ORIGINAL ARTICLE

Complicated relationship between autism with regression and epilepsy

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Abstract

We retrospectively evaluated a set of 205 children with autism and compared it to the partial sub-set of 71 (34.6%) children with a history of regression. From 71 children with regression, signs of epileptic processes were present in 43 (60.6%), 28 (65.12%) suffered clinical epileptic seizures, and 15 (34.9%) just had an epileptiform abnormality on the EEG. In our analysis, autistic regression is substantially more associated with epileptic process symptoms than in children with autism and no history of regression. More than 90% of children with a history of regression also show IQ < 70 and reduced functionality. Functionality and IQ further worsens with the occurrence of epileptic seizures (98% of children with regression and epilepsy have IQ < 70). We proved that low IQ and reduced functionality significantly correlate rather with epileptic seizures than just sub-clinical epileptiform abnormality on EEG.

Clinical epileptic seizures associated with regression significantly influence the age of regression and its clinical type. The age of regression is higher compared to children with regression without epileptic seizures (in median: 35 months of age in patients with seizures while only 24 months in other patients). Patients with seizures revealed regression after 24th months of age in 68% of cases, while patients without seizures only in 27%. However, coincidence with epilepsy also increased the occurrence of regression before the 18th month of age (23% of patients), while only 4% of patients without epilepsy revealed regression before the 18th month. Epileptic seizures are significantly associated especially with behaviour regression rather than speech regression or regression in both behaviour and speech. Also epileptic seizures diagnosed before correct diagnosis of autism were significantly associated with delayed regression (both behavioural and speech regression).

Abbreviations:

AA	– Atypical Autism
AS	– Asperger's Syndrome
ASD	– Autistic Spectrum Disorders
CARS	– Childhood Autism Rating Scale
CAST	– Childhood Asperger's Syndrome Test
CHA	– Childhood Autism
CT	– Computer Tomography
CNS	– Central Nervous System
CSWS/ESES	– Continuous flashes of epileptiform activity (spikes or spike-wave complexes) during slow sleep
DNA	– Deoxyribonucleic Acid
EA	– Epileptiform Abnormalities on EEG
EEG	– Electroencephalography
ES	– Epileptic Seizures (Epilepsy)
HFA	– High Functioning Autism
IQ	– Intelligence Quotient
LFA	– Low Functioning Autism
LKS	– Landau – Kleffner syndrome
MFA	– Medium Functioning Autism
MRI	– Magnetic Resonance Imaging
PDD	– Pervasive Developmental Disorders

INTRODUCTION

Autism is a serious lifelong disorder of the developing brain, which manifests in childhood. Affected children are seriously handicapped and long-term outcomes confirm that autists, except the highly functional ones, are totally dependent and outcasts from society also as adults (Anagnostou & Schevell, 2006; Howlin *et al*. 2004). Autism is characterised by a basic triad of symptoms, which include *deficits in social skills and interactions, deficits in verbal and non-verbal reciprocal communication, and a limited stereotypical repertoire of activities and interests* (Charman, 2005). The broader scale of the "autistic spectrum or continuum (ASD)" (also known as "pervasive developmental disorders" PDD) actually covers a highly heterogeneous group of disorders with multiple cognitive behavioural disorders and developmental specifics (Bailey & Parr, 2003; Hirtz *et al*. 2006; Hirtz *et al*. 2006; Xue Ming *et al*. 2008). In clinical practice there is still no diagnostic biological marker, which is why the diagnosis of autism (except for Rett syndrome) is further defined only on the level of clinical behavioural cognitive syndrome (phenomenological classification) (Rapin & Tuchman, 2006; Ruble & Brown, 2003). Autism has a very varied pathogenesis and aetiology. Furthermore, new information about possible environmental factors in the development of symptoms of autism is available. For instance, a role of polyunsaturated fatty acids (Sliwinski *et al*. 2006) or the effects of mercury in maternal dental amalgam and thimerosal-containing vaccine (Mutter *et al*. 2005, Geier & Geier, 2007), the influence of cortisol related to sex or role of androgenes (Nakayama *et al*. 2007, Geier & Geier, 2006) have been discussed. However, the importance of the risks mentioned above has never been confirmed quite explicitly. Currently it can be summarised that the causes of autism may be hereditary or non-hereditary and research carried out in the past few years shows its strong genetic determination (Brimacombe *et al*. 2007; Folstein *et al*. 2003; Licinio & Alvarado, 2002; Muhle *et al*. 2004; Newschaffer *et al*. 2002).

In the literature, the co-existence of autism and epilepsy is stated in a broad range of 5–38.3% (Canitano, 2007; Hara, 2007; Kelley & Mosh0, 2006; Tuchman & Rapin, 2002; Wrong, 1993). Approximately one third of autistic children will develop epilepsy by adulthood, and all seizure types occur (Volkmar & Nelson, 1990). There is a bimodal distribution of age on onset, with peaks occurring under 5 years and during adolescence (Tuchman & Rapin, 2002). The rate of epilepsy increases significantly among those with mental retardation (Olsson *et al*. 1988). In children with idiopathic autism without associated disorders and family history of epilepsy or other risk factors for epilepsy the prevalence is lower than 6% but it is still much higher than in the overall population (Tuchman & Rapin, 2002)

On the other hand, various epileptic syndromes are described with autistic symptoms, such as other cognitive, developmental, and neurological disorders (Besag, 2004; Goyal, 2007; Kelley & Moshé, 2006). The high coincidence of both types of the dynamic disorders – autism with epilepsy – suggests that autistic behaviour in children may in some cases represent one of many cognitive and behavioural disorders of epileptic origin (Deonna & Roulet-Perez, 2005). The relationship between epilepsy and autism as a potential cause and effect is being intensively researched for autism; mostly for autism with regression (Gabis *et al*. 2005). This is mainly due to the fact that neurologists and epilepsy experts specialising in children have recognised the similarity with cognitive behavioural regression in children with a predominant relationship to special types of epilepsy, such as continuous waves and spikes during slow sleep (spikes or spike-wave complexes - CSWS/ESES) or the Landau-Kleffner syndrome (LKS) (McVicar & Shinar, 2004; Tuchman, 1999).

