

# **Medical Aspects of learning disorders – Role of Nootropic Drugs**

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## **Introduction :-**

Learning disabilities is a term referring to a heterogeneous group of neurobehavioral disorders manifested by significant unexpected specific and persistent difficulties in the acquisition and use of efficient reading (dyslexia), writing (dysgraphia) or mathematical (dyscalculia) abilities despite conventional instruction, intact senses, normal intelligence, proper motivation and adequate socio – cultural opportunity ( **DSM – IV, Shapiro 1993, Shaywitz SE 1998**).

One Hundred years ago, in November 1896, doctor W. Pringle Morgan in Sussex, England, published in the British Medical Journal, the first description of the learning disorder that would come to be known as developmental dyslexia. " Percy F., aged 14, has always been a bright and intelligent boy, quick at games, and in no way inferior to others of his age. His great difficulty has been- and is now – his inability to learn to read ". ( **Shaywitz, S.E. 1996** )

The DSM-IV reports prevalence estimates of 2% to 10% for Learning Disorders ( LDs ), depending on the nature of ascertainment and the definitions applied. While, up to 3% of the children in France present severe and specific language and/or reading disorders. ( **Coste-Zeitoun, D et al 2005** ). In the United Kingdom, estimates of prevalence vary, from 2% to 15% of the population, according to a parliamentary report. ( Postnote, July 2004, Number 226 )

It is estimated that about 5 to 10 % of school-aged population in the United-States has been identified with learning disabilities and that up to

5% of all office visits to a pediatrician and up to 50% of children evaluated in mental health clinics have learning disabilities (Silver L.1993). Dyslexia is the most common type of learning disabilities and it affects 80% of children diagnosed as learning disabled (Shaywitz B et al., 1994).

## **Etiology :**

Evidences for origin of dyslexia have been increasingly accumulating. Although multiple etiologies are proposed for this complex trait, the exact cause still remains unknown; but substantial evidence from genetic and neurological studies suggests that dyslexia is a disorder which is influenced by genetic factors and the underlying deficit is in the language areas of the brain

( Saviour P. and Ramachandra N.B. 2006 ). Recent functional MRI ( fMRI ) brain studies indicate that the disorder may be caused by specific deficits in the left fronto temporal region or atypical asymmetries in the left perisylvian regions (Demonet JF 2004 )

## **Genetics :**

It has been known for decades that learning disorders run in families. In the 1990s, family aggregation studies, twin studies, and genetic linkage analyses confirmed the strong hereditary influences on reading disorder and mathematics disorder. The genetic studies also confirm the heterogeneity of the phenotype ( Connors, C.K. and Schulte, A.C. 2002 ).

It is found that in monozygotic twins different measures of dyslexia ( phonological awareness and phonological coding) are highly heritable(50– 70%) than dizygotic twins ( DeFries, J.C. and Alarcon, M. 1996 ).

As reading is a complex task, this disability could arise from deficiencies in one or more associated cognitive processes. Due to this complex nature, identification of dyslexia genes is difficult task and it is most likely to be influenced by the interaction of many genetic and environmental factors ( Fisher, S.E et al 1999 ).

Evidence has accumulated that location on the short arm of chromosome 6 ( 6p21.3 ), the short arm of chromosome 15, and loci on chromosomes 1,2,3,7 and 18 are related to dyslexia ( see tables listing those studies

in Conners&Schulte 2002 and Savior& Ramachandra 2006 ). Genetic linkage studies have implicated loci on chromosomes 6 and 15 in dyslexia

( **Grigorenko EL , et al 1997** ).

## **Theories :**

The main three theories put forward to explain the etiology of dyslexia are :-

### **( 1 ) The phonological theory of dyslexia**

- Brain recognizes language in a hierarchical order. The upper levels deal with semantics ( the meaning of words ), syntax ( grammatical structure ) and discourse ( connected sentences ). The lower levels of hierarchy deal with breaking sounds into separate small units called phonemes. Thus before words can be comprehended at higher levels in the hierarchy, it has to be decomposed into phonologic constituents that the alphabetic characters represent. To achieve this, the reader should have conscious awareness of the phonological structure of spoken words. If the reader lacks this awareness, he will have difficulty in learning the relationship between letters and sounds, as well as applying those letter/sound correspondences to sound out unknown words ( **Shaywitz, S.E. et al 1998** ).
- Individuals with dyslexia have difficulties with phonological decoding of orthographic symbols, and this is the significant source of reading problems ( **Leonard, C.M. et al 1993** ).
- Since most dyslexics show deficits in phoneme processing, it was suggested that phonological deficit is the most significant and consistent marker of dyslexia ( **Ramus, F. et al 2003** ).
- Brain imaging studies in dyslexics in response to a phonological task indicate under-activation of posterior brain regions ( Wernickes's area , angular gyrus, extrastriate and striate cortex ) and relative over-activation in anterior regions ( inferior frontal

gyrus ). These brain activation patterns provide evidence of an imperfectly functioning brain system for segmenting words into their phonologic constituents (**Shaywitz, S.E et al 1998 and Shaywitz, B.A. et al 2002**).

