CLINICAL

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LOW-DOSE BDNF AND SPECIFIC LEARNING DISABILITIES – A POSSIBLE INDICATION

SUMMARY

Specific Learning Disabilities (SLD) are conditions that present a discrepancy between the levels of academic performance and the potential deduced from the subject's actual intellectual abilities.
Learning disorders involve difficulty in concentration or attention, in language development, or in processing visual and auditory information.
Diagnosis includes intellectual, educational and language assessments as well as medical and psychological assessments.
Treatment consists, first of all, in educational management and in medical, behavioral and psychological therapy.
– In a group of 9 patients Guna-BDNF was added to these treatments with an evident improvement (+50%) vs the control group in test performance and an increase in self-esteem.

KEY WORDS

LOW DOSE MEDICINE, BDNF, NEUROTROPHINS, SPECIFIC LEARNING DISABILITIES

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INTRODUCTION

The acronym **SLD** (Specific Learning Disabilities) refers to a diagnostic category regarding specific developmental learning difficulties pertaining to neurodevelopmental disorders according to the DSM 5 (1,2).

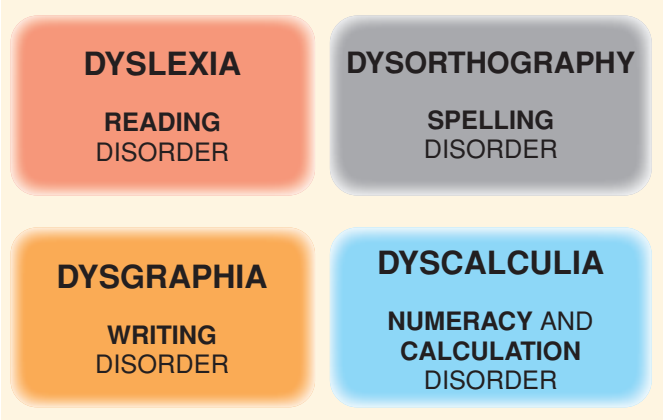
– Neurodevelopmental disorders are neurological conditions that present in early infancy, usually before the start of primary school.

SLDs impair personal, social, scholastic and/or professional development and entail difficulties in the acquisition, retention and application of skills or specific sets of information.
Although these disorders affect children and teenagers who do not usually present particular disabilities or difficulties, without adequate support, they can make scholastic activities difficult.

SLDs are, therefore, a series of disabilities that are relatively common during the developmental age, that can be attributed to a primarily constitutional neurobiological origin, and that regard the acquisition of scholastic skills, intended as tools that make it possible to obtain the formal knowledge proposed through educational processes.

– Each of these disorders concerns different functions and abilities: speech, motor skills, reading, writing, and arithmetic.
The characteristic that is common to them all is the specificity of the deficit, which can be attributed to consistent

FIG. 1



and recognisable areas that are independent of the subject's cognitive level.

– The term 'specific' regards the fact that the disability presents in an individual who does not present neurological conditions (e.g. epilepsy), or secondary defects (hearing or sight impairments), who is of adequate intelligence and does not present any particular cultural disadvantage conditions.

Depending on the type of difficulty, different conditions are identified regarding the specific skills of reading, intended as the ability to decode a text **(dyslexia)**, writing, intended as the ability of phonographic encoding and spelling **(dysorthography)**, graphomotor skills **(dysgraphia)** and arithmetic, disorder affecting numeracy and calculation skills, intended as the ability to understand and work with numbers **(dyscalculia)** (FIG. 1).

The Istituto Superiore di Sanità [Italian National Institute of Health] Consensus Conference (Cc-ISS, 2011) defines SLDs *"disorders that affect a specific area of abilities, without affecting general intellectual functioning. They involve the instrumental skills of scholastic learning"* (TAB. 1).

