Letters to the editor

'Familial alternating hemiplegia of childhood or channelopathy? A report with valuable pathophysiological implications'

SIR–Kanavakis et al.[1] described a family with an autosomal dominant condition of alternating hemiplegic attacks, and suggested alternating hemiplegia of childhood (AHC) as the most likely diagnosis. We agree that AHC is among the diagnostic hypotheses, as some variability occurs in the clinical presentation of this condition. We are aware of one other report, by Mikati et al.[2] of a family with AHC suggesting an autosomal dominant inherence.

The mechanism of AHC remains unknown. Familial cases are interesting, not as oddities but as potential sources of valuable clues to the pathogenesis of the disease. This is illustrated in the report by Kanavakis et al.[1] However, their family has many atypical features. First, none of the patients experienced their first hemiplegic attacks before 18 months of age. In the study by Mikati et al.[2] only seven out of 44 patients were older than 18 months when they had their first hemiplegic attack. In previous series, the latest onsets were 54 months[3] and 56 months.[2] Second, the seizures do not usually antedate the hemiplegic attacks. In the report by Kanavakis et al.[1] three of the four children experienced seizures before the first hemiplegic attack and four of the six affected family members had seizures. In the two largest series reported to date, the frequency of seizures ranged from about 9/44 patients[2] to 6/22 patients.[4] In these two series, seizures did not occur concomitantly with hemiplegic attacks. Third, in the report by Kanavakis et al.[1] no clinical symptoms are reported in any of the four children before 1 year of age or before the onset of seizures or hemiplegic attacks. Abnormal eye movements were noted in all the patients studied by Mikati et al.[2] Of the 24 patients studied by Bourgeois et al.[4] 10 had clinical symptoms in the neonatal period. Finally, flushing was reported in the four children studied by Kanavakis et al.[1] Although flushing was among the autonomic symptoms reported in previous studies, the proportion of affected patients was lower. Mikati et al.[2] noted flushing in 28% of the patients.

Based on these considerations, we suggest that the family described by Kanavakis et al. does not have AHC. Familial channelopathy may be a more likely diagnosis. Kramer et al.[5] reported a family with similar findings: hemiplegic migraine attacks occurred in five family members in three generations, and two of these family members experienced focal seizures during the migraine attacks. The clinical features described by Kramer et al.[5] are very similar to those in the family reported by Kanavakis et al.[1] In both families, the underlying disease may be a channelopathy.

The mutations identified in patients with familial hemiplegic migraine were not looked for in the families described by Kanavakis et al.[1] and Kramer et al.[5] One form of familial hemiplegic migraine (locus *FMH1*) can be caused by mutations in the calcium ion channel gene *CACNL1A4*, and another form is related to a mutation in the *ATP1A2* gene. Another locus for familial hemiplegic migraine (*FMH3*) has been identified on *1q31*. Due to of the occurrence of alternating hemiplegia in the family, genetic testing for a susceptibility locus would be of interest. Knowledge of the site of the locus might provide insights into the mechanism of alternating hemiplegic attacks in this family and in families with AHC.

The clinical symptoms shared with AHC in the family described by Kanavakis et al.[1] in particular the hemiplegic spells, provide interesting pathophysiological hypotheses. Channelopathy has been suggested as the pathophysiological mechanism of AHC because many patients respond to treatment with the calcium-channel antagonist flunarizine. This is the only drug known to date to reduce the severity and/or duration of AHC attacks (Mikati et al.[2] Bourgeois et al.[4]). The unpredictable and paroxysmal nature of AHC symptoms is consistent with channelopathy. The clinical similarities that AHC shares with both hemiplegic migraine and episodic ataxia type 2, two conditions related to mutations in the *a1A* calcium-channel gene subunit *CACNA1A*, prompted investigations of this gene in four patients with AHC (Haan et al.),[6] however, no mutations were found.

The family reported by Kanavakis et al.[1] should be considered as having a channelopathy with alternating hemiplegic spells. Accumulating data about AHC, its variants, and channelopathies with hemiplegic spells is an essential prerequisite to improving the diagnosis of these conditions, developing detailed definitions, and conducting genetic studies which may provide information on the pathophysiological mechanism of hemiplegic spells. Rho and Chugani[7] pointed out this need for establishing a clinical and genetic database as a source of material for research.

