To be or not to be? What makes a child dyslexic. An overview on risk factors and correlated clinical aspects

ABSTRACT

Developmental dyslexia, one of the most common neuro-developmental disorders, is frequently under-diagnosed or diagnosed late. Despite there is consensus on the neurobiological and genetic basis and on the environmental influence, the multi-faceted aspects of dyslexia and the complexity of its phenotypic expression hinder the identification of the risk factors. Indeed, determining risk factors and understanding how they predispose to the reading disability is important for an early diagnosis and a satisfactory rehabilitative outcome. The aim of this paper is therefore to provide an overview on the genetic, biochemical, anatomical and environmental variables involved in the pathogenesis of developmental dyslexia, and on the visual-perceptual aspects that characterize children who struggle to read.

1. INTRODUCTION

Developmental dyslexia is a neurobiological disorder characterized by impairment in reading accuracy and fluency despite conventional instruction and socio-cultural opportunity, in the absence of unfavorable cognitive factors and intellectual disability [1]. Dyslexia, that occurs in approximately 5-10% of the population [2], is often diagnosed late or under-diagnosed [3], probably because consensus on the most suitable diagnostic procedures and on risk factors is still missing [4]. Indeed, early identification of future dyslexics in the school-age population is pivotal, as it allows early intervention, and early intervention improves the rehabilitative outcome [2]. In this perspective, knowledge and detection of anatomical, genetic, social-environmental, biochemical and phonological variables as well as the co-occurring co-morbidities and neuro-ophthalmological abnormalities is a fundamental step toward case identification.

2. ANATOMICAL FACTORS

In post-mortem studies, anomalies in the cerebral maturation of the temporo-parietal, occipital and frontal regions of the left side of the dyslexic brain have been described [5,6]. Moreover, lack of asymmetry between the two cerebral hemispheres, alterations of the corpus callosum [6,7], and especially areas of dysplasia and ectopia in the cortex of the frontal lobe and the left hemisphere [8] have been reported. It is likely that the pathogenetic mechanism responsible for these anatomical changes depends on abnormal neuronal migration [8] and retarded cerebral maturation during the sixth month of gestation, the period in which brain development is most rapid [6, 9].

Involvement of the cerebellum is found in adults with dyslexia [10], in agreement with poor oculomotor control, difficult acquisition of automatic learned tasks, postural instability [11], and impaired procedural learning of many disabled readers [12].

Moreover, in vivo meta-analytic morphofuncional studies found reduced gray matter in small areas as superior temporal sulcus and right superior temporal gyrus [13], left occipito-temporal region, bilateral temporo-parietal area and volumetric reduction of the cerebellum gray matter [14].

3. GENETIC AND BIOCHEMICAL FACTORS

There is compelling evidence that dyslexia has a genetic basis. Due to dominant autosomal inheritance, the prevalence of this disorder is 40-60% if one of the parents is dyslexic, and up to 75% if both parents are affected [9]. In this case, the disability is more severe [15]. Prevalence reaches 80% if, in addition to parents, other relatives are dyslexic [16]; finally, 40% of the siblings of dyslexics suffer from the same condition and the percentage of parents of affected people who meet the criteria for a diagnosis of dyslexia ranges from 27 to 49% [17]. To explain the inheritance pattern, genetic mutations in specific chromosomal loci (in particular genes DCDC2, DYX1C1, ROBO1, KIAA0319 on chromosome 1, 2, 3, 6, 15) seem associated with poor reading ability and phonological deficits [18-20].

According to a strand of research, these genetic alterations cause a hormonal imbalance that, in turn, induces a condition of hyper-autoimmunity [21, 22]. Hormonal alterations concern mostly testosterone: high levels of testosterone would up-regulate the expression of MHC-genes (on the short arm of chromosome 6) in the thymus of the fetus, leading to an abnormal thymus-dependent immune response that would affect the cerebral maturation [23]. This explanation accounts on the one hand for the frequent autoimmune and allergic disorders (asthma, eczema, hay fever) in dyslexics, on the other for the increased prevalence of (dyslexia-related) neuro-developmental problems in families with autoimmune diseases [22, 23]. According to this theory, the thymus-dependent immune over-reaction affects the maturation of the M-system [24]. The magnocellular system is the retino-cortical pathway made of large ganglion cells, involved in processing transient stimuli, and responsible for the saccadic movements. Indeed, an alteration of the magnocellular (M-) system is documented in dyslexia, and is argued to be co-responsible of the reading disability [e.g. 25, 26].

