to communicate through speech as a result of injury to the brain”. Beside “aphasia”, some authors used specific combined expressions, including “childhood aphasia” (Hynd et al., 1995; Hetherington & Dennis, 2004), “Acquired Childhood Aphasia (ACA)” (Ikeda et al., 1993; Martins & Ferro, 1993;

Pitchford et al., 1997; Pitchford & Funnell, 1999; Bottari et al. 2001; Marien et al., 2001; Ortiz et al., 2007; Chilosi et al., 2008; Martins et al., 2009; Kojima et al., 2011; Kozuka et al., 2017), “Acquired Aphasia in Children (AAC)” (Ferro et al., 1982; Aram et al., 1983; VanDongen, Loonen & Van Dongen, 1985; Cranberg et al., 1987; Tanabe et al., 1989; Burd et al., 1990; de Bleser, Faiss & Schwarz, 1995; Gout et al., 2005; Marien et al., 2005).

Only a few studies provided an extended definition for childhood aphasia, describing it as a language deficit following a cerebral lesion sustained after a specific period of typical language development (Paquier & Van Dongen, 1996; Hetherington & Dennis, 2004; Chilosi et al., 2008; Dennis, 2010; Laures-Gore, McCusker, & Hartley, 2017; Kozuka et al., 2017). Some authors suggested the use of aphasia for acquired language disorders appearing after the acquisition of first sentences around two years of age (Van Hout, 1997; Chilosi et al., 2008). Conversely, a brain lesion acquired before the age of two could be the cause of a so-called “developmental language breakdown” (Van Hout, 1997). Similarly, Avila and colleagues (2010) qualified the term “aphasia” as “a language impairment resulting from an encephalic lesion”. They used the term “acquired aphasia” for a brain injury occurred after two years of age and the expressions “dysphasia” or “congenital aphasia” before the age of two.

3.2. Epidemiology of post-stroke childhood aphasia

Only a few of the included studies provided information about epidemiologic data. The prevalence of aphasia in the described stroke populations ranged from 7.4% (Al-Jarallah et al., 2000) to 66% (Avila et al., 2010). Assessment methodology, criteria and samples varied widely and were not extensively described.

Al-Jarallah and colleagues (2000) analyzed the presentations and sequelae of radiologically confirmed nontraumatic intraparenchymal brain hemorrhage in 68 children (aged between 3 months to 18 years) in Texas (lesion site not reported). The presence of aphasia was considered among the sequelae. According to the authors, 50% (N=34) of the sample regained normal neurologic

functioning, 25% (N=17) presented hemiplegia (the most common enduring deficit), while 7.4% (N=5) exhibited residual aphasia.

Avila and colleagues (2010) evaluated the linguistic and communicative performance of 32 children in Brazil, aged between eight months and 12 years at onset, with unilateral ischemic stroke (56% left hemispheric, 44% right hemispheric). The presence of language impairment was found in 66% of the sample (N=21) and age was the only variable significantly associated with such deficit (81% of children < 2 years of age at onset vs. 36% > 2 years).

Similarly, Ndiaye and colleagues (2018) retrospectively investigated the clinical presentation of acute ischemic stroke (50% left middle cerebral artery, 31% right middle cerebral artery, 19% other locations, laterality not specified), confirmed with CT and/or MRI, in 116 children (aged between 2 months and 18 years) in Senegal. The most common manifestations were right hemiparesis (84%, N=97), aphasia (19%, N=22), and partial motor seizures (10%, N=12).

Wilson and colleagues (2017) conducted a retrospective study investigating Acute Ischemic Stroke (AIS) in 3184 children and adolescents (aged >28 days to 20 years) within the 2012 Kids Inpatient Database (KID) in the United States (lesion site not reported). Aphasia was reported in 10% (N=316) of the sample at discharge from the acute ward.

Ligeois and colleagues (2019) analyzed the predictors of aphasia and dysarthria in 62 Australian children aged between 3 and 17 years with an arterial ischemic stroke, located in the left (32%, N=20), in the right (44%, N=27), or in both hemispheres (24%, N=15). Dysarthria and language impairments were found in 74% (N=46) and 50% (N=31) of the sample, respectively. However, no variable of interest, including age and site of lesion, was significantly associated with these conditions.