It is important to stress that children with SLDs are of normal or higher than normal intelligence and they find it easy to obtain an overview, to see the bigger picture.
They are able to grasp the fundamental elements of a discussion or situation, they reason in a dynamic manner and create unusual associations that others find it difficult to develop.
They learn readily from experience and tend to remember facts not in an abstract way but as life experiences, stories and examples.
They think primarily in images, visualising words and concepts in a three-dimensional manner, and memorise things far more readily by pictures.

– They are able *to see things* from different perspectives and they process information in a global manner rather than sequentially.

TAB. 1

SLDs involve a specific area of skills	**Reading Spelling Writing Calculation**
Intact general intellectual function	**QI >70**
SLDs involve the instrumental skills of scholastic learning	**Compensatory tools**

This matter has a considerable social importance, as SLDs are disorders that, from an epidemiological point of view, have an incidence in the general population of **2-3%** of all scholastic difficulties, in most subjects with non-specific learning disabilities or difficulties (about **20%**) (TABS. 2, 3).

At the current time, children and teenagers with SLDs are not entitled to a special needs teacher.
Pursuant to Law 170/2010 (TAB. 3), they are entitled to compensatory learning and technological aids (speech synthesis, recorders, word processing software and programmes with spelling correction functions, calculators) and dispensatory measures that allow them to replace certain types of assessment with equivalent, more suitable ones.

– An analysis of the available literature reveals that the disorders most commonly associated with LSDs are attention deficit and hyperactivity disorder (ADHD) and specific language impairment (SLI).
The 2007 Consensus Conference revealed that in clinical practice, there is a high presence of comorbidities among SLDs and between SLDs and other disorders (dyspraxia, behavioural and mood disorders, anxiety disorders, etc.).
– This high comorbidity results in a great diversity in the functional and expressive profiles with which SLDs present, which has considerable implications on the diagnostic investigation front (CC-2007) (FIG. 2).

DIAGNOSIS

Diagnosis can be difficult.
– As a matter of fact, until the diagnosis is clearly defined, the children, their parents and the school are confused regarding the poor scholastic performance, without understanding the reason for it.

In this initial stage, teachers tend to question the child's effort, and family

conditions, they complain of laziness and lack of commitment, and frequent problems regarding conduct in the classroom.
Teachers also encounter difficulties in understanding why the child, who does not appear to have any particular difficulties within his/her peer group, objects, refuses or is reluctant when asked to read and/or write (3).
– This generates confusion and disarray in the parents, who tend to alternate between strict and punitive behaviour with continuous encouragements to make a greater effort and long periods of waiting, hoping the situation will improve spontaneously.

During this phase, the child feels misunderstood by everyone and starts to question his/her own abilities, which in turn results in lower self-esteem, psycho-affective problems, a feeling of inferiority and even guilt, especially if he/she feels that judged to be lazy and unwilling.
– In these cases, the interpretations and actions of the adults tend to make matters worse.

When a SLD is diagnosed and if the disorder is not adequately treated, the psychological symptoms of the distress can take various, and sometimes opposing, forms: on the one hand the child may have a withdrawn attitude, be introverted and avoid confrontation; this set of reactions can be defined of a depressive or inhibitory type.
On the other hand, the child may demonstrate feelings of anger resulting in disruptive behaviour, challenging teachers and showing aggression towards academic staff and their peers, which inevitably triggers a vicious cycle within the class.

The same child can often present both types of behaviour at different times (4).

Statistically, the diagnosis is most often formulated by teachers at the end of the **second year** of **primary school**, due to the greater exposure to reading and writing; they then notify the parents and a diagnostic pathway is undertaken with the involvement of paediatric neuropsychiatry facilities (FIG. 3).
Primary-care paediatricians can also play a role in identifying a child with SLD by administering a checklist (TABS. 4, 5, 6).
SLDs affect males more commonly than females, with a ratio of **5:1**.

SLDs have a neurobiological origin.

