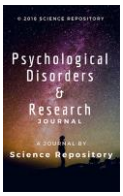

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Research Article

Attention Deficit Disorder in the Neuropediatric Outpatient Clinic. Our Current Experience with Children Over Seven and a Half Years Old

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ABSTRACT

Introduction: Attention deficit disorder, with or without hyperactivity (ADD/ADHD) can appear either alone or associated with diverse cerebral conditions, which may be hereditary or acquired. We review our experience of ADD/ADHD in children over seven and a half years old.

Methods: ADD/ADHD in children born before 1-1-2010, seen at the neuropediatric clinic between 31-12-15 and 19-6-17, is examined globally, by reasons for consultation and by diagnosis.

Results: 41% of the 2,541 children over 7½ years seen at the clinic had ADD/ADHD: 530 cases of ADD/ADHD alone and 513 associated with other conditions. In 15.6% of the cases of ADD/ADHD the reason for consultation was headaches and in 43%, psychomotor delay. ADD/ADHD accompanied 65% of the cases of Asperger's syndrome, 40% of intellectual disability and 23% of the cases of autistic spectrum disorder, 87.5 % of the cases of fragile X syndrome, 48.4% of chromosomopathies, 22% of genopathies, 19% of the cases of cerebral palsy, 50% of Duchenne, 53% of epilepsies, 67% of tics/Tourette, 51% of neurofibromatosis 1, 29 % of tuberous sclerosis and 74% of eastern European adopted children have ADD/ADHD.

Discussion: The importance of neurodevelopmental disorders and ADD/ADHD in neuropediatric practice is revealed.

Introduction

Attention deficit disorder with or without hyperactivity (ADD/ADHD) may occur alone or associated with other neurodevelopmental disorders such as intellectual disability (ID) and autistic spectrum disorder (ASD); all of them are associated with diverse cerebral problems, either inherited or acquired, which means that their prevalence is much greater in neuropediatric outpatients than in the general pediatric population. In the neuropediatric clinic we work with a database of children monitored from May 1990 onwards, protocols and information sheets (Table 1) informing parents of the type of monitoring carried out and explaining the importance of being alert to any problems of attention in children [1]. Over the past few years there has been an increase in the number of cases of ADD/ADHD identified. Children over the age of 7½ monitored at the neuropediatric clinic are reviewed and the cases of ADD/ADHD are analysed.

Methods

In the database we review children born before 1-1-2010 and monitored from 31-12-15 to 19-6-17, either on first visits or check-ups. The total cases and those with ADD/ADHD are analysed: in consultations for psychomotor delay and headaches (Table 2), in different diagnosis groups (Table 3), and associated with different neurodevelopmental disorders (Table 4). The cases of ADD/ADHD alone and ADD/ADHD associated with different pathologies are compiled (Table 3). In addition to ADD/ADHD, the neurodevelopmental disorders considered are ID, ASD (with intellectual disability) Asperger (autistic spectrum disorder with normal intelligence or high capabilities) and cerebral palsy (Table 4). The study has been approved by the local research ethics committee.

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Table 1: Some of the information sheets handed out.

ADD/ADHD (1st version 1,638 2nd version 1,000 and 3rd version 194)	2,832
Headaches	1,634
Psychomotor delay and neurodevelopmental disorders	1,262
Epilepsy (1st version 766, 2nd version 307)	1,073
Cerebral palsy	271
Tics	169
NF1 (1st version 72, 2nd version 64)	136
Absence epilepsy (1st version 43, 2nd version 22)	65
Tuberous sclerosis (1st version 18, 2nd version 16)	34
Duchenne muscular dystrophy (1st version 13, 2nd version 4)	17
Fragile-X	11
Prader Willi syndrome	2

This table shows the number of the information sheets given out up to 19-6-2017. We began to compile these information sheets in 4-2011 with the aim of providing comprehensive, reliable information, agreed upon by specialists in each pathology. The information sheets provide parents, healthcare and early care professionals with a "roadmap", encouraging joint monitoring of children by pediatricians, parents and all others responsible. Some of the information sheets have been revised on one or more occasions, as indicated in the table.

Table 2: Reason for consultation: psychomotor delay and headaches.