Sherman and colleagues (2021) retrospectively investigated swallowing, oral motor, motor speech and language impairments in 106 neonates and children after AIS (41.3% left hemisphere, 26.4% right hemisphere, 32.3% bilateral) in Canada; 24.9% (N=43) of the sample was diagnosed with aphasia.

3.3. Diagnostic tests used in post-stroke childhood aphasia

Specific information about the diagnostic process of post-stroke childhood aphasia was provided by Van Hout (1997), who considered the diagnosis of ACA as a multistage process involving different specialists.

A detailed assessment of post-stroke language abilities was deemed crucial to plan an adequate rehabilitation program. Bottari and colleagues (2001) conducted a cognitive and linguistic assessment without reporting the adopted tests, while Avila et al. (2010) evaluated children linguistic performance through a semi-structured observational assessment, without any further specification. Among case reports and case series, 26 studies reported the use of specific tools to evaluate post-stroke linguistic impairments and/or overall cognitive functioning. For a summary of the assessment tools used in the included studies, see **Appendix 2**. 19 out of the 26 studies reported the use of language development standardized tests; five of these 19 did not complete the linguistic assessment using any specific tool for aphasic disorders. Aphasia tests and batteries, validated for adults, were adopted in 19 studies out of 26. Among them, three studies used these tools to assess preschoolers (Ferro et al., 1982; Martins & Ferro, 1993; Gout et al., 2005). Aram et al. (1998) and Martins et al. (2009) were the only studies reporting the use of assessment tools specific for aphasic disorders in children (i.e., the Northwestern Syntax Screening Test (Lee, 1969) and the Batterie d'évaluation du langage oral de l'enfant aphasique – ELOLA (De Agostini et al., 1998) respectively). Ikeda et al., (1993) did not report the use of language tool but only adopted a general intelligence test for assessment. Overall, out of the 26 studies, general intelligence tests were adopted in 15 studies, while non-verbal intelligence was evaluated by 12 studies. Additionally, 12 studies included clinical evaluations of cognitive functions other than language.

Finally, several studies underlined the importance of neuroimaging evaluation through Computed Tomography (CT) or Magnetic Resonance Imagery (MRI) to confirm the diagnosis of stroke and characterize the cerebrovascular lesion (Paquier and Van Dongen, 1996; O'Hare, 2015 and all the

included case reports and case series, 56 children in total). In 20/56 cases (36%) aphasia occurred after a cortical lesion (including the frontal, parietal, temporal, and occipital lobes), in 17/56 cases (30%) it followed a pure subcortical lesion (including the internal capsule, the thalamus, and the basal ganglia), while in 19/56 cases (34%) it was subsequent to cortico-subcortical damage.

Functional neuroimaging was performed in five studies (Chilosi et al., 2008; Elkana et al., 2011; Zipse et al., 2012; Danelli et al., 2013; Carlson et al., 2016; Kozuka et al., 2017) to determine the activation of perilesional or contralesional areas and specific networks during linguistic tasks (Elkana et al., 2011; Danelli et al., 2013) or during the recovery process (Chilosi et al., 2008; Zipse et al., 2012; Carlson et al., 2016; Kozuka et al., 2017).

3.4. Clinical Manifestation of post-stroke childhood aphasia

Paquier and Van Dongen (1996) and Van Hout (1997) provided an overview of ACA, focusing on the changes in its clinical description that occurred between the late 1970s and the 1990s. O'Hare (2015) and Dennis (2010) highlighted that children can show both non-fluent or fluent aphasia and described different levels of language representation including pragmatics, syntax, semantics, phonology, morphology, speech production and comprehension that can be impaired. O'Hare (2015) also reported how children's recovery is usually greater and faster than in adults; nonetheless pragmatic impairments, problems with making inferences, and written language difficulties often persist. Marien and colleagues (2001; 2002) focused on the particular clinical condition of crossed aphasia, in which the "aphasic syndrome results from a cerebral lesion ipsilateral to the dominant hand". The authors highlighted that Crossed Aphasia in Dextrals (CAD) is not as common in children as previously thought: only five children (2.7%) in a cohort of 180 presented with crossed aphasia, and only two of them were considered to be representative of childhood CAD.