Not only a hormonal imbalance but also depletion of polyunsaturated fatty acids (PUFAs) has been reported (see Aleci, 2017 for a review [27]). PUFAs, namely omega-3 and omega-6, are important structural components of the cell membranes and the cytoskeleton, and their availability is necessary to the neuronal growth [28,29]. Low PUFAs' serum concentration depends on increased serum concentration of phospholipase A2 and/or on deficient dietary intake during the developmental age [28-30]. Of the neurons, magnocells' membranes need particularly high amounts of polyunsaturated fatty acids to preserve flexibility and develop in size [26]: so, reduced availability of PUFAs can explain why the average size of this class of neurons is smaller in dyslexics [29]. The presumed role of PUFAs' depletion in dyslexia is suggested by the lexical improvement after dietary supplementation in disabled readers [31].

It is worth considering that the effect of PUFAs' depletion extends beyond the lexical ability, and determines systemic signs and symptoms like dandruff, dry skin and dry hair, follicular keratosis, soft and brittle nails, pollakiuria, and polydipsia: interestingly, many of these signs have been documented in a mild form also in dyslexic subjects [32-33], to the point that their investigation could help identify cases at the pre-school age. In support of the relationship between PUFAs and dyslexia, reduced levels of PUFAs have been reported also in patients suffering from the neurodevelopmental disorders typically associated with dyslexia (especially attention deficit hyperactivity disorder and dyspraxia) [34].

Finally, increased cerebral levels of glutamate and choline may affect the lexical performance. A high concentration of glutamate and choline is argued to have a detrimental effect on reading via morphological and functional changes in the neuronal membranes and in the white matter; in fact, abnormal levels of these substances have been documented in dyslexics [30,35]. Increased glutamate in the nervous system may determine hyper-excitability of the neuronal pathways involved in reading and learning [36]; in turn, increased cerebral choline levels could be responsible for abnormal neuronal membrane turnover [30] as well as defective neuronal connectivity and myelination [37]. A recent investigation on emergent readers (ranging in age from 6 to 10 years old) with magnetic resonance spectroscopy showed an inverse correlation between glutamate/choline levels in the brain and reading performance and phonological skills (higher concentration = poor performance) [35].

4. MATERNAL MORBIDITIES DURING PREGNANCY AND PERINATAL FACTORS

Dyslexia may be promoted by a maternal immune response (to infection) that involves the fetus [38]. It is interesting considering, in this respect, that an etiological role in neuropsychiatric disorders has been attributed to prenatal maternal immune activation involving the interleukin-17a pathway [39-40].

According to case-control studies, family history of abortion increases the probability of dyslexia, and the risk of miscarriage requiring hospitalization is higher in families with reading disorders compared to controls [38, 41, 42].

Gestational age and birth weight are among the most important perinatal predictors of reading performance and developmental dyslexia [43]. Children with gestational age less than 28 weeks and/or with very low birth weight (<1000 grams) are more exposed to neurodevelopmental disorders, and in many cases they show lower reading ability compared to school-age controls (despite a normal IQ [44,45]). Bowen [44], indeed, found that these children have lower academic outcomes and are more frequently below the expected reading level (48% of the cases vs 13% of age-matched controls). In effect, very low birth weight may be associated with magnocellular pathway/ dorsal stream dysfunctions, and, consequently, may affect the visuomotor and visuospatial performance [46].

Mild neonatal asphyxia and consequent moderate cerebral ischemic hypoxia without neurological symptoms are argued to affect the dendritic development and the plasticity of the visual cortex [47], posing at risk of reading disability [38]. In this regard, there is evidence that mild neonatal encephalopathy due to perinatal asphyxia makes children at risk for reading and spelling difficulties despite a normal intelligence quotient [48].