	Total cases monitored 2,541 children (Prevalence)	Monitored cases with ADD/ADHD	Percentage of monitored cases with ADD/ADHD	New cases (Incidence) since 1-1-2016	New cases with ADD/ADHD since 1-1-2016	Percentage of new cases with ADD/ADHD since 1-1-2016
Psychomotor delay	409	177	43%	25	13*	52%
Headache	727	156	21,4%	347	54	15,6%

Reason for consultation (at any time during the evolution of the child) - psychomotor delay and headaches. Total: 2,541 children monitored from 1-1-2016 to 19-6-2017, born after 31-12-2009 (more than 7½ years old). The table shows the reason for consultation-psychomotor delay and headaches (column 1), the total number of children monitored for each reason for consultation (column 2), the monitored cases that are diagnosed with ADD/ADHD for each reason for consultation (column 3), the percentage of children monitored for each reason of consultation that have ADD/ADHD (column 4), the new cases for each reason for consultation (column 5) and the new cases of ADD/ADHD for each reason for consultation (column 6), and the percentage of new children with ADD/ADHD for each reason of consultation (column 7).

*Consultations regarding psychomotor delay are unusual in children over the age of 7½; the database includes all of the reasons for consultation on the child's record regardless of when they occurred.

Table 3: Some diagnoses.

	Total cases monitored 2,541 children (Prevalence)	Monitored cases with ADD/ADHD	Percentage of monitored cases with ADD/ADHD	New cases (Incidence) since 1-1-2016	New cases with ADD/ADHD since 1-1-2016	Percentage of new cases with ADD/ADHD since 1-1-2016
ADD/ADHD alone*	530			187		
Associated ADD/ADHD**	513			52		
Epilepsy	429	134	31%	36	5	13,9%
Tics	159	107	67,3%	37	20	54%
Perinatal encephalopathy	131	35	26,7%	3	1	3%
Adopted children	87	54	62%	27	11	40,7%
Chromosomopathy-encephalopathy	64	31***	48,4%	1	0	
Rolandic epilepsy	36	10	27,8%	9	3	33,3%
Eastern European adopted children	35	26	74,3%	9	6	
Absence epilepsy	35	19	54,3%	0	0	
Neurofibromatosis 1	35	18	51,4%	0		
Genopathy-encephalopathy	18	4****	22,2%	1*****	1*****	100%
Tuberous sclerosis	14	4	28,6%	0		
Hemispheric tumour	10	3	30%	1	0	

Down's syndrome	9	1	11,1%	1	0	
Fragile-X syndrome	8	7	87,5%	0		
Duchenne muscular dystrophy	8	4	50%	0		
Dravet syndrome with SCN1A mutation	5	2	40%	0		
Myelomeningocele	5	2	40%	0		
Sturge-Weber syndrome	2	2	100%	0		
Prader Willi syndrome	2	2	100%	0	0	
Female fragile-X premutation carrier	1	1	100%	0	0	

Total: 2,541 children monitored from 1-1-2016 to 19-6-2017, born after 31-12-2009 (more than 7½ years old). The table shows the different diagnoses (column 1), the total number of monitored children with each diagnosis (column 2), the monitored cases diagnosed with ADD/ADHD for each diagnosis (column 3), the percentage of monitored children in each diagnosis who have ADD/ADHD (column 4), the new cases of each diagnosis (column 5), the new cases of ADD/ADHD in each diagnosis (column 6), and the percentage of new children in each diagnosis who have ADD/ADHD (column 7).
*ADD/ADHD alone. It may be accompanied by learning disorders, headaches, isolated arachnoid cysts or Chiari malformation type I. Adopted children are included, except Eastern European adopted children, if they do not present any other pathologies.
**Associated ADD/ADHD. It may be associated with: ASD, Asperger, intellectual disability, any type of epilepsy, NF1, tuberous sclerosis, Sturge-Weber syndrome, Tourette or tics, cerebral palsy, genopathy-encephalopathy, chromosomopathy-encephalopathy, Eastern European adopted children (considered probable foetal alcohol effect), dystrophinopathy, acquired encephalopathies (shaken baby syndrome, post-traumatic brain injury, acquired CNS infection), myelomeningocele, brain tumor.
***Chromosomopathies with ADD/ADHD, 30 cases: four cases of 16p11.2 deletion, four cases of 22q11.4 deletion, two cases of 1q21.1 deletion (one also with Fragile-X), two cases of 17q12 duplication and two cases of XYY syndrome. 16 cases of different alterations: 2q24 deletion, 3p26.3 3p26.1 duplication and 3p26.3 deletion, 5q12 deletion, 7q36.3 deletion and 20q13.32 duplication, 8q11 deletion (Silver-Russel-like syndrome), 10p15.3 deletion, 12q15 q21.1 deletion, 15q11 deletion, 15q13.3 deletion,15q26 deletion and 7p22 duplication, 18q deletion, 21q22.3 deletion, 22q11 .1 deletion and Xp22.31 duplication, trisomy 8p12, mosaic tetrasomy 9p, Xq28 duplication and triple X syndrome.
****Genopathies with ADD/ADHD, apart from fragile-X: Kabuki, Silver Russel, Williams Beuren and *****Noonan.