In approximately one third of autistic children, regression or stagnation of speech, communication, and play appear after originally normal development in early childhood. The regression appears early, typically between the 18th and 24th month of life, and is not progressive (Hirtz *et al*. 2006; Rapin, 1991; Roulet-Perez & Deonna, 2006). What usually follows is a stabilised period of various lengths that can last for months – or even years. This is followed by a certain improvement, but not recovery. We also considered Rett syndrome or other rare neurometabolic and genetic disorders, but the search for a specific cause for the regression remains unsuccessful. In those children that also show signs of the epileptic process, the theoretical question arises of possible regressive disorders of epileptic origin, including "sub-clinical" or "hidden" epilepsy, if the child does not show any visible seizures, and only sub-clinical epileptiform changes on EEG are detected. In some individuals this opens a secondary question on the perhaps partial therapeutic effect of anti-epileptic drugs, which are used for treatment of epileptic disorders, on autism

symptoms (Peake *et al*. 2006; Rapin, 1995). The main driving force behind the global clinical research is of course the fact that there is still no significantly successful pharmacological treatment for the core symptoms of autism. Another important motivation is to gain an understanding of the complicated causes of the autistic syndrome and other factors that may secondarily modulate its seriousness and the resulting clinical phenotype.

THE AIM OF THE WORK

Our department is also a diagnostic centre for autism and tertiary centre for diagnostics and treatment of childhood epilepsy. The probability of occurrence of autism in epileptic children is increased compared to the rest of population, as was published by Clarke (Clarke *et al*. 2005). The main aim of our work was to investigate relationship between the studied clinical and diagnostic markers, and their risk in the sub-set of autistic children with a history of regression (N=71) compared to the entire set of autistic children (N=205). We studied the theoretically possible causal relationship between epilepsy and autism with regression, and even more likely – the modulating metachronic influence of epilepsy and/or epileptiform activity on the finer clinical characteristics of autistic regression, mainly its type and the age, when regression is manifested. Another, and also very important motivation for our work was to contribute to the knowledge of complicated causes of autistic regression, and other factors that may secondarily modulate its seriousness and the resulting manifestations.

MATERIALS AND METHODS

A retrospective trial evaluated 205 children with ASDs, in particular with childhood autism (CHA), atypical autism (AA) and Asperger's syndrome (AS). The children were diagnosed as autistic in our department in accordance with the classification criteria of the 10th revision of International Classification of Diseases (World Health Organization, 1993), Childhood Autism Rating Scale scoring (CARS questionnaire) (Schopler *et al*. 1980) and Childhood Asperger's Syndrome Test (CAST questionnaire) (Scott *et al*. 2002). IQ was tested in younger children using the Gesell Developmental Scale and the 4th edition of Stanford-Binet Intelligence Scale, 4th edition in older subjects. Furthermore, we used De Myer's modified classification (DeMyer *et al*. 1981) and divided the whole set into "high-functioning, middle-functioning and low-functioning autists", which partially reflected IQ but mainly their total ability to function in the common social situations of everyday life. In practice it is considered a marker of so-called "social IQ". This complex, clinically significant quantification of severity of social and mental handicap was carried out by the same psychologist and paediatric neurologist for the whole set.

In this way, we made sure that each autistic child in our set was functionally defined through four characteristics: a) ASD type according to MKN-10, b) IQ score, c) total CARS score, and d) functionality grade. In all cases of autistic children with a history of regression N=71 (34.6%) we recorded the age and detailed clinical characteristics. Mainly if it was just a) regression of behaviour, or b) regression of speech related to regression of behaviour, or c) only regression of speech or words, in children where signs of autism were already present before the regression.

Epileptic seizures and epilepsy were classified according to the rules of the Commission on Classification and Terminology of the International League Against Epilepsy from 1981 into partial and generalized and non-classifiable epilepsy and epileptic syndromes according to the accepted classification of epilepsy and epileptic syndromes from 1989 (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) into partial, generalized, epilepsies undetermined as to whether focal or generalized, and non-classifiable. EEG and EEG after sleep deprivation including diurnal sleep, most often 24- or 32-channel, were carried out in all the children, usually repeatedly during the monitoring. In EEG, the background was differentiated into normal or abnormal, and the presence of non-epileptiform abnormality and epileptiform abnormality on EEG was recorded. In the latter, we studied whether it occurred only in one hemisphere (right or left) or was bilateral. Non-epileptic manifestations, such as motor and behavioural stereotypes or affective disturbances, were differentiated carefully in all the children. The detailed familial history, personal history and previous disease outcomes were found out in all subjects; neurological and psychological examinations including determining laterality were performed; most children underwent psychiatric investigations, neuroimaging with CT and/or MRI of the brain, genetic consultations, and in clinically suspected patients karyotype was determined and DNA analysed for tuberous sclerosis (Curatalo *et al*. 2004), fragile-X chromosome, Rett syndrome and congenital defects of metabolism. Within diagnosis, all parents were asked about the children's age when recognizing the first symptoms of autism, while only syndromes of psychomotoric retardation were defined carefully.

RESULTS

The results of our work are consequently presented in **Tables 1–6.** The sequence of the tables and Figures clearly reflects the entire procedure and sequence of analyses and results.

Tables 1–2 show children with regression among other autistic individuals and reveals whether are there