The nine case series and the 23 single cases considered for this review, as well as the demographic and clinical features of their 56 included participants, are presented in **Table 1**. Data about the examined clinical features (comprehension, repetition, written language) were not always available

(e.g., Lietz et al., 2005 and Ortiz et al., 2007 only considered the fluency and the comprehension without reporting a full linguistic description). Written language was never assessed in children below six years of age. Out of the overall sample, initial mutism was reported in 16 children (29%). Among negative symptoms, the most frequent were word-finding difficulties (N=40, 71%), agrammatic/telegrammatic speech (N=17, 30%) and articulation disorders (N=14, 25%). Positive symptoms recurred in many case descriptions, in particular paraphasic errors (N=29, 52%), neologisms (N=14, 25%), and perseverations (N=5, 9%). Jargon and logorrhea were never reported. Data about positive and negative symptoms are reported in **Table 2**.

Follow-up evaluations were performed at different times after the onset of symptoms (ranging from one month to 20 years, see **Table 1**). Most children (N=38, 68%) improved their residual language deficit, while 15 children (27%) completely recovered from aphasia. In one case the child did not show any improvement at follow-up evaluation (Van Dongen, Loonen & Van Dongen, 1985) and in another case the child died on the fourth hospital day (Patel, Smith & Garg, 1995). In one case follow-up was not conducted and information about the clinical outcome was not reported (Goldberg & Benjamins, 1982).

4. DISCUSSION

Aphasia in children is a complex and debated topic. The aim of the present scoping review was to provide a comprehensive overview of post-stroke acquired aphasia in children, focusing in particular on the definition, the epidemiology, the diagnostic process, and the clinical manifestations of this condition. Overall, few studies provided information about aphasia in this specific population: out of 190 full texts screened, the majority focused on children with language disorders due to different or mixed etiologies (e.g., traumatic brain injuries, brain tumors, infectious disorders, epileptic syndromes), and only 46 relevant works were included in this scoping review. Most of the included studies described case series or single cases, while the remaining were review articles (the most recent one being published in 2015) and observational studies. Publication dates of the case series, the single

cases, and the narrative review articles were quite spread in the last forty years while the observational studies were more recent.

Overall, the heterogeneity of information extracted from the included articles often limited the possibility to collect unambiguous data and yielded weak conclusive recommendations for the clinical management of post-stroke ACA. The analysis of the results allowed to identify the areas where current knowledge is more fragile and to outline possible paths for future research.

4.1. Definition of post-stroke childhood aphasia

Compared to the variety of terms found in scientific literature on acquired language disorders in children (O'Hare, 2015), restricting the focus on post-stroke aphasia revealed greater convergence regarding terminology and definition. The main difficulties related to the definition of this disorder concern the fact that aphasia occurs when language skills are still developing and, probably, will evolve in an atypical way. For this reason, most of the authors converge on the use of the term "acquired" to mark the difference between ACA and the developmental language disorders, such as "developmental aphasia", "specific language impairment" and "dysphasia". Considering that post-stroke acquired aphasia is described as a disorder of the linguistic function that occurs after a specific period of typical development, timing for the definition of this disorder should be set. Interestingly, Van Hout (1997), Chilosi et al. (2008), and Avila and colleagues (2010) proposed a cut-off for the definition of ACA after two years of age. This stance is coherent with language development theories that consider this age as a fundamental stage for the expansion of the vocabulary (Goldfield & Reznick, 1990) and the rise of the combinatorial features of language (Nelson, 1985). Additionally, this developmental stage is also considered crucial for the early identification of developmental language disorders (Chilosi et al., 2008). Therefore, according to the above-mentioned studies (Van Hout, 1997; Chilosi et al., 2008; Avila et al., 2010), we believe that the two-year cut-off is a reasonable reference for the diagnosis of post-stroke ACA.

Given the fair robustness of this definition, future research should selectively investigate whether pre- or post-two-year-old brain injuries determine two distinct clinical clusters that significantly differ in terms of linguistic symptoms (cf. Avila et al., 2010), global cognitive functioning, and prognosis. These possible differences could further substantiate the validity of the age cut-off for diagnostic definition of post-stroke ACA.