In infants, the symptoms are practically inexistent, as SLDs affect cognitive areas that infants have not yet developed; warning signs may be observed in preschool children (e.g. speech problems or difficulties learning nursery rhymes).
– The disorder becomes fully evident in school-age children.

Although it is recognised that SLDs have a genetic cause, the cerebral processes involved are yet to be clearly defined, despite the active research in this field.
– The genetic origin is demonstrated by the high familiarity of SLDs; children of parents with SLDs are more likely to have the same disorder than children whose parents do not have SLDs.

Indeed, it is not uncommon for the parents of children with SLDs to report encountering the same difficulties as their child, although it is likely that no specific diagnosis was formulated at the time.
– The neurobiological origin underlying cognitive abnormalities is associated with behavioural symptoms of the disorder, which include an interaction between genetic, epigenetic and environ-

DISABILITIES law 104/1992
«Framework law regarding the assistance, social integration and rights of persons with disabilities»
Assessments are usually carried out by the Local Health Authorities, through medical commissions including a social worker and an expert on the cases to be reviewed, established within the various Local Health Authorities.

TAB. 2

SLDs law 170/2010
«New regulations for specific learning disabilities in the scholastic setting»
SLDs are diagnosed within the specialist care provided by the Italian National Health Service or accredited specialists or facilities.
Use of individualised and personalised teaching, with effective and flexible forms of schoolwork that also take into account the particular characteristics of the subjects involved.
– Incidence 2-3% of all disabilities.

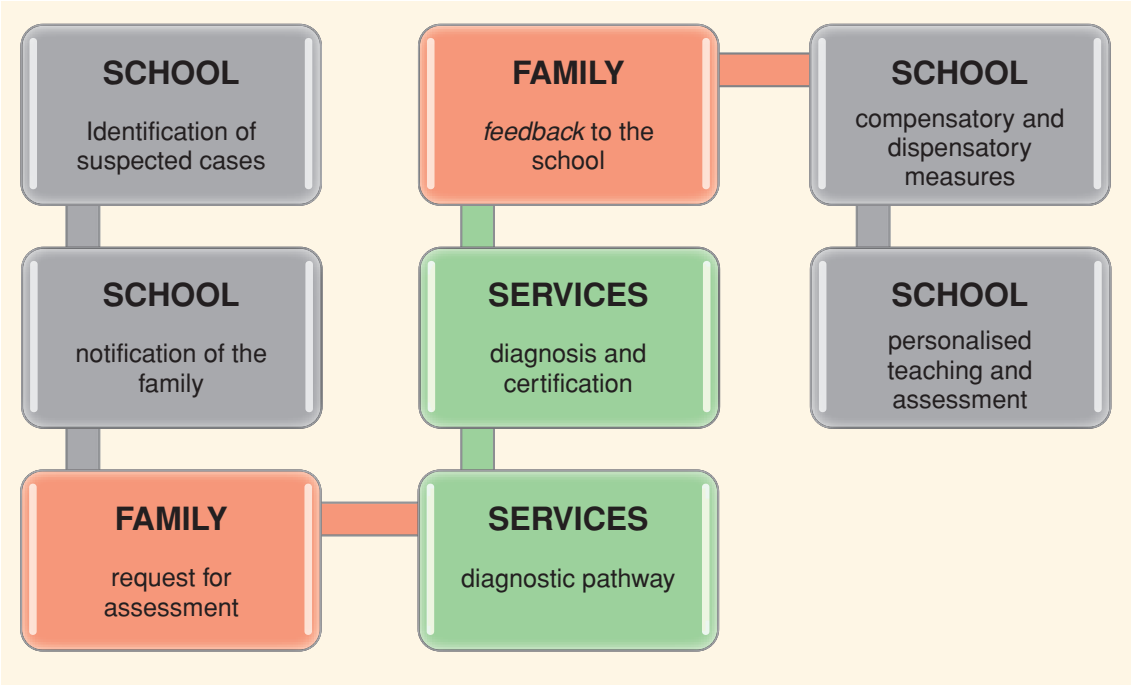
TAB. 3

FIG. 2

SLDs – COMORBIDITIES

OTHER NEUROPSYCHOLOGICAL DISORDERS (e.g. ADHD – Attention Deficit and Hyperactivity Disorder)	SEVERAL CONCOMITANT SLDs	OTHER MENTAL HEALTH DISORDERS (anxiety, depression, behavioural disorders)

FIG. 3



mental factors involving the cerebral capacity to perceive or process verbal or nonverbal information effectively and precisely (DSM-5, 2014).

