Autistic epileptiform regression

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Summary

Autistic regression is a well known condition that occurs in one third of children with pervasive developmental disorders, who, after normal development in the first year of life, undergo a global regression during the second year that encompasses language, social skills and play. In a portion of these subjects, epileptiform abnormalities are present with or without seizures, resembling, in some respects, other epileptiform regressions of language and behaviour such as Landau-Kleffner syndrome. In these cases, for a more accurate definition of the clinical entity, the term autistic epileptiform regression has been suggested.

As in other epileptic syndromes with regression, the relationships between EEG abnormalities, language and behaviour, in autism, are still unclear. We describe two cases of autistic epileptiform regression selected from a larger group of children with autistic spectrum disorders, with the aim of discussing the clinical features of the condition, the therapeutic approach and the outcome.

KEY WORDS: autism, pervasive developmental disorders, regression.

Introduction

Among children affected by autism and pervasive developmental disorders a subgroup of approximately thirty per cent presents a clinical course defined as autistic regression (AR). In these children, the features of autistic spectrum disorders, consisting of a lack of social and emotional reciprocity, language and communication disorders, and stereotyped behaviours, become evident after a period (the first year or two of life) of normal development (1). Progressive loss of previously acquired language and cognitive skills associated with social and affective withdrawal are noted during the second year of life in most cases (2). The etiology of the deterioration usually remains unknown: neither neurometabolic and neurodegenerative nor infectious diseases of the central nervous system are usually identified (3). Abnormal EEG findings, with focal and multifocal epileptiform activity increasing during sleep, have been detected in a considerable percentage of children with AR, especially when evaluated through prolonged sleep EEG (4). A functional basis for AR, with or without seizures, has therefore been proposed; when epileptiform discharges are evident the recommended definition is autistic epileptiform regression (AER) (5,6). As the deterioration in AR occurs insidiously at an early age, the question has been raised of whether the earlier development had, in fact, been completely normal, or whether, instead, a delay had already been occurring but had gone unrecognized. Parents' accounts of a child's early language and behavioural development are often misleading, yet they are the main source of information at our disposal (7).

The paradigm of epileptiform regression is Landau-Kleffner syndrome (LKS), whose hallmark is acquired language impairment associated with EEG abnormalities. LKS usually has onset between 4 and 7 years of age, later than AR, but in some cases onset can occur as early as 3 years of age (8,9). Verbal comprehension may be so severely impaired as to be defined “verbal auditory agnosia” or word deafness; as a consequence of this, expressive language is significantly disrupted. The typical EEG pattern is one of continuous or sub-continuous spike-waves during slow sleep, more frequently bilateral, in centro-temporal regions. Seventy per cent of affected children have seizures of some kind. Behavioural problems, such as hyperactivity and impulsivity, have been described, and social and relational difficulties of varying severity, usually milder than in autism spectrum disorders, have been reported (10). Although the EEG abnormalities are considered to be rather specific, there are cases which remain unclear (11,12).

Case reports

The two children here reported were selected from among a series of 103 children (74 males, 29 females; mean age 10.1 yrs, SD 4.3 yrs) with autistic spectrum disorder consecutively evaluated during a one-year period at the Department of Child Neuropsychiatry of the General Hospital of Siena, a tertiary care referral centre for autism and pervasive developmental disorders. All the patients underwent an EEG (a standard 1 hour sleep EEG) as part of the diagnostic work up, which was when abnormal patterns were detected in the two cas-
es here described. Both children had a clear history of regression and paroxysmal EEG recordings consistent with the definition of AER. A thorough description of the cases is provided because of their peculiar clinical course.