## **( 2 ) The cerebellar theory of dyslexia**

- This theory postulates that the cerebellum of dyslexics is slightly dysfunctional. Evidence for this theory comes from poor dyslexic performance in coordination, balance and time estimation (**Fawcett, A.J. et al 1996** ).
- The normal pattern of cerebellar asymmetry is anomalous in dyslexia. The ratio of left grey matter was greater in the cerebella of those with dyslexia than in the controls. Those with more symmetric cerebella made more errors on a nonsense word reading measure of phonological decoding deficit (**Rae, C. et al 2002** ). The right cerebellum has also shown to display a functional deficit in dyslexics, exhibiting decreased blood flow in response to both learned and novel motor tasks (**Nicolson, R et al 1999** )
- There are evidences of reduced cerebellar activity in dyslexics performing a motor learning task. There are indirect evidences of cerebellar dysfunction in dyslexics which include delayed motor milestones such as crawling, walking and a characteristic clumsiness (**Fawcett, A. J. and Nicolson, R. 1999** ).

## **( 3 ) The magnocellular theory of dyslexia**

- Neurons in the magnocellular layers of the lateral geniculate nucleus are sensitive to motion perception and temporal resolution and are important for the control of eye movements (**Eden, G. F. et al 1996** ).
- Impaired function of magnocellular pathway will lead to destabilization of binocular fixation, which leads to visual confusion and letters then appear to move around. It has been found that binocular control of dyslexics is poor. Their eyes are unsteady when they are attempting to view small letters, hence their vision is unstable and tend to make visual reading errors (**Stein, J. and Walsh, V. 1997** ).

- Postmortem studies of dyslexic individuals have shown that magnocells ( large neurons ) of the lateral geniculate nucleus were disordered and 20% smaller than that of controls ( **Livingstone, M. S. et al 1991 and Galaburda, A. M. et al 1994** ).

## **Remediation and medication**

- The Frequency of learning disorders and the poor outcome associated with learning disabilities ; namely higher unemployment rates, social adjustment and marital problems, all makes it imperative that professionals involved in providing medical care to children be active participants in the management strategies and treatment plans of individuals with learning disabilities ( **Tuchman R 2000** ).

- The primary use of medication for children with learning disabilities is to open up a window of opportunity for education intervention . Medications such as methylphenidate , antidepressants , such as Fluoxetine and mood stabilizers such as lithium carbonate or valproic acid may directly enhance certain cognitive processes . These drugs are usually used because Attention Deficit and Hyperactivity Disorder coexists in 40% of the population of children with learning disabilities , further more , affective disorders such as anxiety disorders, Depression , mania or phobia may coexist with LDs, and there is increasing evidence that in some children with LDs, subclinical epileptiform discharges do cause transient

cognitive impairment without clinical seizures , in which case the use of valproic acid

resulted in improvement in cognitive performance and this improvement was proportional to the reduction in epileptiform discharges

- My review is focused on the Nootropic drug piracetam and studies of its use in the management of learning disabled children.

## **Background**

Dyslexia is the most frequently reported LD in literature concerning medical management . There is no one single unified theory that explains the etiology and neuropathology of dyslexia . Management of learning disabilities needs a multimodal approach to the child . This includes developing a relationship with the family, making recommendations regarding educational strategies , and discussing and using medications when appropriate ( **Tuchman R 2000 , Sunil Karande 2005** ) .

The nootropic drug piracetam , which reached clinical practice in 1971, had proved efficacy in animal studies ( **Krejci I 1984 , Petkov VD 1990, Neumann HJ 1989 ,Gramatte T 1986** ) , acute stroke ( **DeDeyn PP 1997** ) , Rehabilitation of aphasia ( **Kessler J 2000** ) , and cortical myoclonus ( **Genton P 1999** ) . Those results encouraged a lot of research on piracetam use in learning disabled children the subject which I shall follow in this review .

## **Objectives :-**

To review the studies , research work reports and case reports on the use of nootropic drug piracetam in the management of learning disabled

children .

## **Search Strategy :-**

I have searched MEDLINE, MEDSCAPE , and PubMed through CDC and NIH .

Also I used search sites to reach and contact a lot of researchers , clinicians and

scientific offices of pharmaceutical companies to collect studies .

Reference lists of relevant articles were searched and authors contacted when feasible to bring

reprints of prominent papers .

## **Piracetam and dyslexia**

( **Wilsher , Atkins , Manfield 1985** ) reviewed 13 experiments of piracetam , which were performed on several different patient populations as well as normal

volunteers reporting improvements in verbal learning , naming , sequencing , coding , tempo, vigilance , and reading .

( **Dimond and Brouwers 1976** ) performed a well controlled double-blind

experiment on young normal volunteers ( university students ). They found a

significant improvement in verbal learning after 14 days of piracetam medication.

