Minireview Article

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.

Keywords: Dyslexia, Risk Factors, Vision, Magnocellular, Screening.

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 (see table 1). 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, suggesting a contribution of early fetal damage, presumably via abnormal immune response [21, 41, 42]. In this respect, Gilger [41] reported that miscarriage is more frequent in families with disabled readers, in accordance with Hughdal and colleagues [21]. More recently, an Italian case-control study by Mascheretti confirmed that maternal risk of miscarriage increases significantly the risk of developing dyslexia [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 (see table 1).
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]).Even maternal alcohol consumption during pregnancy could be a relevant risk factor, since alcohol exerts a detrimental effect on the cerebellum, leading to many of the functional deficits typical of dyslexia and learning disabilities [53].
Finally, a family history of neuropsychiatric diseases, 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 [54], and modulate the reading development [55]: 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 [56]. Moreover, the parental involvement in helping children to learn to read and write exerts a positive effect on early language and literacy skills [57].
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 [58].

6. NEUROPSYCHIATRIC CORRELATED FACTORS

Reading disability makes the children more exposed to emotional difficulties during life [59]. Indeed, about 60% of dyslexics meet the criteria for at least one of the following neuropsychiatric problems: depressive moods, anxiety symptoms, somatoform disorders, poor self-esteem, behavioral problems, aggressiveness, even if these disorders have no a causal role for dyslexia [60-63]. In turn, ADHD, reported in up to 40% of disabled readers, shares several genetic risk factors with dyslexia [60].

7. PHONOLOGICAL AND LINGUISTIC PRE-SCHOOL 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 at a pre-school stage [4, 64]. 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 [64].
Considered that the M-cells process transient stimuli [65], impaired phonological decoding of brief auditory stimuli in dyslexia may depend on a magnocellular deficit.

A linguistic impairment is common in disabled readers [66, 67]; 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 [67, 68]. According to Ebro and associates, the linguistic parameters predict reading ability in 79-84% of the children at a pre-school age with familial risk for developmental dyslexia [69].

8. VISUAL PERCEPTUAL AND VISUO-MOTOR FACTORS

Despite population studies do not support a relationship between dyslexia and reduced visual acuity [70], refractive defects [71-73], latent or manifest strabismus [70, 72, 73], abnormal motor and sensory fusion and amblyopia [73], weak accommodative power [71-73], or convergence insufficiency [73], there is evidence of subtle visual-perceptive alterations in a relevant number of disabled readers (see table 1, see Aleci, 2013 for a review [74]). These alterations, not detectable during a routine eye examination, may account for many of the visual signs and symptoms complained by dyslexics: moving or "jumping" letters, syllables or words, intermittent blurring, eye fatigue, eye redness, headache, repetitive blinking, and ocular strain [75-77].
Importance has been ascribed to a deficit of fine ocular movements: in fact, during reading, dyslexic children show more and longer fixations, more and longer backward saccades (regressions) and more and shorter forward saccades compared to normal readers [78-82]. Since these alterations are absent outside the lexical task [78-80], a primitive, causal role of the fixation/saccadic pattern on the reading disablity is unlikely.
A different strand of research invokes unstable ocular dominance that generates fixation instability [e.g. 83, 84]. Fixation instability, that is the oscillation of the visual axes around letters and syllables, hampers their recognition and positional encoding [84]. This alteration is found to affect up to 75% of dyslexics versus 10% of the controls [83].
Not only visual-motor alterations but also subtle visual-processing abnormalities involving the magnocellular pathway, at a pre- school age, have been advocated:
- contrast sensitivity at low spatial frequencies and high temporal frequencies [e.g. 85];
- coherent motion perception [e.g. 86, 87];
- visual persistence time [88];
- visual-spatial attention [89, 90];
- spatial relationship perception [91, 92] and increased paracentral crowding [93]. 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 [93], and this may account for their reading difficulty [93, 94].
Likewise, increased spatial relationship anisotropy (SRA) in a class of dyslexic readers has been documented [91, 92]. SRA has been defined as the biased perceptual contraction of the visual space along the horizontal axis, so that letters and syllables are perceived as closer, generating abnormal crowding [91]. The same alteration is found also in adult disabled readers [92]. In support of this hypothesis, reading rate and reading accuracy of dyslexics with abnormal spatial relationship anisotropy benefit from increased inter-letter spacing [91].
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 at pre-school level [87]. Therefore, investigating these alterations with specific psychophysical tests at the beginning of the school age 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.