Table 1. Characteristics of patients with autism stratified according to regress

Characteristics of patients	Patients without regress (N = 134; 65.4 %)	Patients with regress (N = 71; 34.6 %)	p value
Male sex (boys)	96 (71.6 %)	49 (69.0 %)	0.694
Age (yrs)	10 (5; 15)	9 (5; 14)	0.925
Age at diagnosis of autism * (yrs)	6.7 (3.2; 12.7)	4.8 (2.6; 12.0)	**< 0.001**
Type of autism			
Asperger's syndrome	21 (15.7 %)	0 (0 %)	
Atypical autism	39 (29.1 %)	18 (25.4 %)	
Childhood autism	74 (55.2 %)	53 (74.7 %)	**<0.001**
Functionality of autism			
High	57 (42.5 %)	18 (25.4 %)	
Medium	49 (36.6 %)	30 (42.3 %)	**0.034**
Low	28 (20.9 %)	23 (32.4 %)	
CARS & IQ			
CARS score *	38 (31; 47)	40 (32; 49)	**0.046**
CARS > 39	46 (41.8 %)	40 (58.0 %)	**0.035**
IQ total *	60 (18; 100)	47 (25; 70)	**0.012**
IQ < 35	34 (25.4 %)	22 (30.9 %)	0.393
IQ < 70	83 (61.9 %)	64 (90.1 %)	**< 0.001**
Diagnostics			
Abnormal neurology examination	64 (47.8 %)	38 (53.5 %)	0.432
Hypotonia	18 (13.4 %)	14 (19.7 %)	0.244
Spasticity (cerebral palsy)	30 (22.4 %)	15 (21.1 %)	0.835
EEG abnormal background	71 (52.9 %)	44 (61.9 %)	0.215
EEG non-epileptiform abnormalities	42 (31.3 %)	22 (30.9 %)	0.958
CT	26 (19.4 %)	22 (31.0 %)	0.065
MRI	47 (35.1 %)	27 (38.0 %)	0.675
CT & MRI	55 (41.0 %)	32 (45.1 %)	0.579
Screens for inborn errors of metabolism	1 (0.8 %)	4 (5.6 %)	0.121
Genetic screening	14 (10.5 %)	10 (14.1 %)	0.446
Hearing impairment	7 (5.2 %)	5 (7.0 %)	0.602
Optical impairment	38 (28.4 %)	16 (22.5 %)	0.363
Handedness & motor deficits			
Right handed	58 (43.3 %)	24 (33.8 %)	0.187
Left handed	27 (20.2 %)	13 (18.3 %)	0.751
Nondescript	35 (26.1 %)	27 (38.0 %)	0.079
Other (low functionality)	14 (10.4 %)	7 (9.9 %)	0.894
Gross motor deficits (clumsy and uncoordinated movements	91 (67.9 %)	41 (57.8 %)	0.150
Mild motor deficits	115 (85.8 %)	53 (74.7 %)	0.063
Epilepsy			
Epileptic seizures before autism	13 (9.7 %)	15 (21.1 %)	**0.026**
Epilepsy before regres	-	18 (64.3 %)	-
Epileptiform abnormalities on EEG and/or seizures	60 (44.8 %)	43 (60.6 %)	**0.031**
Epileptiform abnormalities on EEG without seizures	57 (42.5 %)	41 (57.8 %)	**0.038**
Epileptic seizures	36 (26.9 %)	28 (39.4 %)	**0.043**
Age of first seizures * (month)	22 (3; 96)	19 (5; 84)	0.951
Behavioral abnormities			
Fidgetiness	96 (71.6 %)	50 (70.4 %)	0.854
Hyperactivity	52 (38.8 %)	37 (52.1 %)	0.067
Excitability	91 (67.9 %)	51 (71.8 %)	0.561
Anxiety	47 (35.1 %)	22 (30.9 %)	0.556
Follow – up of family history			
Abnormalities in family history	58 (43.3 %)	31 (43.7 %)	0.956
Epilepsy	12 (8.9 %)	7 (9.9 %)	0.832
Psychiatric disorders	32 (23.9 %)	15 (21.1 %)	0.653
Autism	3 (2.2 %)	1 (1.4 %)	0.675
Social pathology	9 (6.7 %)	0 (0 %)	**0.005**
Neurologic a/nebo psychologic pathology	12 (8.9 %)	1 (1.4 %)	**0.018**
Genetic	6 (4.5 %)	6 (8.5 %)	0.260
Migraine	4 (2.9 %)	4 (5.6 %)	0.363
Follow – up of personal history			
Risk factors in sum	97 (72.4 %)	47 (66.2 %)	0.356
Prenatal risk factors	67 (50.0 %)	27 (38.0 %)	0.102
Perinatal risk factors	47 (35.1 %)	33 (46.5 %)	0.112
Postnatal risk factors	52 (38.8 %)	28 (39.4 %)	0.929

[1] Continuous variables (marked with *) are summarized as median with 10 % - 90 % percentiles (in parenthesis). Binary outcomes are expressed as N and percentage (in parenthesis). [2] Significance level of tests for difference between groups: Mann-Whitney U test for continuous variables and ML Goodness of fit test for binary codes

CARS: Childhood Autism Rating Scale (CARS) questionnaire. CARS score was estimated in N = 179 patients. **IQ:** Intelligence quotient

Table 2. Risk factors with significant association with regress

Risk factors [1]	Patients with regres	Odds ratio [2]	
		(95 % conf. limits)	p level
Childhood autism			
No: N = 78	23.1 %	2.39 (1.26; 4.51)	p = 0.007
Yes: N = 127	41.7 %		
Autism of medium or low functionality			
No: N = 75	24.0 %	2.18 (1.15; 4.13)	p = 0.016
Yes: N = 130	40.8 %		
Epileptic seizures			
No: N = 141	30.5 %	1.77 (1.01; 3.28)	p = 0.044
Yes :N = 64	43.8 %		
Epileptiform abnormalities on EEG without seizures			
No: N = 107	28.0 %	1.84 (1.02; 3.31)	p = 0.039
Yes :N = 98	41.8 %		
Epileptic seizures before autism			
No: N = 177	31.6 %	2.49 (1.11; 5.61)	p= 0.027
Yes: N = 28	53.6 %		
CARS > 39 *			
No: N = 93	31.2 %	1.92 (1.03; 3.55)	p = 0.036
Yes: N = 86	46.5 %		
IQ total < 70			
No: N = 58	12.1 %	5.62 (2.38; 13.27)	p < 0.001
Yes: N = 147	43.5 %		

[1] Only factors with statistically significant association are included (see also Table 1).
[2] Odds ratio calculated from uni-variate logistic regression models with 95% confidence limits and level of statistical significance (calculated on the whole sample, N = 205).
* CARS score was estimated in N = 179 patients.

any significant and/or specific associations with risk factors.

- Incidence of regression in the examined data set reached nearly 35% with the same distribution of sex and age as in the other autistic children
- Patients with regression were diagnosed as autistic significantly earlier (comp. 6.7 yr of age without regression vs. 4.8 yrs with regression). This fact could be correlated with the prevailing type of autism among patients with regression: nearly 75% of them suffered from CHA accompanied with low functionality and decreased IQ score.
- Both IQ and CARS score indicated significantly decreased functionality of children with regression in comparison with the others. The differences were more remarkable and significant in IQ scoring.
- Detailed analysis revealed a significant cut off in IQ value (IQ < 70) that very significantly separates children with regression from the others. More than 90% of children with regression had IQ < 70 while in the others it was only 62%.
- In correlation with decreased functionality, there was increased coincidence of nondescript handedness in children with regression, however with only borderline significance.
- Occurrence of regression was evidently associated with signs of epileptic disorders, both epileptic seizures and epileptiform abnormalities on EEG. Children with diagnosed regression also revealed an increased incidence of epilepsy before diagnosis of autism.
- No significant association with regression was found in the full set of neurological examination including CT&MRI findings. Similarly, no really significant risk factor for regression was identified in personal and family medical history and in behavioural abnormalities.
- Separated risk analysis of identified risk factors in **Table 2** proved their significance and led to a corresponding odds ratio (OR). In fact, there are two basic, mutually correlated, families of risk factors. The first cluster of risk factors is associated with low functionality of patients with regression, associated with CHA and reduced intelligent quotient. The second group of factors is specifically associated with epilepsy, both with seizures and positive epileptiform discharges on EEG.