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Stéphane Auvin MD[a]
Sylvie Joriot-Chekaf MD
Jean-Christophe Cuvellier MD
Louis Vallée MD

Correspondence to:
[a]*Service de Neurologie Pédiatrique*
Hôpital Roger Salengro
Boulevard du Pr J Leclercq
59037 Lille Cedex, France
E-mail: s-auvin@chru-lille.fr

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'Kanavakis et al. reply'

SIR–Auvin et al. noticed atypical features in the family with the presumptive diagnosis of alternating hemiplegia of childhood[1] (AHC) and they propose familial channelopathy as a more likely diagnosis.

We support the diagnosis of AHC as the most likely diagnosis in this family because: (1) the clinical features of the sporadic cases of AHC are similar with respect to both ictal and interictal phenomena. However, in the family we described the disease is inherited with an autosomal dominant trait. Disorders with this mode of inheritance present with a wide spectrum of the disease characteristics regarding the age at onset and the clinical features and their severity as well. (2) Medical history was primarily obtained by the mother, thus the difficulties arising from her cognitive impairment are obvious. Hemiplegic attacks of a few minutes duration are not considered significant – on the contrary they are common and 'normal' characteristics of her family. Therefore, the exact details of the family medical history cannot be clearly defined. (3) Situations included in the differential diagnosis of AHC have been excluded by appropriate extensive laboratory evaluation. (4) Finally, familial hemiplegic migraine seems to share a number of clinical features with AHC. Presence or absence of headache has been difficult to ascertain in affected family members, but is certainly not reported as a primary or significant symptom. The mother admits episodes of occasional generalized headache (2–3 episodes per year). Any relationship to her episodes of motor impairment is unclear.

However, based on the assumption that the pathophysiology of AHC is unclear, we decided to proceed with our family for further molecular investigation. At present, these studies are in progress with regard to a possible channelopathy and a mutation has been identified. The results of this study will be published as soon as they are well documented.

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Emmanuel Kanavakis
Athina Xaidara
Dimitra Papathanasiou-Klontza
Alexandros Papadimitriou
Stavroula Velentza
Sotiris Youroukos

Correspondence to:
Emmanuel Kanavakis
Associate Professor – Chair
Medical Genetics, Athens University
Athens, Greece
E-mail: ekanavak@cc.uoa.gr

Reference

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'Attention deficits and subclinical epileptiform discharges: are EEG diagnostics in ADHD optional or essential?'

SIR–We read with interest two recent papers in 'Developmental Medicine & Child Neurology'[1,2] regarding the association of childhood epilepsy and attention-deficit–hyperactivity disorder (ADHD). Both studies were focused on neuropsychiatric disorders in children with epilepsy. Based on a recent study on ADHD and associated subclinical electroencephalogram (EEG) discharges,[3] we would like to present arguments concerning an association between epilepsy and ADHD from a child psychiatrist's perspective.

We examined Rolandic spikes in 483 children with ADHD without epilepsy and found a significantly higher frequency of spikes than expected ($p<0.001$); we based our expected value for frequency on epidemiological studies.[3] None of the patients had a bioelectrical status epilepticus during slow-wave sleep. Our data replicated previous reports on the same incidence of focal epileptiform discharges in children with ADHD without epilepsy.[4] In our study, children with ADHD with Rolandic spikes were significantly younger at admission than those with ADHD only. This suggests that Rolandic spikes, or underlying mechanisms of epileptogenesis, either decrease the vulnerability threshold or advance the onset of ADHD. As the temporal sequence of the manifestation of subclinical epileptiform activity in relation to ADHD cannot be assessed in retrospect, we must remain speculative as to whether our data present an example of the successive comorbidity outlined by Noeker and Haverkamp.[2] Future studies will have to determine whether antiepileptic treatment instead of, or adjunctive to, stimulants is justified for this ADHD subgroup.

Our study, in contrast to the findings of Dunn et al.,[1] showed that children with ADHD plus Rolandic spikes tend to exhibit more hyperactive-impulsive symptoms than those with ADHD only. As in most psychiatric samples,[5] these symptoms were evident in a larger proportion of those diagnosed with ADHD combined type than ADHD inattentive type. In addition, preliminary results of an ongoing neuropsychological study suggest that children with ADHD with Rolandic spikes show a higher frequency of impulsive behaviour compared with children with ADHD without spikes. This is indicated by a significantly larger amount of commission errors in a cued continuous performance task.[6] These findings add to the data provided by Noeker and Haverkamp,[2] who reported selective and sustained attention deficits in their patients with epilepsy.