Consistently high serum bilirubin level (> 340 µmol / l) [49] seems to be another perinatal risk factor. Bilirubin neurotoxicity involves the basal ganglia, globus pallidus, subthalamic nuclei, hippocampus, diencephalon, midbrain, pons, and brain stem nuclei as well as the cerebellum [50]: these are brain structures that, indeed, take part in the motor, sensory and cognitive function, reading (presumably) included [49].

Finally, retinopathy of prematurity, even when promptly treated in infants with very low weight at birth, may have a detrimental effect on reading development. However, as pinpointed by Takeuchi and associates, this theory requires further investigation [51].

5. ENVIRONMENTAL FACTORS

Environmental maternal factors during pregnancy and in the perinatal period may contribute to the development of the reading skills in the child.

In particular, smoking during pregnancy may affect reading achievements [52]. Indeed, nicotine exposure looks to be a fairly good predictor of school-age reading abilities: in children born at term, the association between maternal exposure to high amounts of nicotine (> 17mg/day) and decreased or delayed reading ability has been documented (correlation between nicotine level and reading ability ranging from r=0.54-0.84), and increased risk of developing reading disorders has been reported in the exposed subjects (Wilk's Lambda=0.989 [52]).

Finally, a family history of neuropsychiatric diseases and maternal use of antipsychotics in the prenatal period pose the use of these drugs at risk for dyslexia in the offspring: Liu [38] found these familial conditions are slightly more frequent in dyslexic students than in controls (prevalence: 2.3% vs 0.8%, respectively).

Not only health-related but also social and cultural environmental factors play a role. Familial socioeconomic status and home literacy environment are good predictors of early reading skills [53], and modulate the reading development [54]: the educational level of the family, the job of the mother, and the frequency with which parents tell stories to their children and encourage them to read outside of school assignments, in fact, help developing reading ability [55]. The parental involvement in helping children to learn to read and write exerts a positive effect on early literacy skills [56].

According to an Italian study, very young parental age increases the risk of dyslexia [42], probably because the offspring of younger mothers often grows in a relatively poorly educated and socially disadvantaged familial environment [57].

6. NEUROPSYCHIATRIC CORRELATED FACTORS

Approximately 60% of dyslexics meet the criteria for at least one of the following neuropsychiatric disorders [58]: depressive moods, anxiety symptoms, somatoform disorders, poor self-esteem, behavioral problems, aggressiveness, and other externalizing disorders like attention deficit hyperactivity disorder (ADHD) [59-62]. ADHD, in particular, is reported in up to 40% of disabled readers [58].

7. PHONOLOGICAL FACTORS

It is well known that phonological problems play a substantial role in the lexical task, at least in a class of patients [e.g. 4]. The so-called "phonological" dyslexics struggle to acquire a normal reading ability because they do not learn to split the sounds of a word and have problems in matching speech sounds (phonemes) with the visual counterparts, namely graphemes [4]. In effect, difficulty in phonological awareness, whose role is pivotal when processing words, is an early manifestation and a strong predictor of developmental dyslexia [4,63]. Phonological deficits prevent the acquisition of letters, and poor letter knowledge represents one of the first signs of dyslexia in children at risk for reading difficulties [63].

Considered that the M-cells process transient stimuli [64], impaired phonological decoding of brief auditory stimuli in dyslexia may depend on a magnocellular deficit.

A linguistic impairment is common in disabled readers [65-66]; language delay (first words pronounced beyond 18 months) is an early marker of learning disorders and is frequently reported in relatives of persons with dyslexia [66, 67]. According to Ebro and associates, the linguistic parameters predict reading ability in 79-84% of the children with familial risk for developmental dyslexia [68].

8. VISUAL PERCEPTUAL AND VISUO-MOTOR FACTORS

Despite population studies do not support a relationship between dyslexia and reduced visual acuity [69], refractive defects [70-72], latent or manifest strabismus [69, 71, 72], abnormal motor and sensory fusion and amblyopia [72], weak accommodative power [70-72], or convergence insufficiency [72], there is evidence of subtle visual-perceptive alterations in a relevant number of disabled readers (see Aleci, 2013 for a review [73]). These alterations, not detectable during a routine eye examination, account for many of the signs and symptoms complained by dyslexics: the sensation of moving or "jumping" letters, syllables or words, intermittent blurring, eye fatigue, eye redness, headache, repetitive blinking, and ocular strain [74-76].