In particular, the Analytic Anamnestic Protocol (AAP) [95, 96] is a multiple-choice questionnaire that inquires about familial, general, past and recent specialist medical history to detect the role of visuomotor an visuosensory impairment in dyslexia. Visual-motor and visual-sensory scores are assigned to each question. Disabled readers reported worse score, especially in the sensory domain, and ROC curve demonstrated adequate specificity and sensitivity in support of the potential role of this 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 -Dominant autosomal inheritance -Hyper-autoimmunity/ autoimmune and allergic co-occurring disorders	[18] Grigorenko et al., 1997; [19] Paracchini, Scerri, & Monaco, 2007; [20] Marino et al., 2012; [9] Stein & Talcott, 1999; [23] Geschwind & Behan, 1982;
Biochemical factors	-Polyunsaturated fatty acids (PUFAs) deficiency -Increased brain Glutamate and Choline levels	[30] Richardson, Cox, Sargentoni, & Puri, 1997; [29] Livingstone, Rosen, Drislane, & Galaburda, 1991; [28] Zavodnik, Zaborowski, Niekurzak, & Bryszewska, 1997; [30] Richardson, Cox, Sargentoni, & Puri, 1997; [35] Pugh et al., 2014;
Anatomical factors	-Anomalies in the maturation of temporal, occipital and frontal cerebral regions -Lack of asymmetry of the two cerebral lobes/ corpus callosum abnormalities -Cortical dysplasia/ ectopia -Cerebellar abnormalities	[5] Galaburda & Kemper, 1979; [6] Habib, 2000; [6] Habib, 2000; [7] Cohen, Cambell, & Yaghmai, 1989; [8] Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; [10] Nicolson et al., 1999;
Perinatal factors	-Maternal infectious diseases, neonatal asphyxia -Family history of abortion -Risk of miscarriage requiring hospitalization -Gestational age < 28 weeks/ very low birth weight -Treated retinopathy of prematurity -High neonatal serum bilirubin level	[38] Liu et al., 2016; 41] Gilger, Pennington, Green, Smith, & Smith, 1992 [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 -Young parental age -Family history of neuropsychiatric disorders, maternal use of antipsychotics -Low familial socio-economic status/ home	[52] Cho, Frijters, Zhang, Miller, & Gruen, 2013 [42] Mascheretti et al., 2015 [38] Liu et al., 2016 [56] Sun et al., 2013; [54] Dilnot,

	literacy environment	Hamilton, Maughan, & Snowling, 2017
Psychological factors	-Neuropsychiatric disorders/ ADHD comorbidity	[60] Willcutt, Pennington, & DeFries, 2000
Phonological and linguistic factors	-Phonological deficits, difficulty in phonemic awareness -Auditory processing deficit -Linguistic deficit/ speech delay -Poor letter knowledge	[4] Vellutino, Fletcher, Snowling, & Scanlon, 2004 [65] Farmer & Klein, 1995 [68] Duff, Reen, Plunkett, & Nation, 2015; [67] Pennington & Bishop, 2009 [69] Elbro, Borstrom, & Petersen, 1998; [64] Snowling, 2013
Visuo-motor factors	-Abnormal saccade/ fixation pattern during reading -Fixation instability (unstable ocular dominance)	[79] Rayner, 1985; [80] De Luca, Di Pace, Judica, Spinelli, & Zoccolotti, 1999 [83] Stein & Fowler, 1981
Visual-perceptual factors	-Reduced magnocells-mediated visual functions (coherent motion perception, magnocells-mediated contrast sensitivity) -Visual persistence time -Visual-spatial attention -Abnormal spatial relationship perception -Visual crowding reinforcement	[86] Cornelissen, Richardson, Mason, Fowler, & Stein, 1995; [87] Kevan & Pammer, 2008; [85] Evans, Drasdo, & Richards, 1994 [88] Winters, Patterson, & Shontz, 1989 [89] Kinsey, Rose, Hansen, Richardson, & Stein, 2004; [90] Vidyasagar & Pammer, 2010 [91] Aleci, Piana, Piccoli, & Bertolini, 2012 [93] Bouma & Leigen, 1977