Other potential causes include:

- maternal illness or substance abuse during pregnancy
- complications during pregnancy or delivery (e.g. blood loss or spotting, septicaemia, prolonged delivery or emergency delivery)
- neonatal problems (prematurity, low birth weight, severe jaundice, perinatal asphyxia, post-term birth, breathing difficulties).

Postnatal risk factors include **1)** exposure to environmental toxins (e.g. lead, heavy metals, pesticides, endocrine-disrupting chemicals), **2)** Central Nervous System infections, **3)** cancers and their treatments, **4)** trauma, **5)** malnourishment, **6)** severe social isolation, and **7)** affection deprivation.

It is important to remember that certain studies have identified a relationship between SLDs and **the dysfunctional aspects** of cerebral mechanisms that **do not** in any way affect intelligence.

When a psychological trauma interferes with normal pyschobiological development in children and adolescents, there is a shift from a brain (and body) focused on learning and a brain (and body) focused on survival.

- The **learning brain** is engaged in exploring (acquisition of new knowledge and of new neuronal synaptic connections), the **survival brain** tries to anticipate, prevent and protect against the damage caused by potential or actual dangers; it identifies threats and activates bodily resources to achieve hyperalertness and deploy defensive adjustments.
- The **survival brain** surrenders to rapid automatic processes that involve the more primitive parts of the brain [brainstem (especially the midbrain), limbic system structures, such as the amygdala], largely bypassing the areas of the brain involved in more complex adjust-

TAB. 4

PAEDIATRICIAN CHECKLIST
– PRE-SCHOOL AGE AND YEAR 1 OF PRIMARY SCHOOL

The **child**:

- struggles to understand verbal instructions and messages
- has difficulties expressing him/herself clearly when recounting an episode he/she was involved in or witnessed
- has difficulties making him/herself understood to strangers
- has difficulties holding pencils or pens
- struggles to draw a person whose head, body, arms and legs are recognisable
- is clumsy and lacks dexterity
- has difficulties perceiving new words and repeating them immediately after hearing them
- has difficulties understanding the quantities the numbers 1 to 4 correspond to; counting to 5; recognising which of two sets of objects (maximum of five objects) is larger and which is smaller.

Source: C. Toso, **2009**. Associazione Culturale Pediatri.

ments to the environment (anterior cingulate cortex, insula, prefrontal cortex, etc.) (5,6).

Prolonged corticosteroid activation and the hyperadrenergic state induced by constant alarm states result in the inhibition of neurogenesis, thereby hindering dendritic development and the formation of synapses, they induce "pruning" actions on existing nervous connections and induce cell death processes that result in the shrinking of the hippocampus (7).

As mentioned previously, the neurobiological bases of SLDs have been consolidated.
In the case of **dyslexia**, the best known of these disorders, the neurobiological origin was already suspected more than a century ago.
– In 1891-2, the French neurologist Jules Déjerine (8,9) suggested that the reading problems, defined by Hinshelwood (10) as "reading blindness", were due to anatomical lesions present in the left posterior region of the brain, which plays a critical role in reading processes.
The decisive turning point in the knowledge of the pathogenetic bases of dyslexia came with the advent of dynamic neuroimaging techniques such as PET or Functional Magnetic Resonance.
– These methods are able to show changes in the activation of cerebral areas as a consequence of given tasks and – therefore – make it possible to define the differences in functioning of areas of the cerebral cortex in dyslexic individuals.