Table 3 shows separated cohort of patients with regression (N = 71) was then characterized with respect to the coincidence of epilepsy:

- Signs of epileptic process (both epileptic seizures and epileptiform abnormalities on EEG) did not associate with sex, age, or age at diagnosis of autism and did not correlate with type of autism. On the other

Table 3. Characteristics of patients with regress in association with epileptic disorders

Characteristics of patients	Patients with regress (N = 71)			
	Without epilepsy (N = 28)	With epilepsy (N = 43)	With epilepsy (N = 43)	
			Epileptic seizures (N = 28)	Only EEG abnormities (N = 15)
Sex (boys)	18 (64.3 %)	13 (86.7 %)	18 (64.3 %)	13 (86.7 %)
Age (yrs) [1]	8 (5; 13)	10 (5; 15)	9 (5; 17)	10 (5; 14)
Regres				
Age of regres (months) [1]	24 (18; 56)	30 (12; 48)	35 (15; 65)*	24 (10; 38)*
Age < 18 months	1 (3.6 %)*	10 (23.3 %)*	6 (21.4 %)	4 (26.7 %)
Age > 24 months	13 (46.4 %)	23 (53.5 %)	19 (67.9 %)*	4 (26.7 %)*
Regres of speech	21 (75.0 %)	29 (67.4 %)	16 (57.1 %)*	13 (86.7 %)*
Regres of behavior	19 (67.9 %)	34 (79.1 %)	25 (89.3 %)*	9 (60.0 %)*
Interaction: regres of behavior and speech	12 (42.9 %)	20 (46.5 %)	13 (46.4 %)	7 (46.7 %)
Autism [2]				
Age at dg of autism [1] (yrs)	5 (3; 11)	4 (2; 12)	5 (2; 13)	4 (3; 8)
Atypical autism	7 (25.0 %)	11 (25.6 %)	7 (25.0 %)	4 (26.7 %)
Childhood autism	21 (75.0 %)	32 (74.4 %)	21 (75.0 %)	11 (73.3 %)
Functionality of autism				
High	8 (28.6 %)	10 (23.3 %)	5 (17.9 %)	5 (33.3 %)
Medium	15 (53.6 %)	15 (34.9 %)	10 (35.7 %)	5 (33.3 %)
Low	5 (17.9 %)*	18 (41.9 %)*	14 (50.0 %)*	4 (26.7 %)*
CARS score [1]	39 (32; 49)	40 (33; 48)	40 (33; 45)	40 (33; 52)
CARS > 39	14 (50.0 %)	26 (63.4 %)	17 (65.4 %)	9 (60.0 %)
IQ total [1]	52 (30; 82)*	40 (20; 61)*	34 (10; 54)*	56 (31; 64)*
IQ < 35	9 (32.1 %)	13 (30.2 %)	9 (32.1 %)	4 (26.7 %)
IQ < 70	22 (78.6 %)†	42 (97.7 %)†	27 (96.4 %)	15 (100 %)
Follow-up of personal history				
Prenatal risk factors	12 (42.9 %)	15 (34.9 %)	11 (39.3 %)	4 (26.7 %)
Perinatal risk factors	16 (57.1 %)	17 (39.5 %)	13 (46.4 %)	4 (26.7 %)
Postnatal risk factors	12 (42.9 %)	16 (37.2 %)	12 (42.9 %)	4 (26.7 %)
Diagnostics				
Abnormal neurology examination	14 (50.0 %)	24 (55.8 %)	17 (60.2 %)	7 (46.7 %)
Hypotonia	3 (10.7 %)	11 (25.6 %)	6 (21.4 %)	5 (33.3 %)
Spasticity (cerebral palsy)	6 (21.4 %)	9 (20.9 %)	8 (28.6 %)	1 (6.7 %)
EEG abnormal background	11 (39.3 %)†	33 (76.7 %)†	23 (82.1 %)	10 (66.7 %)
EEG non-epileptiform abnormalities	7 (25.0 %)	15 (34.9 %)	12 (42.9 %)	3 (20.0 %)
CT	9 (32.1 %)	13 (30.2 %)	10 (35.7 %)	3 (20.0 %)
MRI	7 (25.0 %)*	20 (46.5 %)*	15 (53.6 %)	5 (33.3 %)
CT & MRI	10 (35.7 %)	22 (51.2 %)	17 (60.7 %)*	5 (33.3 %)*
Screens for inborn errors of metabolism	1 (3.6 %)	3 (7.0 %)	3 (10.7 %)	0
Genetic screening	5 (17.9 %)	5 (11.6 %)	4 (14.3 %)	1 (6.7 %)
Hearing impairment	3 (10.7 %)	2 (4.7 %)	2 (7.1 %)	0
Optical impairment	6 (21.4 %)	10 (23.3 %)	10 (35.7 %)†	0†
Handedness & motor deficits				
Right handed	11 (39.3 %	13 (30.2 %)	10 (35.7 %)	3 (20.0 %)
Left handed	3 (10.7 %)	10 (23.3 %)	6 (21.4 %)	4 (26.7 %)
Nondescript	14 (50.0 %)	13 (30.2 %)	7 (25.0 %)	6 (40.0 %)
Other (low functionality)	0*	7 (16.3 %)*	5 (17.9 %)	2 (13.3 %)
Gross motor deficits (clumsy and uncoordinated movements	14 (50.0 %)	27 (62.8 %)	19 (67.9 %)	8 (53.3 %)
Mild motor deficits	21 (75.0 %)	32 (74.4 %)	23 (82.1 %)	9 (60.0 %)
Behavioral abnormities				
Fidgetiness	18 (64.3 %)	32 (74.4 %)	18 (64.3 %)*	14 (93.3 %)*
Hyperactivity	14 (50.0 %)	23 (53.5 %)	13 (46.4 %)	10 (66.7 %)
Excitability	19 (67.9 %)	32 (74.4 %)	18 (64.3 %)*	14 (93.3 %)*
Anxiety	11 (39.3 %)	11 (25.6 %)	8 (28.6 %)	3 (20.0 %)
Follow – up of family history				
Epilepsy	2 (7.1 %)	5 (11.6 %)	5 (17.9 %)*	0*
Psychiatric disorders	9 (32.1 %)	6 (14.0 %)	2 (7.1 %)	4 (26.7 %)
Autism	1 (3.6 %)	0	0	0
Social pathology	0	0	0	0
Neurologic a/nebo psychologic pathology	1 (3.6 %)	0	0	0
Genetic	3 (10.7 %)	3 (7.0 %)	3 (10.7 %)	0
Migraine	2 (7.1 %)	2 (4.7 %)	0	2 (13.3 %)

1 Continuous variables are summarized as median with 10 % - 90 % percentiles (in parenthesis).

2 No patients with Asperger syndrome were diagnosed within the cohort with regres

* † Marks for statistically significant difference between groups with / without epilepsy and separately tested between patients with seizures and with only EEG abnormities (Mann-Whitney U test; ML Goodness of fit test): * $p < 0.05$, † $p < 0.01$.