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

9. CONCLUSIONS

Developmental dyslexia is a neurodevelopmental 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 familial nature of the disorder is probably the main risk factor. 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

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

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.

REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.

2. Peterson RL, Pennington BF. Developmental dyslexia. Annu Review Clini Psychol. 2015;11:283-307.

3. Barbiero C, Lonciari I, Montico M, Monasta L, Penge R, Vio C, Tressoldi PE, Ferluga V, Bigoni A, Tullio A, Carrozzi M, Ronfani L, The Submerged Dyslexia Iceberg: How Many School Children Are Not Diagnosed? Results from an Italian Study. PLoS One. 2012;7(10):e48082.

4. Vellutino FR, Fletcher JM, Snowling MJ, Scanlon DM. Specific reading disability (dyslexia): What have we learned in the past four decades? J Child Psychol Psychiatry. 2004;45(1):2-40.

5. Galaburda AM, Kemper TL. Cytoarchitectonic abnormalities in developmental dyslexia: a case study. Ann Neurol. 1979;6(2):94-100.

6. Habib M. The neurological basis of developmental dyslexia. An overview and working Hypotesis, Brain. 2000;123 Pt 12:2373-99.

7. Cohen M, Cambell R, Yaghmai F. Neuropathological abnormalities in developmental dysphasia. Ann Neurol. 1989;25(6):567-70.

8. Galaburda AM, Sherman GF, Rosen GD, Aboitiz F, Geschwind N. Developmental dyslexia: four consecutive patients with cortical anomalies. Ann Neurol. 1985;18(2):222-33.

9. Stein J, Talcott J. Impaired neuronal timing in developmental dyslexia - the magnocellular hypotesis. Dyslexia. 1999;5:59-77.

10. Nicolson RI, Fawcett AJ, Berry EL, Jenksin IH, Dean P, Brooks DJ. Association of abnormal cerebellar activation with motor learning difficulties in dyslexic adults. Lancet. 1999;353(9165):1662-7.

11. Stoodley CJ, Stein JF. Cerebellar Function in Developmental Dyslexia. The Cerebellum. 2013;12(2):267–76.

12. Nicolson RI, Fawcett AJ, Brooks RL, Needle J. Procedural learning and dyslexia. Dyslexia. 2010;16(3):194-212.

13. Richlan F, Kronbichler M, Wimmer H. Structural abnormalities in the dyslexic brain: a meta-analysis of voxel-based morphometry studies. Hum Brain Mapp. 2013;34(11):3055-65.

14. Linkersdörfer J, Lonnemann J, Lindberg S, Hasselhorn M, Fiebach CJ. Grey matter alterations co-localize with functional abnormalities in developmental dyslexia: an ALE meta-analysis. PLoS One. 2012;7(8):e43122.

15. Wolff PH, Melngailis I. Family patterns of developmental dyslexia: Clinical findings. Am J Med Genet. 1994;54(2):122-31.

16. Schumacher J, Hoffman P, Schmal C, Schulte-Korne G, Nothen MM. Genetics of dyslexia: the evolving landscape. J Med Genet. 2007;44(5):289-97.