It is known that both acute and chronic stress reduce the production of **BDNF** - Brain Derived Neurotrophic Factor in the hippocampus, where they also cause structural changes and neuronal damage, (11,12) and that BDNF tends to diminish in old age (13).

– Furthermore, BDNF protects against the toxicity of certain substances, by increasing the production of **glutathione reductase** (14).

PAEDIATRICIAN CHECKLIST
– HALFWAY THROUGH YEAR 1 AND YEAR 2 OF PRIMARY SCHOOL

The **child**:
- has not yet learned to read simple words (year 1) or sentences and short passages (year 2)
- has not yet learned to write simple words (year 1); makes a lot of mistakes when writing (year 2)
- has handwriting that is not legible to strangers
- has difficulties counting forwards to 20
- is unable to establish whether a number up to 20 is greater than another
- is poorly motivated in his/her schoolwork and frequently presents avoidance behaviour in relation to studying.

Source: C. Toso, **2009**. Associazione Culturale Pediatri.

TAB. 5

PAEDIATRICIAN CHECKLIST
– FROM YEAR 3 OF PRIMARY SCHOOL ONWARDS

The **child**:
- has obvious difficulties reading and writing correctly
- has difficulties writing in joined-up writing
- has difficulties reading books or other material on his/her own (e.g. toy assembly instructions)
- has difficulties reading to him/herself (is still only able to read out loud or whispering)
- has difficulties understanding what he/she is reading
- has difficulties learning the multiplication tables
- has difficulties arranging numbers in columns correctly.

Source: C. Toso, **2009**. Associazione Culturale Pediatri.

TAB. 6

It is therefore reasonable to presume that patients with SLDs have a **deficiency** of **BDNF** due to exposure to acute and/or chronic, psychological and physical stress.

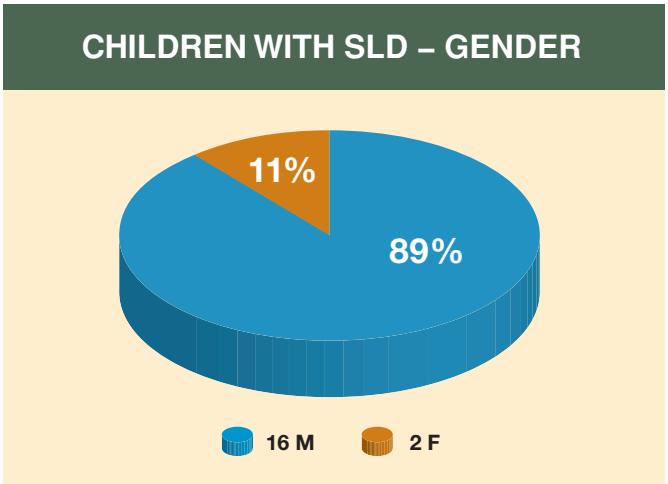
CURRENT TREATMENT

Although the treatment of Learning Disorders hinges primarily on scholastic management, it may also include medical, behavioural and psychological treatment.

– The effectiveness of teaching programmes may require a curative, compensatory, rehabilitative or strategic approach (i.e. teaching the child how to learn).
Some children require special teaching in just one subject and can continue to attend their classes normally.
Others require individual and intensive educational programmes.

– Medicinal products have a mild effect on scholastic performance, intelligence and learning abilities in general, although certain psychostimulants, like methylphenidate and certain amphetamine preparations, can improve the degree of attention and concentration, and therefore allow the child to perform assignments more effectively.