4.2. Epidemiology of post-stroke childhood aphasia

Epidemiological data on post-stroke childhood aphasia were reported only by a few studies, and were inferred from the incidence of stroke. The sample size of the included papers reporting epidemiological information presented a great variability. The majority of the studies considered a small population with the exception of Wilson and colleagues (2017) who analyzed 316 children and adolescents with aphasia. As highlighted by Feigin and colleagues (2014), about 83,000 strokes occur annually in children. Among them, about 20-30% show aphasic disorders (Carlson et al., 2016). This percentage is comparable to that of the adult population, in which post-stroke aphasia occurs in about one third of cases, with an incidence ranging between 21% and 37% (Brust et al., 1976; Pedersen et al., 1995; National Aphasia Association, 1999). Among the included studies, the prevalence of aphasia following ischemic or hemorrhagic stroke varied between 7.4% (Al-Jarallah et al., 2000) and 66% (Avila et al., 2010). As for Wilson et al. (2017) and Ndiaye et al. (2018), we were not able to determine whether children below the age of two with post-stroke linguistic impairment were diagnosed with aphasia. We retrieved data from different countries all over the world, but the paucity of the studies and the information did not allow any generalization based on the geographical distribution. Concerning the case reports and case series included in the present work, data (see **Table 1**) were in line with the scientific literature on pediatric stroke (Tsze & Valente, 2011; Steinlin, 2012), with slightly more boys than girls presenting with aphasia (M/F=1,15). Moreover, most children were right-handers and experienced a left hemispheric stroke. These results are similar to those of the adult population (National Aphasia Association, 1999) and in contrast with Lenneberg's standard doctrine,

in which aphasia was considered more common after damage to the right hemisphere (Lenneberg, 1967). It is worth noting that, in the included studies, the definition of aphasia as well as the age at onset were often underspecified and might not correspond to those we explicated in the previous paragraph. Overall, given the lack of data, future studies on stroke populations should always report the presence of aphasia, explaining its definition and specifying the criteria adopted for the differential diagnosis, the age of the subjects involved and the underlying causes of the stroke (e.g., heart problems, blood disorders, dehydration, etc.).

4.3. Diagnostic tests used in post-stroke childhood aphasia

Diagnosis of ACA can be described as a multistage process conducted by different health specialists (pediatricians, neurologists, neuropsychologists, speech-language pathologists) aimed at exploring the residual linguistic abilities of children after acquired brain injury (Van Hout, 1997). To date, no specific criteria are available for the diagnosis of post-stroke aphasic disorders in children. Nevertheless, an extensive assessment of both linguistic and cognitive functioning is essential in order to determine the patient's clinical profile and set up specific rehabilitation programs.

Different tools for the clinical assessment of language abilities were used across the included studies, ranging from tests for aphasia in adults to tests for language developmental disorders in children. Only two authors adopted specific tools for aphasic disorders in children (Aram et al., 1983; Martins et al., 2009). Moreover, the approaches to global cognitive evaluation included a mixture of verbal and non-verbal tests and intelligence tests across all studies. Among the included case studies and series, adult aphasia batteries were adopted with school-aged children after the age of six (see **Appendix 2**). However, language tests for adults with aphasia cannot be considered adequate for post-stroke children because their normative data are defined on the basis of a population characterized by a complete language and literacy development. In addition, many of these tests have specific norms for age and education level even within the adult population. Therefore, their use with a different population is poorly reliable. Moreover, even tests of language development may not

always be appropriate tools for the assessment of ACA because they are not designed based on aphasia-specific interpretive models. The development of a comprehensive battery for the cognitive and linguistic evaluation specific for children with post-stroke aphasia would be an essential step for the improvement of clinical and functional diagnosis. On the one hand, following a neurolinguistic perspective, tools that allow to distinguish between different aphasic syndromes (i.e., Broca's aphasia, Wernicke's aphasia, etc.) should be developed for both clinical and research purposes. These instruments, indeed, facilitate communication among clinicians and increase homogeneity in group studies. On the other hand, implementing assessment tools based on the psycholinguistic models of language processing would likely improve functional diagnoses (i.e., to locate the level of impairment within the model) and rehabilitation programs.

Regarding the neuroimaging evaluation, in the last decades, CT or MRI were adopted much more frequently to characterize the brain lesion (Paquier & Van Dongen, 1996; O'Hare, 2015). In the included studies, structural neuroimaging techniques were always performed in order to support the clinical diagnosis of stroke. Yet, data about the localization and size of the acquired brain lesions were not frequently reported and the disparity in patterns of cortical damage did not allow a clear anatomic-clinical correlation. Interestingly, functional neuroimaging was used in the most recent studies for the examination of brain activation and reorganization patterns in experimental conditions. Since the site and size of the brain lesion are among the most significant determinants of post-stroke aphasia prognosis in adults (Plowman et al., 2012; Watala & Balarabe, 2015), future works on ACA should include and analyze neuroimaging data. This information could help to better understand the clinical profile of post-stroke childhood aphasia, the anatomic-functional connectivity of language in children and the recovery process.