17. Pennington BF, Gilger JW. How is dyslexia transmitted? In: Chase CH, Rosen GD, Sherman GF, editors. Developmental dyslexia: neural, cognitive and genetic mechanisms. Baltimore: New York Press; 1999.

18. Grigorenko EL, Wood FB, Meyer MS, Hart LA, Speed WC, Pauls DL. Susceptibility loci for distinct components of developmental dyslexia on chromosome 6 and 15. Am J Hum Genet. 1997;60(1):27-39.

19. Paracchini S, Scerri T, Monaco AP. The genetic lexicon of dyslexia. Ann Rev Genomics Hum Genet. 2007;8:57–79.

20. Marino C, Meng H, Mascheretti S, Rusconi M, Cope N, Giorda R, Molteni M, Gruen JR. DCDC2 genetic variants and susceptibility to developmental dyslexia. Psychiatr Genet. 2012;22(1):25-30.

21. Hugdahl K, Synnevmg B, Satz P. Immune and autoimmune diseases in dyslexic children. Neuropsychologia. 1990;28(7):673-9.

22. Pennington BF, Smith SD, Kimberling WJ, Green PA, Haith MM. Left-handedness and immune disorders in familial dyslexics. Arch Neurol. 1987;44(6):634-9.

23. Geschwind N, Behan P. Association of left handedness with immune disease and developmental learning disorder. Proc Natl Acad Sci U S A. 1982;79(16):5097-100.

24. Corriveau R, Huh G, Shatz C. Regulation of Class I MHC gene expression in the developing and mature CNS by neural activity. Neuron. 1998;21(3):505-20.

25. Stein J, Walsh V. To see but not to read; the magnocellular theory of dyslexia. Trends Neurosci. 1997;20(4):147-52.

26. Stein J. The magnocellular theory of developmental dyslexia. Dyslexia. 2001;7(1):12-36.

27. Aleci C. Rationale of polyunsaturated fatty acids supplementation in the frame of the magnocellular theory of dyslexia. J Adv Med Pharm Sci. 2017;12(4):1-9.

28. Zavodnik IB, Zaborowski A, Niekurzak A, Bryszewska M. Effect of free fatty acids on erythrocyte morphology and membrane fluidity. Biochem Mol Biol Int. 1997;42(1):123-33.

29. Livingstone MS, Rosen GD, Drislane FW, Galaburda AM. Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia. Proc Natl Acad Sci USA. 1991;88(18):7943-7.

30. Richardson AJ, Cox IJ, Sargentoni J, Puri BK. Abnormal cerebral phospholipid metabolism in dyslexia indicated by phosphorus-31 magnetic resonance spectroscopy. NMR Biomed. 1997;10(7):309-14.

31. Lindmark L, Clough P. A 5-month open study with long-chain polyunsaturated fatty acids in dyslexia. J Med Food. 2007;10(4):662-6.

32. Richardson AJ, Calvin CM, Clisby C, Schoenheimer DR, Montgomery P, Hall JA et al. Fatty acid deficiency signs predict the severity of reading and related difficulties in dyslexic children, Prostaglandins Leukot Essent Fatty Acids. 2000;63(1-2):69-74.

33. Taylor KE, Higgins CJ, Calvin CM, Hall JA, Easton T, McDaid AM, Richardson AJ. Dyslexia in adults is associated with clinical signs of fatty acid deficiency. Prostaglandins Leukot Essent Fatty Acids. 2000;63(1-2):75-8.

34. Richardson A, Phil D. Fatty acids in dyslexia, dyspraxia, ADHD and the autistic spectrum. Nutrition Pratictioner. 2001;3(3):18-24.

35. Pugh KR, Frost SJ, Rothman DL, Hoeft F, Del Tufo SN, Mason GF et al. Glutamate and choline levels predict individual differences in reading ability in emergent readers. J Neurosci. 2014;34(11):4082-9.