Table 4. Coincidence of epilesy and EEG findings in patients with regress

Epilepsy and EEG findings	Patients with regress and epileptic disorders (N = 43)			
	All patients (N = 43)	**Regress of speech** [1] (N = 29)	**Regress of behavior** [1] (N = 34)	**Interaction: regress of behaviour and speech** [1] (N = 20)
Age at dg of autism (yrs) [2]	4 (2, 12)	5 (2; 12)	4 (2; 12)	4 (2; 9)
Age of regres (months) [2]	30 (12; 48)	24 (12; 60)	30 (12; 48)	24 (12; 48)
Age < 18 months	10 (23.3 %)	7 (24.1 %)	9 (26.5 %)	6 (30.0 %)
Age > 24 months	23 (53.5 %)	14 (48.3 %)	18 (52.9 %)	9 (45.0 %)
Epilepsy before dg of autism	15 (34.9 %)	11 (37.9 %)	12 (35.3 %)	8 (40.0 %)
Epileptic seizures	28 (65.1 %)	16 (55.2 %) [b]	25 (73.5 %) [a]	13 (65.0 %)
Simple partial with/without SGS	8 (18.6 %)	4 (13.8 %)	8 (23.5 %) [a]	4 (20.0 %)
Complex partial with/without SGS	12 (27.9 %)	8 (27.6 %)	11 (32.4 %)	7 (35.0 %)
Generalized	15 (34.9 %)	9 (31.0 %)	13 (38.2 %)	7 (35.0 %)
Absence	2 (4.7 %)	1 (3.5 %)	2 (5.9 %)	1 (5.0 %)
Myoclonc	3 (6.9 %)	2 (6.9 %)	3 (8.8 %)	2 (10.0 %)
Clonic	3 (6.9 %)	3 (10.3 %)	3 (8.8 %)	3 (15.0 %)
Tonic	6 (13.9 %)	2 (6.9 %) [b]	5 (14.7 %)	1 (5.0 %) [b]
Atonic	7 (16.3 %)	5 (17.2 %)	7 (20.6 %) [a]	5 (25.0 %)
Tonic-clonic	1 (2.3 %)	0	1 (2.9 %)	0
Infantile spasms	6 (13.9 %)	4 (13.8 %)	4 (11.8 %)	2 (10.0 %)
Unclassified	8 (18.6 %)	3 (10.3 %) [b]	6 (17.7 %)	1 (5.0 %) [b]
Epilepsies and epileptic syndromes				
Localization- related	12 (27.9 %)	8 (27.6 %)	11 (32.4 %)	7 (35.0 %)
Generalized	12 (27.9 %)	7 (24.1 %)	10 (29.4 %)	5 (25.0 %)
Epilepsies undetermined whether focal or generalized	1 (2.3 %)	0	1 (2.9 %)	0
Special syndromes	4 (9.3 %)	1 (3.5 %) [b]	4 (11.8 %)	1 (5.0 %)
EEG findings				
Abnormity of background activity	33 (76.7 %)	19 (65.5 %) [b]	24 (70.6 %) [a]	10 (50.0 %) [b]
Non-specific abnormities	15 (34.9 %)	7 (24.1 %) [b]	12 (35.3 %)	4 (20.0 %) [b]
Specific abnormities	34 (79.1 %)	24 (82.8 %)	28 (82.4 %)	18 (90.0 %)
Type I (focal)	34 (79.1 %)	22 (75.9 %)	25 (73.5 %)	13 (65.0 %) [b]
Type II (generalized)	18 (41.9 %)	12 (41.4 %)	16 (47.1 %)	10 (50.0 %)
Specific abnormities: side				
EEG: bilateral	18 (41.9 %)	11 (37.9 %)	13 (38.2 %)	6 (30.0 %)
EEG: sin	8 (18.6 %)	5 (17.2 %)	6 (17.7 %)	3 (15.0 %)
EEG: dx	8 (18.6 %)	6 (20.7 %)	6 (17.7 %)	4 (20.0 %)

[1] Subgroups are not disjoint and therefore are not mutually statistically tested. The only test was performed separately within each subgroup comparing incidence of a given abnormity (row) against the rest of patients as referent set. [a,b] Marks of significantly increased ([a]) or decreased ([b]) incidence of given abnormity in analyzed subgroup in comparison with the rest patients as referent set (ML Goodness of fit test; $p < 0.05$).

[2] Continuous variables are summarized as median with 10 % - 90 % percentiles (in parenthesis).

Table 5. Coincidence of epilepsy and EEG findings in patients with regress and epileptic seizures