Table 4: Neurodevelopmental disorders.

	Total cases monitored 2,541 children (Prevalence)	Monitored cases with ADD/ADHD	Percentage of monitored cases with ADD/ADHD	New cases (Incidence) since 1-1-2016	New cases with ADD/ADHD since 1-1-2016	Percentage of new cases with ADD/ADHD since 1-1-2016
ADD/ADHD	1,043			239		
Intellectual disability	591	241	40.8%	28	12	42.8%
Cerebral palsy	228	44	19.3%	9	4	44.4%
Autistic spectrum disorder with intellectual disability	149	34	22.8%	3	0	
Asperger: ASD with normal or high intellectual capacity	60	39	65%	8	2	25%

Total: 2,541 children monitored from 1-1-2016 to 19-6-2017, born after 31-12-2009 (more than 7½ years old). The table shows different neurodevelopmental disorders and cerebral palsy (column 1), the total number of monitored children with each disorder (column 2), the monitored cases diagnosed with ADD/ADHD in each disorder (column 3), the percentage of monitored children in each diagnosis who have ADD/ADHD (column 4), the new cases of each diagnosis (column 5) and the new cases of ADD/ADHD in each disorder (column 6) and the percentage of new children with each disorder who have ADD/ADHD (column 7).

Results

The neuropediatric database from 15-5-1990 to 19-6-2017 comprised 20,612 children, of which 2,649 were diagnosed with ADD/ADHD (12.85%). From 1-1-2000 to 30-6-2017 the identified cases increased to 16.24% (of 15,769 children, 2,561 were diagnosed with ADD/ADHD), reaching 22.83 % between 1-1-2010 and 30-6-2017 (1,799 of 7,878). Between 31-12-15 and 19-6-17 3,857 children were seen at the clinic (on a first visit or check-up); 2,541 of these children were born before 1-1-2010, the mean age was 10.6 years old, minimum age 7½ and maximum age 19 years and 11 months. In 1,043 of the cases (41%) the child was diagnosed with ADD/ADHD: mean age 11.5 years, minimum 7.5 years and maximum 19 years and 11 months. Tables 2-4 shows the data

obtained. 227 children (21.8%) did not receive pharmacological treatment for ADD/ADHD at any time.

Discussion

ADD/ADHD was identified shortly before the year 2000. In the first 7 years of this century, 3.8% of our patients were diagnosed with ADD/ADHD, although only non-symptomatic cases of ADD/ADHD were included [1]. Currently the prevalence of ADD/ADHD at all ages is 22.8%. The diagnoses of ADD/ADHD at the Hospital Universitario de Getafe increased from 8.1% in 2002 to 27.6% in 2013 [2]. At our outpatient clinic the current prevalence of ADD/ADHD among school children seen over the past 18 months is 41%, 1,043 children, 530 cases of ADD/ADHD alone and 513 associated with other pathologies. Incidence is greater in cases of ADD/ADHD alone, 187 of 239 new cases (72.4%). Children with ADD/ADHD alone are referred to the clinic regarding problems with school performance or learning and, more infrequently, due to behavioural problems.

There is a lower incidence of ADD/ADHD associated with pathologies (52 cases), but a similar prevalence as these are chronic problems that require long-term monitoring. Hendriksen *et al.* identified ADD/ADHD in 38.6% of 685 children with neurological disabilities (mean age 10.3 years old) [3]. Previous studies of ADD/ADHD in children referred for headaches indicate that headaches mainly conceal inattention type ADD/ADHD, that academic and social failure leads to tension-type headaches and that prophylactic treatment for headaches is ineffective and that treatment should target attention deficit problems [4, 5]. 15.6% of children with headaches have ADD/ADHD, and the prevalence is 21% due to the fact that ADD/ADHD has a longer follow-up period than that of most headaches.