36. Essa MM, Vijayan RK, Castellano-Gonzalez G, Memon MA, Braidy N, Guillemin GJ. Neuroprotective effect of natural products against Alzheimer's disease. Neurochem Res. 2012;37(9):1829-42.

37. Laycock R, Crewther DP, Crewther SG. The advantage in being magnocellular: a few more remarks on attention and the magnocellular system. Neurosci Biobehav Rev. 2008;32(8):1409-15.

38. Liu L, Wang J, Shao S, Luo X, Kong R, Zhang X et al.. Descriptive epidemiology of prenatal and perinatal risk factors in a Chinese population with reading disorder. Sci Rep. 2016;6:36697.

39. Patrich E, Piontkewitz Y, Peretz A, Weiner I, Attali B. Maternal immune activation produces neonatal excitability defects in offspring hippocampal neurons from pregnant rats treated with poly I:C. Sci Rep. 2016;6:19106.

40. Choi GB, Yim YS, Wong H, Kim S, Kim H, Kim SV, Hoeffer CA, Littman DR, Huh JR. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science. 2016;351(6276):933-9.

41. Gilger JW, Pennington BF, Green P, Smith SM, Smith SD. Reading disability, immune disorders and non-right-handedness: twin and family studies of their relations. Neuropsychologia. 1992;30(3):209-27.

42. Mascheretti S, Marino C, Simone D, Quadrelli E, Riva V, Cellino MR et al.Putative risk factors in developmental dyslexia: a case-control study of Italian children. J Learn Disabil. 2015;48(2):120-9.

43. Mascheretti S, Andreola C, Scaini S, Sulpizio S. Beyond genes: A systematic review of environmental risk factors in specific reading disorder. Res Dev Disabil. 2018;82:147-52.

44. Bowen JR, Gibson FL, Hand P. J. Educational outcome at 8 years for children who were born extremely prematurely: A controlled study. J Paediatr Child Health. 2002;38(5):438-44.

45. Samuelsson S, Finnstrom O, Flodmark O, Gaddlin P, Leijon I, Wadsby M. A longitudinal study of reading skills among very-low-birthweight children: Is there a catch-up? J Pediatr Psychol. 2006;31(9):967-77.

46. Downie AL, Jakobson LS, Frisk V, Ushycky I. Periventricular brain injury, visual motion processing, and reading and spelling abilities in children who were extremely low birthweight. J Int Neuropsychol Soc. 2003;9(3):440-9.

47. Ranasinghe S, Or G, Wang EY, Ievins A, McLean MA, Niell CM et al. Reduced Cortical Activity Impairs Development and Plasticity after Neonatal Hypoxia Ischemia. J Neurosci. 2015;35(34):11946-59.

48. van Handel M, Swaab H, de Vries LS, Jongmans MJ. Long-term cognitive and behavioral consequences of neonatal encephalopathy following perinatal asphyxia: a review. Eur J Pediatr. 2007;166(7):645-54.

49. Hokkanen L, Launes J, Michelsson K. Adult neurobehavioral outcome of hyperbilirubinemia in full term neonates-a 30 year prospective follow-up study. PeerJ. 2014;2:e294.

50. Johnson L, Bhutani VK. The clinical syndrome of bilirubin-induced neurologic dysfunction. Semin Perinatol. 2011;35(3):101-13.

51. Takeuchi A, Koeda T, Takayanagi T, Sato K, Sugino N, Bonno M, Kada A, Nakamura M, Kageyama M. Reading difficulty in school-aged very low birth weight infants in Japan. Brain Dev. 2016;38(9):800-6.

52. Cho K, Frijters JC, Zhang H, Miller LL, Gruen JR. Prenatal exposure to nicotine and impaired reading performance. J Pediatr. 2013;162(4):713-18.

53. Coffin JM,Baroody S, Schneider K, O'Neill J. Impaired cerebellar learning in children with prenatal alcohol exposure: a comparative study of eyeblink conditioning in children with ADHD and dyslexia. Cortex. 2005;41(3):389-98.