Epilepsy and EEG findings	Patients with regress and epileptic seizures (N = 28)		
	All patients (N = 28)	**Seizures after dg of autism** (N = 13) [1]	**Seizures before dg of autism** (N = 15) [1]
Age at dg of autism (yrs) [2]	5 (2, 12)	5 (2; 11)	5 (2; 13)
Age of regres (months) [2]	32 (12; 65)	29 (8; 48)	34 (16; 65)
Age < 18 months	6 (21.4 %)	4 (30.8 %)	2 (13.3 %)
Age > 24 months	17 (60.7 %)	7 (53.9 %)*	12 (80.0 %)*
Epileptic seizures			
Simple partial with/without SGS	8 (28.9 %)	5 (38.4 %)	3 (20.0 %)
Complex partial with/without SGS	12 (42.9 %)	7 (53.9 %)	5 (33.3 %)
Generalized	15 (53.6 %)	7 (53.9 %)	8 (53.3 %)
Absence	2 (7.1 %)	1 (7.7 %)	1 (6.7 %)
Myoclonc	3 (10.7 %)	0*	3 (20.0 %)*
Clonic	3 (10.7 %)	1 (7.7 %)	2 (13.3 %)
Tonic	6 (21.4 %)	3 (23.1 %)	3 (20.0 %)
Atonic	7 (25.0 %)	2 (15.4 %)	5 (33.3 %)
Tonic-clonic	1 (3.6 %)	1 (7.7 %)	0
Infantile spasms	6 (21.4 %)	2 (15.4 %)	4 (26.7 %)
Unclassified	8 (28.6 %)	4 (30.8 %)	4 (26.7 %)
Epilepsies and epileptic syndromes			
Localization- related	12 (42.9 %)	7 (53.9 %)	5 (33.3 %)
Generalized	12 (42.9 %)	4 (30.8 %)	8 (53.3 %)
Epilepsies undetermined whether focal or generalized	1 (3.6 %)	0	1 (6.7 %)
Special syndromes	4 (14.3 %)	2 (15.4 %)	2 (13.3 %)
EEG findings			
Abnormity of background activity	23 (82.1 %)	11 (84.6 %)	12 (80.0 %)
Non-specific abnormities	12 (42.9 %)	7 (53.9 %)	5 (33.3 %)
Specific abnormities	23 (82.1 %)	8 (61.5 %)†	15 (100 %)†
Type I (focal)	19 (67.9 %)	9 (69.2 %)	10 (66.7 %)
Type II (generalized)	17 (60.7 %)	8 (61.5 %)	9 (60.0 %)
Specific abnormities: side			
EEG: bilateral	13 (46.4 %)	4 (30.8 %)*	9 (60.0 %)*
EEG: sin	4 (14.3 %)	3 (23.1 %)	1 (6.7 %)
EEG: dx	2 (7.1 %)	2 (15.4 %)	0

[1] Patients with epilepsy before and after dg of autism were mutually compared (ML Goodness of fit test: * $p < 0.05$, † $p < 0.01$).
[2] Continuous variables are summarized as median with 10 % - 90 % percentiles (in parenthesis).

hand patients with regression and epilepsy revealed significantly more frequently decreased functionality and IQ quotient. Nearly 98% of patients with regression and epilepsy had an IQ < 70%. Further comparison suggested that low functionality and decreased IQ score were significantly correlated with epileptic seizures rather than with only sub-clinical epileptiform discharges on EEG without clinical seizures.

- Regarding age of regression, coincidence with epilepsy in general did not influence the age. However, occurrence of seizures led to a significantly prolonged age of regression (in median: 35 months of age in patients with seizures while only 24 months in the other patients). Patients with seizures revealed regression after 24th month of age in 68%, while patients without seizures only in 27%. Coincidence with epilepsy however also increased occurrence of regression before 18th month of age (23% of patients), while only 4% of patients without epilepsy revealed regression before the 18th month.
- Epileptic seizures are significantly associated namely with regression of behaviour rather than with regression of speech only. No specific interaction with ep-

Table 6. Coincidence of epilepsy and EEG findings in patients with regress according to age at diagnosis of regress

Epilepsy and EEG findings	Patients with regress and epileptic seizures (N = 28)		
	All patients (N = 28)	**Regress diagnosed ≤ 24 month of age** (N = 9) [1]	**Regress diagnosed > 24 month of age** (N = 19) [1]
Epileptic seizures			
Simple partial with/without SGS	8 (28.9 %)	4 (44.4 %)	4 (21.1 %)
Complex partial with/without SGS	12 (42.9 %)	4 (44.4 %)	8 (42.1 %)
Generalized	15 (53.6 %)	4 (44.4 %)	11 (57.9 %)
Absence	2 (7.1 %)	1 (11.1 %)	1 (5.3 %)
Myoclonc	3 (10.7 %)	1 (11.1 %)	2 (10.5 %)
Clonic	3 (10.7 %)	2 (22.2 %)	1 (5.3 %)
Tonic	6 (21.4 %)	2 (22.2 %)	4 (21.1 %)
Atonic	7 (25.0 %)	3 (33.3 %)	4 (21.1 %)
Tonic-clonic	1 (3.6 %)	1 (11.1 %)	0
Infantile spasms	6 (21.4 %)	3 (33.3 %)	3 (15.8 %)
Unclassified	8 (28.6 %)	2 (22.2 %)	6 (31.6 %)
Epilepsies and epileptic syndromes			
Localization- related	12 (42.9 %)	3 (33.3 %)	9 (47.4 %)
Generalized	12 (42.9 %)	5 (55.6 %)	7 (36.8 %)
Epilepsies undetermined whether focal or generalized	1 (3.6 %)	1 (11.1 %)	0
Special syndromes	4 (14.3 %)	0	4 (21.1 %)
EEG findings			
Abnormity of background activity	23 (82.1 %)	7 (77.8 %)	16 (84.2 %)
Non-specific abnormities	12 (42.9 %)	4 (44.4 %)	8 (42.1 %)
Specific abnormities	23 (82.1 %)	8 (88.9 %)	15 (78.9 %)
Type I (focal)	19 (67.9 %)	6 (66.7 %)	13 (68.4 %)
Type II (generalized)	17 (60.7 %)	8 (77.8 %)	9 (52.6 %)
Specific abnormities: side			
EEG: bilateral	13 (46.4 %)	4 (44.4 %)	9 (47.4 %)
EEG: sin	4 (14.3 %)	1 (11.1 %)	3 (15.8 %)
EEG: dx	2 (7.1 %)	1 (11.1 %)	1 (5.3 %)

[1] No statistically significant difference was found between patients with regres diagnosed before and after 24 months (ML Goodness of fit test)
[2] Continuous variables are summarized as median with 10 % - 90 % percentiles (in parenthesis).

ilepsy was found when simultaneous regression of speech and behaviour was examined.

- There were only rare associations between neurological and generally diagnostic findings and coincidence of epilepsy. Patients with regression and epileptic seizures revealed more frequent MRI or CT positivity, and patients with any type of epileptiform abnormalities had more frequent EEG abnormal background and MRI positivity.
- Patients with regression and epileptic seizures revealed more frequent optical impairment and a positive family history of epilepsy. On the other hand, these patients had less frequently reported behavioural abnormalities, namely fidgetiness and excitability.

In **Tables 4–6** are given the diagnostic typology of epileptic seizures and/or disorders with respect to given types of regression.