FIG. 4



MATERIALS AND METHODS

This study enrolled a total of **18 patients** (16 M; 2 F) (FIG. 4) aged between 6 and 9 years diagnosed with SLD in paediatric neuropsychiatry hub centres who were administered:
– the WISC-IV (Wechsler Intelligence Scale for Children), the gold-standard clinical tool for assessing cognitive abilities in children of between 6 years and 16 years and 11 months of age.
The WISC-IV makes it possible to calculate 5 composite scores: total intelligence quotient (TIQ) representing the overall cognitive abilities of the child and 4 additional scores, namely 4 Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI) and the Processing Speed Index (PSI)
– writing and spelling tests pertaining to the assessment battery for writing and spelling skills (BVSCO)
– MT reading tests.

Lastly, in order to obtain a personality profile, each parent was separately administered the *Child Behaviour Checklist* (FIG. 5).

Patients who, at the time of diagnosis, also presented other types of current or known comorbidities were excluded from the study.
– The children were split *random* into 2 groups (A, B).
Both groups were assigned compensatory learning and technological aids and dispensatory measures at school and speech therapy in an outpatient setting.

Patients in **Group A** were also administered **Guna-BDNF**, 20 drops via the sublingual route, morning and evening before meals (TAB. 7).

Patients in **Group B** were not administered Guna-BDNF.

• BDNF, which was isolated in 1982 by Yves- Alain Barde *et* Al. (15), is a 25 kDa homodimeric protein produced by the Central and Peripheral Nervous System, and particularly in the hypothalamus, hippocampus, cerebral cortex (frontal lobe, occipital lobe, insula, sensory and motor cortex), amygdala, salivary glands, kidney, prostate, retina, endothelial cells and in the follicular fluid.

BDNF acts by activating the receptors p75 and Trk.

During development, the neuropeptide plays a key role in neuronal survival, migration and phenotypical differentiation, as well as in axonal and dendritic growth and in the formation of synapses.
In adult life, its main function is to regulate synaptic plasticity and it is involved in learning, memory and behavioural processes.
BDNF has also been detected in serum with concentrations 10 time greater than those of plasma.

– BDNF is the most active of all neurotrophins in terms of neo-neurogenesis.

It has a protective action against injuries involving the dopaminergic brain structures.
It exerts its effect primarily on the serotonergic neurons (16).
Furthermore, in one *in vivo* study it was also demonstrated that Guna-BDNF reaches the brain within 24 hours of oral administration and reaches peak levels after 48 hours. It remains in the cerebral tissue for a long time even in the absence of further treatment , as it triggers the physiological production systems underlying good endogenous anti-ageing functioning (17).

During the treatment, no side effects were reported and there were no dropouts.

FIG. 5

CHILD BEHAVIOUR CHECKLIST

The first part acquires information on the various areas of personal and social functioning.

The second part consists of 118 items taking the form of statements regarding behaviour in various areas and emotional problems.

The scores are compared with reference value, to obtain two overall scores, one for skills (activity, social life, school) and one for behavioural and emotional problems, and two separate profiles; a skills profile and psychological and/or mental disease profile.

MEDICINAL PRODUCT	POSOLOGY
GUNA-BDNF	20 drops morning and evening

TAB. 7

– At the 1-year follow-up visit conducted at the paediatric neuropsychiatry centres, the same tests indicated above were re-administered and an improvement in performance was observed in both groups (A, B).

▶ **Group A** achieved a **50%** ≈ higher score than Group B in the various items.

DISCUSSION AND CONCLUSIONS

SLDs are changes in normal development with a neurobiological origin and they affect the acquisition of certain scholastic skills. The characteristic common to this group of disorders is the specificity of the deficit.
SLDs cannot be cured, but they are susceptible to appropriate compensatory measures and neuropsychological training, especially as regards speech, memory, and attention.

At the current time, there is no specific pharmacological therapy that has a significant impact on these functions.

▶ The considerable result obtained by administering Guna-BDNF on the performance of subjects with SLDs allowed these young patients to obtain better scholastic performance and a more effective inclusion in their peer groups, thereby sparing them detrimental feelings of inadequacy and isolation.

– It would be appropriate to enrol further patients and for other studies to be conducted in order to confirm the validity of the low-dose treatment proposed. ■

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