(**Wilsher , Atkins , and Manfield 1979** ) conducted a double-blind study on 16

young adult dyslexics and 14 controls , using a three-week administration of

piracetam ( 4800 mg per day ) and studied the effects upon verbal learning . The

dyslexic's previous learning pattern was characterized by taking almost twice as

long to learn the task , and making three times as many forgetting mistakes as controls . After treatment , piracetam group improved their verbal learning by 15 % and their forgetting score was almost halved . (Simeon 1980 ) experiment consisted of a double – blind administration of 4800mg per day of piracetam or placebo in 4 weeks sessions . The sample consisted of 3 groups ( 25 children ) of learning disordered boys aged 8 to 14 years . All children were at least 1 year behind their age in reading , spelling , or arithmetic . The results revealed a significant improvement after neuropsychologist's global judgment and improved memory .

**(Wilsher , Atkins , and manfield 1985 )** conducted an eight-week double – blind experiment on 46 dyslexic boys (42 having reading and spelling problems and 4 having only spelling problems ) , their age group was 8-13 years and they were of above – average intelligence. The used dosage was 3300mg piracetam or placebo. The results showed substantial improvement of treated patients of reading gain scores ( Neale ) and showed changes in rate and accuracy of reading (Neale Analysis of Reading Ability ). The free writing test showed that the piracetam group's increase in number of words is twice that of the placebo group , and their spelling mistakes decreased by 6.37 % .

**( DiIanni and associates 1985 )** conducted a study by six investigators following a common protocol . Eligible patients were males , between the ages of 8 years and 13years , 11months , with English as the primary language . The total

number was 257 boys , 133 were treated with piracetam and 124 were treated with matching placebo . Dose of piracetam was 3300mg daily. Duration of study was 12 weeks . The results showed a positive change in the speed of reading, with significant differences between treatment in favor of the piracetam – treated patients . A difference in digit span was observed , but not statistically significant between treatment groups. Those results provide the same evidence in ( **Wilsher et al 1985** ) , that piracetam can increase the rate of reading in dyslexic children. They also proved that piracetam was found to improve auditory short-term memory as in ( **Dimond 1976 and Wilsher et al 1979** ) .

( **Levi and Sechi 1987** ) studied 127 children (94 males and 33 females ) , between ages 7 years , 6 months and 12years , 6 months . The children were assigned oral drug treatment on a double-blind basis , half of them received 3200 mg of piracetam daily for 20 weeks , the other half received a matching placebo during the same time . Results proved that the story-telling performance measure (long – term memory ) shows an improvement only in piracetam group. Also the performance on the Anagram task shows a marked improvement only in the piracetam group . During this test ever longer stimuli words used in order to study the meta linguistic skills of the child . ( **DiIanni 1985** ) demonstrated a very important correlation between the later and the child's reading abilities. Results showed also that piracetam group made significant gains in reading accuracy.

The results of the initial study ( **Wilsher et al 1979** ) encouraged a collaborative multicenter large study ( **Wilsher et al 1987** ) . This was conducted by 5 investigators, including 225 children with a primary diagnosis

of developmental reading disorder ( DSM- III ) , and between the ages of 7 year 6months and 12 year 11 months , 112 of whom were treated with piracetam, while 113 were treated with a matching placebo . Duration of study was 36 weeks.

Results of piracetam group showed improvement in the Gray Oral total passage score , which represents a global improvement in ability that combines reading accuracy and speed. Also there was a consistent improvement in reading comprehension shown by the significant effects upon both Gray and Gilmore comprehension scores.

**(Van Hout & Giurgea 1990 )** reported their double-blind controlled study of 36

right handed dyslexic boys, aged between 8year, 9months and 12y,11months.

The primary language of children was French , duration of study was 12

weeks. Each child of treatment group received piracetam at dosage of either

1.5g for children under 10 years or 3.3g for those above 10 years . The results showed that the treated group read more words and had better

accuracy level, as well as improved phonological word decoding skills. But

the researchers said; we did not find an increase of digit span as described

in **(DiIanni et al ; 1985 )**, and were unable to show any left hemisphere

functional enhancement .

## **Conclusion**

Interest and knowledge about Learning Disabilities ( including dyslexia ) is increasing. And multidisciplinary research is providing more fundamental understanding of the nature of this disorder, especially after extensive genetic studies, and genome-based screening, which is a new field of exploring several problems. And the great benefits gained from the safe and non-invasive functional magnetic resonance imaging ( fMRI ), which is eligible for studies on children, as opposed to PET ( Positron Emission Tomography ), which is not allowed for use during childhood period due to use of isotopes.

Learning disabilities are a major educational problem in the modern community which needs high potential of challenge tolerance in students and workers. Pupils suffering these disabilities must be identified as early as possible, and directed to appropriate evidence-based remediation and medication, among which nootropic drugs should have a role, which will widen with the introduction of more types of this class of drugs and further study of their efficacy, safety and duration of use.

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