54. Dilnot J, Hamilton L, Maughan B, Snowling MJ. Child and environmental risk factors predicting readiness for learning in children at high risk of dyslexia. Dev Psychopathol. 2017;29(1):235-44.

55. Friend A, DeFries JC, Olson RK. Parental education moderates genetic influences on reading disability. Psychol Sci. 2008;19(11):1124-30.

56. Sun Z, Zou L, Zhang J, Mo S, Shao S, Zhong R, Ke J, Lu X, Miao X, Song R. Prevalence and Associated Risk Factors of Dyslexic Children in a Middle-Sized City of China: A Cross-Sectional Study. PLoS One. 2013;8(2):e56688.

57. Senechal M, LeFevre, JA. Parental involvement in the development of children's reading skill: A five-year longitudinal study. Child Dev. 2002;73(2):445-60.

58. Fergusson DM, Lynskey MT. Maternal age and cognitive and behavioural outcomes in middle childhood. Paediatr Perinat Epidemiol. 1993;7(1):77-91.

59. Casey R, Levy SE, Brown K, Brooks-Gunn J. Impaired emotional health in children with mild reading disability. J Dev Behav Pediatr. 1992;13(4):256-60.

60. Willcutt EG, Pennington BF, DeFries JC. Twin study of the etiology of comorbidity between reading disability and attention-deficit/hyperactivity disorder. Am J Med Genet. 2000;96(3):293-301.

61. Maughan B, Rowe R, Loeber R, Stouthamer-Loeber M. Reading problems and depressed mood. J Abnorm Child Psychol. 2003;31(2):219-29.

62. Beitchman JH, Wilson B, Brownlie EB, Walters H, Inglis A, Lancee W. Long-term consistency in speech/language profiles: II. Behavioral, emotional, and social outcomes. J Am Acad Child Adolesc Psychiatry. 1996;35(6):815-25.

63. Willcutt EG, Pennington BF. Psychiatric comorbidity in children and adolescents with reading disability. J Child Psychol Psychiatry. 2000;41(8):1039-48.

64. Snowling MJ. Early identification and interventions for dyslexia: a contemporary view. J Res Special Educ Needs 2013;13(1):7-14.

65. Farmer ME, Klein RM. The evidence for a temporal processing deficit linked to dyslexia: A review. Psychon Bull Rev. 1995;2(4):460-93.

66. Bishop DV, Snowling MJ. Developmental dyslexia and specific language impairment: Same or different? Psychol Bull. 2004;130(6):858-86.

67. Pennington BF, Bishop DV. Relations among speech, language, and reading disorders. Annu Rev Psychol. 2009;60:283-306.

68. Duff FJ, Reen G, Plunkett K, Nation K. Do infant vocabulary skills predict school-age language and literacy outcomes? J Child Psychol Psychiatry. 2015;56(8):848-56.

69. Elbro C, Borstrom I, Petersen DK. Predicting dyslexia from kindergarten: The importance of distinctness of phonological representations of lexical items. Read Res Q. 1998;33(1):36-60.

70. Aasved H. Ophtalmological status of School children with dyslexia. Eye (Lond). 1987;1(1):61-8.

71. Lennerstrand G, Ygge J. Dislexia; ophtalmological aspects 1991, Acta Ophthalmol (Copenh). 1992; 70(1):3-13.

72. Norn MS, Rindziunski E, Skydsgaard H. Ophthalmologic and orthoptic examinations of dyslectics. Acta Ophthalmol (Copenh). 1969;47:147-60.

73. Creavin AL, Lingam R, Steer C, Williams C. Ophthalmic abnormalities and reading impairment. Pediatrics. 2015;135(6):1057-65.

74. Aleci C. Dyslexia: A visual approach. New York: Nova Science Publishers Inc; 2013.

75. Cornelissen P, Bradley L, Fowler S, Stein J. What children see affects how they read. Dev Med Child Neurol. 1991;33(9):755-62.