Children with developmental delay are more likely to be diagnosed with ADD/ADHD [6]. 43% of the children over the age of 7½, who were seen for psychomotor delay, have ADD/ADHD, either alone or associated with ID, ASD or Asperger. It is often the case that autistic symptoms improve after the first 2 or 3 years of the child's life, and that children with an overall developmental delay, with or without ASD, have ADD/ADHD from the age of 5-6 and older. Our information sheet on psychomotor delay and neurodevelopmental disorders indicates: "in general the symptoms of ASD tend to improve" and it explains "the evolving nature of psychomotor development and the great variability in the development of different children", and that "from 5 years and older in some cases treatment will be considered for possible problems in attention if this is your child's case".

Many genetic problems affecting brain development that are referred to the neuropediatric clinic due to psychomotor delay, such as fragile-X syndrome, including premutations, are accompanied to a variable degree by ID, ASD and ADD/ADHD [7-9]. Table 4 shows the prevalence of neurodevelopmental disorders in neuropediatric outpatients and the association between them; ADD/ADHD is associated with 65% of Asperger, 40% of ID and 23 % of ASD cases. ADD/ADHD is present in 87.5 % of fragile-X syndromes, 48.4% of chromosomopathies (not including Down's syndrome) and 22% of other genopathies. All of them may be accompanied by ID, ASD and ADD/ADHD to a variable extent and with different degrees of affectation.

Cerebral palsy is also accompanied, to a variable degree, by neurodevelopmental disorders, including affectation of attention and executive function. Gabis *et al.* reported ADD/ADHD in 22.5% of children with cerebral palsy, which is similar to our 19% [10]. Our information sheet indicates: "when monitoring children with cerebral palsy we check for associated complications and alterations, such as: visual deficits, hypoacusis, cognitive deficit, language disorders, ASD, learning disorders, hyperactivity, attention deficit." ADD/ADHD has been reported in 23-32% and inattention in 44% of Duchenne patients [11]. Four of our eight patients over the age of 7½ monitored for Duchenne disorder present ADD/ADHD. Our information sheet indicates: "in some cases it is accompanied by intellectual disability alone or associated with autistic spectrum disorder and attention deficit disorder."

ADD/ADHD figures among children with epilepsy are between 16.7% and 50%, influenced by antiepileptic drugs, the type of epilepsy and the underlying brain impairment [12, 13]. ADD/ADHD is present in 31% of our cases monitored for epilepsy; the incidence is lower (14%), showing that the worst cases of epilepsy are monitored for longer and are more frequently accompanied by ADD/ADHD than epilepsies that evolve more favorably. ADD/ADHD has been diagnosed in 53% of the cases of absence epilepsy and in 28% of rolandic epilepsies. The figures of ADD/ADHD in children with rolandic epilepsy are between 31% and 70%, and attention deficit is diagnosed in a third of children with absence epilepsy [14, 15]. Some antiepileptic drugs can cause or worsen ADD/ADHD symptoms and in some cases should be withdrawn. Several studies indicate that Ethosuximide or Lamotrigine should be considered as first-line treatment for absence epilepsies in order to avoid the negative effects that Valproate has on attention [15].

In certain cases, attention deficit may improve with treatment for epilepsy but, if this is not the case, then treatment for ADD/ADHD should be considered. There are numerous references to the effectiveness and safety of treating children with epilepsy and ADD/ADHD with stimulants [13, 16]. Our information sheets on epilepsy/absence epilepsy indicate: "treatment aims to ensure that children have no seizures/absences or very few and that these are as mild as possible, but not at any cost. It is important to make sure that treatment is tolerated well and to be alert to any possible side effects, especially those affecting attention, behaviour or school performance."