The characterization of patients with regression shown in **Table 3** therefore suggested three main characteristics of regression that should be important also from a practical point of view:

- type of regression (behavioural or regression of speech or both)
- regression accompanied with epileptic seizures, with respect to age when the seizures occurred (before or after diagnosis of autism)
- age of regression, namely the group with regression after age of 24 months that again appeared to be associated with epilepsy and namely with epileptic seizures.

Because all the mentioned types of regression are to some extent associated with epileptic seizures and epileptiform abnormalities on EEG, we performed de-

tailed diagnostic typology of the seizures and disorders in **Tables 4–6:**

- Analyses in **Table 4** confirmed that epileptic seizures are significantly associated with regression of behaviour while no such risk association occurred in the case of speech regression. Patients with behavioural regression (independent of speech regression) revealed increased coincidence of EEG abnormal background and of several types of seizure (focal simple and general atonic).
- Type of regression associated neither with epileptiform EEG discharges nor with laterality of found abnormalities **(Table 4)**.
- Epileptic seizures diagnosed before autism were significantly associated with delayed regression (both behavioural and speech regression). The detailed typology of patients with regression after the 24th month of age revealed increased incidence of myoclonic seizures and generally epileptiform abnormalities on EEG - namely bilateral **(Table 5)**.
- Although coincidence of epileptic seizures significantly increased the age of regression, no specific association between type of epileptic abnormality/ seizure and risk of delayed regression was found **(Table 6).**

DISCUSSION

In our set of 205 autistic children, autism with a history of regression was represented by 71 cases (34.6%) with the same distribution of sex and age as in other autistic children. The occurrence of regression is on the upper limit of the range given for sets of autistic children (Canitano & Zapella, 2006; Rapin, 1991). An interesting fact is that the sub-group with regression shows no difference between the distributions of both sexes. The explanation of this is the low IQ of the regression children in our set (over 90% IQ< 70). Autism is characterised by the prevalence of affected boys, which is usually 3–4 boys : 1 girl, just as in other neurodevelopmental disorders such as dyslexia, attention deficit and hyperactivity syndrome and language development disorders. This rate, however, significantly changes (1-2 boys:l girl), if the IQ is lower, which is the situation in our set (Danielsson *et al*. 2005; Olsson *et al*. 1988; Rutter *et al*. 2003).

In our set, patients with regression were diagnosed as autistic significantly earlier (comp. 6.7 yr of age without regression vs. 4.8 yrs with regression). Regression is a conspicuous clinical change, and therefore it is logical that these children are diagnosed earlier. The suitable age for diagnostics of CHA, from which most of regression children in our set recruit, is usually around three years. In fact the diagnosis of childhood autism is rather late in our region, as we have published earlier in "The course of diagnosis in autistic patients: the delay between recognition of the first symptoms by parents and correct diagnosis" (Ošlejšková *et al*. 2007b).

Occurrence of regression in our set was evidently associated with signs of epileptic disorders – with epileptic seizures and with only sub-clinical epileptiform abnormalities on EEG. Children with diagnosed regression also revealed increased incidence of epilepsy before diagnosis of autism. Children with regression and epilepsy revealed significantly more frequently decreased functionality and IQ quotient. Nearly 98% of patients with regression and epilepsy had IQ < 70%. Further comparison suggested that low functionality and decreased IQ scoring were significantly correlated with epileptic seizures rather than with only sub-clinical epileptiform discharges on EEG without clinical seizures. The influence of epileptic seizures on the decrease of functionality and IQ correlates with results of a study carried out on 77 childhood autism children where the autistic regression was more frequent in epileptic children than in non-epileptic patients (Hrdlicka *et al*. 2004). The authors also found that abnormal development during the first year of age was significantly associated with epileptiform activity and that epilepsy significantly correlates with mental retardation. As was mentioned before, on the other hand it was also proved that the rate of epilepsy is increased significantly among those with mental retardation (Olsson *et al*. 1988).

The fact that there are more pathologically positive CT or MRI findings in our set of regression children documents the possibility of greater distribution of symptomatic epilepsies and secondary autism. Patients with regression and epileptic seizures revealed more frequent optical impairment and positive family history with epilepsy. Frequent association with sight impairment is a very interesting finding, which can be, however, only hypothetically commented on and explained through a common ontogenetic origin of the nervus opticus and central neural system (CNS). Significant occurrence of epilepsy in a family is not a surprise but an expected result.

The role of epileptiform abnormality on EEG and epilepsy occurring with a history of regression in autism was and is a long-term globally discussed problem. There are many studies often with controversial results, which are difficult to compare, are complicated, and most of them conclude with the statement that the relation between autistic regression and signs of epileptic process are unclear and require further research.

Most unclear is the relationship between autistic regression and only sub-clinical epileptiform flashes on EEG. Only very little is known of what the sub-clinical epileptiform flashes occurring during the development of a child's central neural system mean, and how they influence this development (Canitano *et al*. 2005; Gordon, 2000). Epileptiform activity in autistic patients is present in 10.3% to 72.4% of patients and sub-clinical abnormalities in 6.1% to 31%, in cases with regression around 20% (Kagan-Kushnir *et al*. 2005, Roulet-Perez & Deonna, 2006). Also in our previously published paper on the risk factors that are significantly associat-

ed with speech disorders in autistic children, we found a significant association of speech regression and focal epileptiform abnormality on EEG, just as with laterality other than right-handedness. In other speech disorders within the same set with ASD (retarded speech development and aphasia), epileptic seizures were significantly and independently associated, mainly infantile spasms and myoclonic seizures, laterality other than right-handedness, seriously reduced IQ score, and hypotonia (Ošlejšková *et al*. 2007a). From the listed and other literature resources it becomes evident that the percentage of abnormality capture differs greatly in various studies. The high percentage of epileptiform abnormality capture on EEG in our set of autistic regression children could be explained by the low IQ of the set, but mainly by coincidence of the two following circumstances: a) our department is also a specialised tertiary centre for diagnostics and therapy of childhood epilepsy, which surely modulates the spectrum of patients sent to us – we have more of those with autism and epilepsy, and children with signs of epileptic process somehow relating to autistic regress, and b) it is also sure that the frequency of epileptiform activity registration strongly depends on the variable circumstances under which the EEG is taken. This covers the children's age, basic aetiology, and co-existence of mental retardation and epilepsy. Not less important are the technical factors such as the length of the EEG record, number of EEG records, expert focus of the workplace and erudition of the staff that read the EEG, as well as the fact if sleep is monitored during day or night (Tuchman & Rapin, 2002). The combination of all the mentioned factors may contribute to the relatively high capture (near 35%) of sub-clinical epileptiform abnormality on EEG in our set of regression children.