Among signs, in the recent past particular importance was attributed to a deficit of fine ocular movements: in fact, during reading, dyslexic children show increased number and duration of fixations, increased number and length of backward saccades (regressions) and more forward saccades with lower amplitude compared to normal readers [77-81]. Yet, these oculomotor alterations are absent outside the lexical task [77-79], so that a primitive, causal role of the fixation/saccadic pattern in the reading difficulty is unlikely.

A different strand of research invokes unstable ocular dominance that generates fixation instability [e.g. 82-83]. Fixation instability, that is the oscillation of the visual axes around letters and syllables, hampers their recognition and positional encoding [83]. This alteration is found to affect up to 75% of dyslexics versus 10% of the controls [82].

Not only visual-motor alterations but also subtle sensory abnormalities have been advocated. In particular:
- contrast sensitivity at low spatial frequencies and high temporal frequencies [e.g. 84];
- coherent motion perception [e.g. 85, 86];
- visual persistence time [87];
- visual-spatial attention [88-89];
- spatial relationship perception [90, 91] and increased paracentral crowding [92]. Visual crowding is a physiological effect that depends on the interference of flanking letters on the recognition of a central character if letters are so close to falling within a spatial interval, called "critical spacing". In dyslexics, the critical spacing is found to be larger in the paracentral region [92], and this account for their reading difficulty [92, 93].

In previous studies, we documented increased spatial relationship anisotropy in a class of dyslexic readers. We have defined spatial relationship anisotropy (SRA) as the biased perceptual contraction of the visual space along the horizontal axis. We found that spatial relationship anisotropy is above average in dyslexic children, and argued that this perceptual contraction makes letters and syllables illusory closer, generating abnormal crowding [90]. The same alteration is subsequently found also in adult disabled readers [91]. In support of this hypothesis, reading rate and reading accuracy of dyslexics with abnormal spatial relationship anisotropy benefit from increased inter-letter spacing [90].

As underlined by Kevan and Pammer, subtle visual impairments in children with familial risk of dyslexia may be detected (with appropriate tools) even before they learn to read, suggesting that the normal development of the visual-perceptive function is pivotal to the normal acquisition of the reading skill [86]. Therefore, investigating these alterations with specific psychophysical tests can provide important pieces of information. In addition to the instrumental diagnosis, self-report inventories focused on the aspects described in this paper are a promising tool for screening purposes and early identification.

For example, the Analytic Anamnestic Protocol (AAP) [94-95] is a multiple-choice questionnaire consisting of four sections (familial medical history, general medical history, past and recent specialist medical history) devised to detect signs and symptoms reported by the patients or by their closest family members to identify future disabled readers from normal readers at an early stage [94-95]. In the AAP, a visual-motor and a visual-sensory score are assigned to each question and a total cumulative score for both domains is obtained. Interestingly, disabled readers appeared to have worse scores, especially in the sensory domain. ROC curve demonstrated adequate specificity and sensitivity for the AAP,

in support of its potential role as a diagnostic tool. In table 1 the risk factors and the clinical aspects related to dyslexia considered in this paper are summarized.