ADD/ADHD has been reported in 35-90% of Tourette syndrome cases [17]. Fernández-Álvarez reported tics associated with ADD/ADHD alone in 39% of cases and associated with ADD/ADHD plus obsessive compulsive disorders in 20% of cases, and Tourette syndrome accompanied by ADD/ADHD alone in 42% of cases and by obsessive compulsive disorder in 24% of cases [18]. Treatment with stimulants is appropriate for ADD/ADHD accompanied by tics, although in some cases it can aggravate tics [17-19]. 67% of children with tics/Tourette referred to our outpatient clinic were also diagnosed with ADD/ADHD. The most frequent reason for monitoring children with tics/Tourette is that they show signs of ADD/ADHD. Our information sheet states: "tics are frequently accompanied by other disorders such as ADD/ADHD, obsessive compulsive disorder and learning disorders."

Inattention has been reported in 63-67% of children with neurofibromatosis 1 (NF1) and ADD/ADHD in between 38 and 58.33%

[20-22]. In our experience, ADD/ADHD was present in 51% of the cases of NF1. Our information sheet on NF1 indicates: "ID is present in 4-8% of cases and learning, language and attention disorders in 30-60% of cases", "Monitoring of learning problems: educational psychology support and/or specific treatment as for ADD/ADHD". It has been shown that treatments with stimulants that act on neurotransmitters improve leaning disorders and cognitive, academic and social functions in children with NF1 [20, 23].

ADD/ADHD is associated with tuberous sclerosis in between 19% and 31% of cases, and deficits in one or more attentional functions have been diagnosed in 90% of the cases of tuberous sclerosis [24-26]. In our experience, 29% of tuberous sclerosis cases are accompanied by ADD/ADHD. Our information sheet indicates: "Neuropsychiatric disorders: ASD, attention deficit/hyperactivity, anxiety, depression, aggressiveness and sleep problems."

62% of adopted children present ADD/ADHD, mainly children adopted from Eastern Europe where there is a high percentage of foetal exposure to alcohol (74%). Foetal alcohol spectrum disorder is accompanied by impairment of language, memory and executive functions, hyperactivity, impulsiveness, social and behavioural difficulties [27].

There is effective pharmacological treatment for executive brain dysfunction (ADD/ADHD alone or associated with other neurodevelopmental disorders). None of the problems associated with ADD/ADHD (ASD, tics, obsessive-compulsive disorder, anxiety, learning disorders, oppositional-defiant disorder, depression), contraindicate pharmacological treatment.

Frontal lobe impairment may cause a dysfunction of the executive brain that produces an organisational defect and defects in the control of attention and impulses. However, the executive brain is not limited to the frontal lobe; the different regions of the cerebral cortex are densely interconnected, and their functional relationships are not clearly known. Cognitive and attention functions are not located solely in the frontal lobe and they depend on adequate neuronal circuits throughout the brain, which explains the high prevalence of ADD/ADHD in different encephalopathies [28]. Neurodevelopmental disorders (such as epilepsy and movement disorders) are frequently a sign of synaptopathies and there are treatment prospects aimed at regulating the function of neurotransmitters in the synaptic vesicles [29]. There are already effective drugs to enhance the executive brain function.

Our ADD/ADHD information sheet indicates:

i. "Inattention may occur alone (and may go unnoticed), and it is usually the biggest problem; in some cases, it is accompanied by impulsiveness. Hyperactivity alone is not usually a problem requiring treatment".
ii. "No diagnosis can exclude ADD/ADHD. It occurs in people of normal intelligence, with ID and with high capacities. It can be associated with ASD and Asperger syndrome. It can be accompanied by tics, oppositional-defiant disorder, depression, anxiety and with learning disorders such as dyslexia. It can cause headaches".
iii. "Psychostimulants are effective in 80% of cases of ADD/ADHD. They help regulate correct functioning of brain neurotransmitters, necessary for the executive brain function. Response can be very positive and can be observed from the beginning of treatment"
iv. "The decision to continue treatment and to adjust it according to response and tolerance under the guidance of professionals, lies with parents and, as they grow older, the children themselves."

21.8 % of our patients diagnosed with ADD/ADHD have not received any pharmacological treatment in spite of being at least 7½ and the fact that we usually recommend it from 6 years onwards. This study shows the importance of neurodevelopmental disorders and ADD/ADHD in neuropediatrics and the fact that treatment is rejected in one in five cases. It is necessary to carry out further studies on the effectiveness and tolerance of treatment in the short, medium and long term in cases of ADD/ADHD alone and those associated with different pathologies.

Conflicts of Interest

None.

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