4.4. Clinical manifestations of post-stroke childhood aphasia

In contrast with Lenneberg's standard doctrine (1967), that described childhood aphasia as invariably non-fluent with the absence of positive symptoms and unimpaired comprehension, a great diversity

in clinical manifestations was reported in our review. Despite O'Hare (2015) described aphasia in children as predominantly non-fluent, with initial mutism, agrammatic speech, word-finding difficulties, and articulatory disorders, the author highlighted that positive symptoms may also appear (e.g., neologisms, paraphasias, jargon, logorrhea, verbal stereotypes, perseverations, and circumlocutions or paragrammatical speech). Moreover, language comprehension can be mildly to severely impaired, with marked difficulties to make inferences. This description is consistent with the results that emerged from our analysis of the included case series and single cases (cf. **Tables 1** and **2**). According to the standard doctrine (Lenneberg, 1967), the aphasic symptomatology in children was invariable, regardless of the lesion site. On the contrary, we found that the clinical manifestations of ACA differed as the location of the brain injury varied. This confirms that different aphasic profiles (i.e., Broca's aphasia, Wernicke's aphasia, conduction aphasia, etc.) can appear in post-stroke children as in adult population, with variable impairments involving both speech production and comprehension at all the different levels of language representation. As previously discussed, the reported data did not allow to identify a reliable correlation between symptoms and lesion sites. Interestingly, predominant phonologic and syntactic deficits appear after perinatal and neonatal brain injury, while a majority of semantic impairments arise when the cerebral lesion occurs after the age of two (Avila et al., 2010). According to the author, during the first year of age language development is realized mainly by the acquisition of the phonemes and the first combinatorial aspects of language (e.g., phonotactic constraints, proto-words, and gestures combinations), while the semantic aspects might be still processed in a multimodal way. Hence, in the examined literature a conclusive integration between aphasia models in adults and developmental language models is lacking and should be implemented.

Concerning the prognosis, Lenneberg's standard doctrine (1967) claims that aphasia recovery in children was rapid, complete, and directly related to the age at symptoms onset. This belief has been contradicted by more recent studies. Even if post-stroke children usually show greater and faster recovery than adults, long-term impairment and consequent learning difficulties are usually detected

(Van Hout, 1997; O'Hare, 2015). Consistently, among the case descriptions included in the present work the majority of children showed residual language impairment at follow-up (ranging from one month to 20 years, see **Table 1**), while in 27% of children aphasia completely resolved (Aram et al., 1983; Tanabe et al., 1989; Martins et al., 1993; DeBleser et al., 1995; Garg & DeMyer, 1995; Marien et al., 2001; Gout et al., 2005; Lietz et al., 2005; Ortiz et al., 2007; Vinayagamani et al., 2018). The optimistic view of childhood aphasia as a transient phenomenon was then rejected: the recovery appears to be more incomplete and the prognosis less favorable than previously thought. In particular, our findings not only confute Lenneberg (1967) idea of a complete recovery for unilateral lesion occurred before puberty but also fail to identify age-at-onset as a prognostic factor. Paquier and Van Dongen in their narrative review (1996) proposed that different variables (type of aphasia, site and size of the brain lesion, etiology) could influence the recovery process. The data we retrieved, specifically focused on post-stroke childhood aphasia, did not outline clear predictors of clinical recovery. It follows that, as regards the positive prognostic factors of ACA, further studies are needed to better investigate this important issue.

The last point of the standard doctrine (Lenneberg, 1967) highlighted that acquired aphasia after right cerebral lesion in right-handed children (crossed aphasia) was frequent. However, out of 180 cases of crossed aphasia in dextrals described since 1975, only five (2.7%) were children and only two of them were considered representative of childhood CAD (Marien et al., 2001; Marien et al., 2002). Moreover, crossed aphasia does not seem to be more frequent in children than in the adult population (Marien et al., 2001) and its clinical manifestations are similar to those observed following left hemisphere brain injury, with a great variety of aphasic symptomatology (Marien et al., 2001; Marien et al., 2002). According to Lenneberg's view (1967), the higher prevalence of CAD in children and the favorable prognosis were proofs in favor of the equipotentiality of the brain hemispheres for language development. We showed that recent data contradict these two assumptions and support the idea of an early lateralization of the linguistic function in the left hemisphere.