76. Evans BJ, Patel R, Wilkins AJ, Lightstone A, Eperjesi F, Speedwell L, Duffy J. A review of the management of 323 consecutive patients seen in a specific learning difficulties clinic. Ophthalmic Physiol Opt. 1999;19(6):454-66.

77. Raghuram A, Hunter DG, Gowrisankaran S, Waber DP, Self-reported visual symptoms in children with developmental dyslexia. Vision Res. 2019;155:11-16.

78. Adler-Grinberg D, Stark, L, Eye movements, scan paths, and dyslexia, American J Optom Physiol Opt. 1978;55(8):557-570.

79. Rayner K. Do faulty eye movements cause dyslexia? Developmental Neuropsychology. 1985; 1(1):3-15.

80. De Luca M, Di Pace E, Judica A, Spinell D, Zoccolotti P. Eye movement patterns in linguistic and non-linguistic tasks in developmental surface dyslexia. Neuropsychol. 1999;37(12):1407-20.

81. Pavlidis GT. The dyslexia syndrome and its objective diagnosis by erratic eye movements. In: Rayner K, editor. Eye movements and reading. New York: Academic Press; 1983.

82. Pavlidis GT. (1985). Eye movements in dyslexia: their diagnostic significance. Journal of Learning Disabilities. 1985;18(1):42-50.

83. Stein JF, Fowler MS. Visual Dyslexia. Trends Neurosci. 1981;4:77-80.

84. Stein J, Fowler S. Diagnosis of dyslexia by means of a new indicator of eye dominance. Br J Ophtalmol. 1982;66(5):332-36.

85. Evans BJ, Drasdo N, Richards IL. An investigation of some sensory and refractive visual factors in dyslexia. Vision Res. 1994; 34(14):1913-26.

86. Cornelissen P, Richardson, A, Mason A, Fowler S, Stein J. Contrast sensitivity and coherent motion detection measured at photopic luminance levels in dyslexics and controls. Vision Res. 1995;35(10):1483-94.

87. Kevan A, Pammer K. Visual deficits in pre-readers at familial risk for dyslexia. Vision Res. 2008;48(28):2835-9.

88. Winters RL, Patterson R, Shontz W. Visual persistence and adult dyslexia. J Learn Disabil. 1989;22(10):641-5.

89. Kinsey K, Rose, M, Hansen P, Richardson A, Stein J. Magnocellular mediated visual-spatial attention and reading ability. Neuroreport. 2004;15(14):2215-18.

90. Vidyasagar TR, Pammer K. Dyslexia: A deficit in visuo-spatial attention, not in phonological processing. Trends Cogn. Sci. 2010;14(2):57-63.

91. Aleci C, Piana G, Piccoli M, Bertolini M. Developmental dyslexia and spatial relationship perception. Cortex. 2012;48(4):466-76.

92. Aleci C, Saldutto V, Canavese L. Detecting Visuoperceptive Defects in Adolescent and Adult Disabled Readers with the TETRA AnalyzerTM. Pathological Sample and Comparison with Normal Readers. Ophthalmology Research: An International Journal. 2017;7(4):1-12.

93. Bouma H, Legein CP. Foveal and parafoveal recognition of letters and words by dyslexics and by average readers. Neuropsychol. 1977;15(1):69-80.

94. Martelli M, Di Filippo G, Spinelli D, Zoccolotti P. Crowding, reading, and developmental dyslexia. J Vis. 2009;9(4):14.1-18.

95. Aleci C, Canavese L. A computational approach to the anamnestic collection in neuro-ophthalmology: The Analytic Anamnestic Protocol. Research. 2015;2:1421.

96. Aleci C. Can Self-reported Ocular Motor and Perceptive Alterations Predict a Reading Disability? A Pilot Study on the Analytic Anamnestic Protocol. Cureus. 2019;11(9):e5555.