Genetical Factors	-Mutations on chromosome 1, 2, 3 , 6, 15	[18] Grigorenko et al., 1997; [19] Paracchini, Scerri, & Monaco, 2007; [20] Marino et al., 2012;
	-Dominant autosomal inheritance	[9] Stein & Talcott, 1999;
	-Hyper-autoimmunity/ autoimmune and allergic co-occurring disorders	[23] Geschwind & Behan, 1982;
Biochemical factors	-Polyunsaturated fatty acids (PUFAs) deficiency	[30] Richardson, Cox, Sargentoni, & Puri, 1997; [29] Livingstone, Rosen, Drislane, & Galaburda, 1991; [28] Zavodnik, Zaborowski, Niekurzak, & Bryszewska, 1997;
	-Increased brain Glutamate and Choline levels	[30] Richardson, Cox, Sargentoni, & Puri, 1997; [35] Pugh et al., 2014;
Anatomical factors	-Anomalies in the maturation of temporal, occipital and frontal cerebral regions	[5] Galaburda & Kemper, 1979; [6] Habib, 2000;
	-Lack of asymmetry of the two cerebral lobes/ corpus callosum abnormalities	[6] Habib, 2000; [7] Cohen, Cambell, & Yaghmai, 1989;
	-Cortical dysplasia/ ectopia	[8] Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985;
	-Cerebellar abnormalities	[10] Nicolson et al., 1999;
Perinatal factors	-Maternal infectious diseases, neonatal asphyxia -Family history of abortion	[38] Liu et al., 2016; 41] Gilger, Pennington, Green, Smith, & Smith, 1992
	-Risk of miscarriage requiring hospitalization -Gestational age < 28 weeks/ very low birth weight -Treated retinopathy of prematurity -High neonatal serum bilirubin level	[42] Mascheretti et al., 2015 [44] Bowen, Gibson, & Hand, 2002; [45] Samuelsson et al., 2006 [51] Takeuchi et al., 2016 [49] Hokkanen, Launes, &Michelsson, 2014
Environmental factors	-Maternal smoking during pregnancy	[52] Cho, Frijters, Zhang, Miller, & Gruen, 2013 [42] Mascheretti et al., 2015 [38] Liu et al., 2016
	-Young parental age -Family history of neuropsychiatric disorders, maternal use of antipsychotics -Low familial socio-economic status/ home literacy environment	[55] Sun et al., 2013; [53] Dilnot, Hamilton, Maughan, & Snowling, 2017
Psychological factors	-Neuropsychiatric disorders/ ADHD comorbidity	[58] Willcutt, Pennington, & DeFries, 2000
Phonological and linguistic factors	-Phonological deficits, difficulty in	[4] Vellutino, Fletcher, Snowling, &

	phonemic awareness	Scanlon, 2004
	-Auditory processing deficit	[64] Farmer & Klein, 1995
	-Linguistic deficit/ speech delay	[67] Duff, Reen, Plunkett, & Nation, 2015; [66] Pennington & Bishop, 2009
	-Poor letter knowledge	[68] Elbro, Borstrom, & Petersen, 1998; [63] Snowling, 2013
Visuo-motor factors	-Abnormal saccade/ fixation pattern during reading	[78] Rayner, 1985; [79] De Luca, Di Pace, Judica, Spinelli, & Zoccolotti, 1999
	-Fixation instability (unstable ocular dominance)	[82] Stein & Fowler, 1981
Visual-perceptual factors	-Reduced magnocells-mediated visual functions (coherent motion perception, magnocells-mediated contrast sensitivity)	[85] Cornelissen, Richardson, Mason, Fowler, & Stein, 1995; [86] Kevan & Pammer, 2008; [84] Evans, Drasdo, & Richards, 1994
	-Visual persistence time	[87] Winters, Patterson, & Shontz, 1989
	-Visual-spatial attention	[88] Kinsey, Rose, Hansen, Richardson, & Stein, 2004; [89] Vidyasagar & Pammer, 2010
	-Abnormal spatial relationship perception	[90] Aleci, Piana, Piccoli, & Bertolini, 2012
	-Visual crowding reinforcement	[92] Bouma & Leigen, 1977

Table 1. Risk factors and the clinical aspects related to dyslexia.

9. CONCLUSIONS

Developmental dyslexia is a neuropsychiatric condition that affects reading and, consequently, scholastic achievement. Investigating the risk factors with screening protocols is helpful to predict lexical difficulties in pre-school children and to start early habilitative programs.

Arguably, dyslexia has a neurological and genetic basis: the familiarity of the disorder is probably the main risk factors. The effect of the environment during pregnancy and in the perinatal period associated with the familial and genetic background is probably the recipe for the reading disability. In addition, socio-economic and cultural aspects can interact with the environmental and familial/genetic predisposing influence. Self-report inventories may help investigate the variables described in this paper. In this respect, a rapid self-report, the Analytic Anamnestic Protocol (AAP), has been devised on purpose[1] and looks a promising solution for early screening. In addition, early examination of subtle ophthalmological alterations in the oculomotor and especially visual-sensory domain may help to better characterize disabled readers. It remains that an interdisciplinary approach that makes use of validated and user-friendly instruments is the best solution to predict the onset of developmental dyslexia before the scholastic difficulties are reported.

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1 *Available at: www.visualeci.com/dyslexia.*

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