Future studies should better analyze the clinical presentation of aphasia in children, attempting to clusterize the symptoms and trace them back to the classic aphasic classification. The prognosis should be also investigated focusing on those factors that might influence the recovery process (i.e., stroke type, lesion site, lesion size, aphasia profile, age-at-onset, associated disorders etc.). Periodic follow-ups should also be scheduled and documented in order to monitor the evolution of symptoms and enhance our knowledge on language recovery during development.

4.5. Strengths and Limitations

To the best of our knowledge, this is the first attempt to provide a structured overview on post-stroke acquired childhood aphasia. To ensure a broad and fine analysis of the literature, three electronic bibliographic databases were searched, articles were examined by four independent reviewers, and findings were discussed within an interdisciplinary team (neurologist, phoniatrician, neuropsychologists, and speech-language therapists). Nevertheless, some limitations are worth noting. It was not possible to undertake a more systematic approach because the retrieved studies on this topic were not sufficiently homogeneous in terms of aim and methodology. This limited the strength of evidence and the possibility to provide incontrovertible recommendations for the clinical practice. Consequently, our point of view in the discussion is mainly grounded on single or small groups of studies and it should be confirmed in the future. Moreover, this review did not include the gray literature and potentially relevant articles published in languages other than English. Future perspectives of this line of research should also consider different etiologies other than stroke to provide a comprehensive understanding and useful comparisons of aphasic disorders in children.

5. CONCLUSIONS

The present review summarizes and consolidate the most updated understanding of post-stroke acquired childhood aphasia (ACA). In particular, post-stroke ACA can be defined as a language disorder frequently identified following a cerebrovascular injury that occurs after two years of age.

The traditional point of view on this disorder (i.e., “standard doctrine”) has been challenged during the last decades and its clinical manifestations are now considered more similar to the adult syndromes than previously thought.

In conclusion, the present review on post-stroke ACA allows us to make some ultimate considerations and give some recommendations for the clinical management and future research on this brain disorder, aimed at improving its knowledge and treatment. Firstly, epidemiological information is limited; to date, ACA affects approximately one-third of the post-stroke pediatric population and deserves to be better evaluated. Therefore, multicenter studies that favor a more careful clinical characterization and a better definition of the prognostic predictive aspects should be promoted. Secondly, the analysis of assessment procedures in this population revealed a fair variability and the absence of specific diagnostic tool for ACA. Consequently, there is a need to develop and validate adequate tests for a comprehensive evaluation and an effective monitoring of the recovery process. Assessments should also include the determination of the global cognitive profile explored through the adoption of age-appropriate non-verbal cognitive tests. In addition, considering that in ACA the disruption of language occurs in a developmental context, itself characterized by variability and possible disorders, it is advisable to collect a careful premorbid history for a correct diagnosis. Thirdly, beyond the neuroradiological diagnostic evaluations, we believe that the aphasic condition in childhood deserves greater attention as far as neuroimaging research is concerned, with particular reference to anatomical-functional correlations. In this sense, further functional studies should be carried out in the future to better document the improvement of the post-injury clinical condition during the rehabilitation program. Furthermore, in perspective, it will be possible to better consider the evolutionary potential of the cerebral cortex and the structural connectivity between the different brain regions during the course of childhood and adolescence, aspects recently documented with macro- and microstructural magnetic resonance analysis (Norbom et al, 2020; Norbom et al, 2021). Finally, future longitudinal studies are needed to evaluate the efficacy of specific treatments and possible rehabilitation outcomes in ACA. In this context, it will be advisable to improve the strategies

aimed at a personalized rehabilitation, which takes into account the individual differences related to age, the clinical expression of the aphasic disorder, the neuroimaging parameters, and the possible future biological markers of cerebrovascular lesions, all potentially affecting the prognosis.

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8. DISCLOSURES OF INTEREST

The authors report there are no competing interests to declare. The authors report no conflict of interest

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