In accordance with Hughes we registered a high variability of EEG abnormalities (Hughes & Melyn, 2005) (data not shown). In our opinion it is likely that the epileptiform flashes precede the later occurrence of epilepsy in the later life of the child, which is described in the work of Hara, but this cannot be reliably derived from our analyses (Hara, 2007). Currently, in accordance with the published data we can summarise that direct causal influence of sub-clinical epileptiform abnormality on the occurrence of autistic regression is not clearly proven (Kagan-Kushnir *et al*. 2005; Kelley KR & Moshé, 2006; Roulet-Perez & Deonna; 2006). However, the convincing results of our study clearly suggest that epileptiform activity does significantly relate to the occurrence of regression, which was discovered also by other authors (Canitano *et al*. 2005). There is probably an analogy with other cognitive behavioural defects that can also be induced by sub-clinical epileptiform activity (Binnie *et al*. 1991; Scott & Neville, 1998).

A causal relationship of the sub-clinical epileptiform abnormality on EEG with regression is almost impossible to document entirely in clinical practice, as the patient, almost as a rule, comes with already developed symptoms of autism or regression for the diagnosis, and even if we detect a positive EEG, we almost never have the opportunity to detect the exact time sequence of the pathological findings. In the case of clinically evident epileptic seizures the results of our study confirm that they also significantly relate to regression. The most important result of our analysis is the finding of the significant influence of epileptic seizures on more detailed clinical characteristics of regression: the age of regression and its clinical type. The age of regression is higher in children suffering epileptic seizures compared to children without epileptic seizures (in median: 35 months of age in patients with seizures while only 24 months in other patients). Patients with seizures revealed regression after the 24th month of age in 68%, while patients without seizures only in 27%. Coincidence with epilepsy however also increased occurrence of regression before the 18th month of age (23% of patients), while only 4% of patients without epilepsy revealed regression before the 18th month. Epileptic seizures are significantly associated with regression of behaviour rather than speech regression or regression of both speech and behaviour. Also epileptic seizures diagnosed before correct diagnosis of autism were significantly associated with delayed regression (both behavioural and speech regression). A detailed typology of patients with regression after the 24th month of age revealed increased incidence of myoclonic seizures and generally epileptiform abnormalities on EEG, namely bilateral. Our results correlate with the data in the literature. It seems that most of the regression cases in idiopathic autism, which occur typically between 18–24 months, do not relate to epileptic signs (Roulet-Perez & Deonna, 2006). On the other hand, in the case of regression with atypical clinical characteristics, mainly later regression cases after the 24th month of age – there is a possibility and also a probability of at least a partial causal relationship with epilepsy, which we have proved. It can even be the diffusion of clinical regressive autistic phenotypes with atypical LKS, in the case of which there is often speech regression occurring together with behaviour regression and autistic manifestations (Canitano & Zapella, 2006; McVicar & Shinar, 2004; Tuchman, 1999; Tuchman & Rapin, 2002).

CONCLUSIONS

The experts agree on the necessity of prospective longitudinal monitoring of evident causal, partially causal, or modulating relations between autistic regression and clinical or sub-clinical epilepsy. The results of our analyses did prove a significant relationship between signs of epileptic process and autistic regression. It is likely that this mostly does not cover the direct and only causal reason, but rather a relationship that influences the final phenotype of autism and its severity. The topic remains controversial despite the high number of texts that were published.

Our work on the large set of autistic children proves that the signs of epileptic process statistically significantly relate to the very early or late autistic regression and epileptic seizures also further reduce the IQ and functionality of these children, i.e. worsen the resulting clinical seriousness of autism and autism with regression. From our results we consider as very likely also the time continuity or speech and behaviour regression from toddler age to pre-adolescence, i.e. during the entire post-maturity development of the CNS. This is a spectrum (continuum) ranging from the "atypical autistic regression" through "autistic regression", "atypical LKS", "typical LKS" to "childhood disintegrative disorder" around 10–13 years of age. This is a more accurate description of reality than the conventional and accepted definition of specialised and separate nosological units that are common in the current understanding of regressive developmental disorders.

For clinical practice the following is crucial: in cases of behavioural autistic regression at atypical age (outside the 18 – 24 months boundary) the signs of epileptic process should be actively sought, and due to the high probability of epilepsy the subtle clinical symptoms of epileptic seizures should be differentiated. Currently it is not recommended to use anti-epileptic drugs for the therapeutic influence of just sub-clinical epileptiform flashes, but the clinically evident epileptic seizures should be rather properly treated and responsibly monitored along with the recording of the behavioural, cognitive, and emotional outcome of the child. We expect a positive change in the compensation of epileptic seizures, but in the mentioned atypical cases the overall positive change of autistic and other cognitive manifestations cannot be ruled out either. At the same time it is necessary to flexibly react to any negative responses in the mood and behaviour of the child, which also cannot be fully precluded in autistic children treated with anti-epileptic drugs (Canitano, 2007; Peake *et al*. 2006). Evidence for the effectiveness of anticonvulsants and corticosteroids in reducing seizures and/or autistic symptoms is based primarily on case series and case reports, with only one published randomised trial (Di Martino & Tuchman, 2001; Kagan-Kushnir *et al*. 2005). Further detailed studies and trials are therefore necessary.

The correct individual solution of complicated cases of parallel occurrence of epilepsy and autism (especially with regression) can be detected only by creatively co-operating experts from multiple fields of medicine (child neurologists, psychiatrists, and paediatrists), as well as non-medical fields (psychologists and educationalists), and remarks and comments from family members are also an invaluable source of information.

STATISTICAL DATA ANALYSIS

All statistical tests were performed on the intention-to-treat principle, and no case was excluded prior to the analyses. A value $\alpha < 0.05$ was taken as a universal limit for statistical significance in all analyses. Only standard robust descriptive statistics were used to express differences among subgroups of cases (median supplied with 10% - 90% percentiles; estimates of relative frequency). The ML chi-square test was applied to study associations among binary or categorical outcomes. The robust Mann-Whitney U test was applied to estimate differences between subgroups of patients in continuous variables.

A univariate approach was applied to examine the contribution of examined risk factors to the incidence of regression. Logistic regression was used for analysing the relationship between predictor variables and regression, coded at two levels (0/1, 1 being the risk event). The odds ratio with corresponded 95% confidence limits was estimated on the basis of logistic regression models. (Altman, 1991, Zar, 1984)

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