In conclusion, these results give rise to two points: firstly, whether there is a relationship between ADHD symptoms and the presence of the epileptiform discharges; and secondly, the importance of performing EEGs in the diagnostic assessment of ADHD.

The EEG remains controversial, as part of the routine assessment of ADHD. The American Academy of Child and Adolescent Psychiatry practice parameters for the assessment and treatment of children with ADHD[7], advise an EEG only in the presence of clinical suggestions of seizure disorders, focal neurological signs, or degenerative conditions in children and adolescents with psychiatric disorders. However, there is an increasing awareness that a considerable proportion of children, not only those with Rolandic epilepsy but also non-epileptic children with subclinical Rolandic discharges, have associated neuropsychiatric deficits resembling features typically observed in ADHD.[3,8] The similarity between Rolandic epilepsy and ADHD is demonstrated by the following shared diagnostic features: deficits of executive functions; inhibition of control; being easily distracted; showing impulsive behaviour; and externalizing behavioural symptoms.[9,10] Moreover, both begin in early childhood and occur more frequently in

males. Like Rolandic epilepsy, some cases of ADHD seem to be limited by puberty. Another similarity is the cerebral immaturity suggested by electroencephalography.

As some children with ADHD, without seizures, degenerative conditions, or focal neurologic signs show abnormalities such as Rolandic spikes in a routine EEGs, the inclusion of EEGs in ADHD diagnostics seem essential to the identification of this subgroup. The EEG is the indicator of the need for specific testing, further evaluation and, perhaps, adequate therapy.

Not performing routine EEG could result in the oversight of subclinical epileptic discharges in a considerable number of children with ADHD. We suggest that the update of practice parameters for the assessment and treatment of children with ADHD until puberty should include EEG, regardless of the lack of a prior history of overt seizures or other obvious neurological conditions.

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Katja Becker MD[a]
Judith K Sinzig MD[b]
Martin Holtmann MD[c]

[a]*Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim*
[b]*Department of Child and Adolescent Psychiatry and Psychotherapy, University of Cologne*
[c]*Department of Child and Adolescent Psychiatry and Psychotherapy, J W Goethe-University, Frankfurt/Main*

Correspondence to:
[a]*Department of Child and Adolescent Psychiatry and Psychotherapy*
Central Institute of Mental Health
Mannheim, Germany
E-mail: kbecker@zi-mannheim.de

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'Developmental delay or failure to arrive?'

The use of precise terminology is important in our communication with parents and other professionals. However, ill thought-out terminology is counter-productive and weakens the language. It may also let 'political correctness' override medical realities.

We question the continued usefulness of the phrase 'developmental delay' for parents and professionals. The problem with the term developmental delay is that it does not define the length of delay. When does persistent delay stop being a delay? A visual representation of a time line showing a child's development at a shallower gradient than the general paediatric population, tailing off to a final lower level, may help. Parents can then see the extent to which the their children are behind their peers and that although they will make progress, they will always be behind.

We feel that developmental delay is not an appropriate description in these cases. We propose that at an early stage we should talk about developmental disorders, difficulties, or problems, rather than developmental delay. Otherwise parents may have unrealistic or inappropriate expectations. Developmental delay can engage us in a *folie à deux* with the parents, and only postpones the inevitable day when we have to be candid with them. Perhaps we fear that we will appear uncompassionate or uncaring, being caricatured as in those ludicrous media stories in which a seemingly healthy and healed child is now presented as 'My miracle child that proved the doctors wrong'. We have to meld compassion with honesty.

Paediatric neurodisability is not like the greatly lamented British Rail, which did get you there in the end. Even now when we are told the train is delayed, we tacitly accept that a train will ultimately arrive and eventually take us to our destination. A delay implies ultimate arrival at the chosen goal: yet a cure is not within sight for the majority of those with a paediatric neurodisability. 'Developmental delay' is misleading. It is time for us to shunt it into the sidings of medical history.

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Dr Andrew N Williams[a]
Dr Charles Essex[b]

Correspondence to:
[a]*Consultant Neurodevelopmental Paediatrician, Child Development Centre, Northampton General Hospital, Northampton, NN1 5BD*
E-mail: anw@doctors.org.uk
[b]*Consultant Neurodevelopmental Paediatrician, Child Development Unit, Gulson Hospital, Coventry, CV1 2HR*
E-mail: room101@ntlworld.com