Case 1

Case 1, a girl, was born at term after an uncomplicated pregnancy and delivery. Her early development was normal: she walked at 14 months, spoke her first words at 11–12 months, and at 24 months was able to form three-word phrases using an age-appropriate vocabulary and displaying good comprehension. Symbolic play developed normally between the ages of 2 and 3 years, during which time she was sociable with her peers and acquiring further language skills. However, by the age of 3½ years she had undergone a remarkable behavioural change: she had become passive and irritable, had lost interest in playing and showed a loss of social reciprocity. Myoclonic jerks of the head occurred daily (in the absence of any previous history of seizure). Her expressive language regressed, but most notably, she showed poor comprehension. At the age of 4½ years, when she was first evaluated in our department, she was withdrawn, did not interact, and was hyperactive. Stereotypies (both stereotyped hand movements and stereotyped handling of objects) were evident, and her play skills were very limited. She did not talk and was generally unresponsive to verbal language. Altogether these features justified her diagnosis of autistic disorder according to DSM-IV (1). Her Childhood Autism Rating Scale (CARS) score was 35, corresponding to mild/moderate autism (13). Routine laboratory examination, serum amino acids, lactate and pyruvate levels were in the normal range. An EEG revealed multifocal frontal and centro-temporal spikes and spike-wave complexes when awake which increased, becoming subcontinuous, during sleep (Fig. 1). Treatment with valproate was started, at 20 mg/kg. She quickly showed a remarkable improvement and after one month her social relatedness, interest in objects and in play were, according to her parents, substantially restored; furthermore, she was no longer restless and hyperactive. On an EEG (both awake and asleep) performed six months later, paroxysmal discharges were no longer present (Fig. 2). Her recovery of language was slower, beginning with her uttering single words, but the positive evolution of her picture, also in this regard, was later confirmed. One year later, at the age of 5 years, her expressive language was fluent, characterized by whole sentences and good prosody, and when evaluated using a standardized Italian language test for preschool children, was found to be in the range corresponding to a mild delay. Her mental level was borderline (IQ of 75 on the Weschsler Preschool and Primary Scale of Intelligence, WIPPSI). Her CARS score had fallen to 21, putting her in the non autistic range (the cut-off score for autism is 30). A mild attention deficit with hyperactivity was noted, but no difficulties in social relationships with parents or peers were observed, and she was sociable at school and at home.

Case 2

Case 2, a boy, was born at term after an uncomplicated pregnancy and delivery. Acquisition of developmental milestones, including language, was reportedly normal until the age of 2 years, when he had an age-appropriate vocabulary and was starting to use phrases. However, after the age of 2 he underwent a deterioration associated with disruptive behaviour, and he began to be socially isolated. In addition, he lost interest in everyday activities, gaze avoidance was frequently observed, and his language decreased rapidly to the point that, just one month after onset of the deterioration, he was not uttering any words at all. He underwent a thorough clinical and neurological evaluation, which was unremarkable, and a complete metabolic and laboratory investigation, which gave findings in the normal range. On clinical and behavioural examination, his picture was consistent with a diagnosis of autistic disorder. The following year, the evolution was characterized by an alternating course with regard to expressive language: periods in which speech was almost completely absent alternated with other periods in which he would talk, using single words. His verbal comprehension was more severely affected. Social awareness and reciprocity were fragmented: he demonstrated adequate emotional and affective responses only at times. At the age of 5 years, his CARS score was 45, that is, within in the range of autistic disorder; a sleep EEG revealed epileptiform discharges: subcontinuous left centro-temporal spike-wave
complexes were strikingly evident (Fig. 3). He did not experience seizures, but valproate was introduced, at 20 mg/kg, together with clobazam at 1 mg/kg.

At the age of 6 years, an EEG sleep recording did not show any notable changes, with subcontinuous left centro-temporal spike-waves persisting in the absence of seizures. The child showed an improvement in his behaviour, especially in social relatedness, his CARS score had fallen to 27 and he was more willing to interact. His emotional expressions and general awareness of context had also increased notably. He started to engage in simple play, although his praxic skills remained limited. However, there was no real recovery of his language skills. He used only a few, single words, his comprehension was very poor, he followed verbal commands only occasionally, and he was mostly unresponsive to spoken language. He was learning new words and simultaneously losing others in an alternating and unstable pattern. As a result, his vocabulary was difficult to assess.

At the age of 6½ years, the epileptiform discharges had disappeared, both when awake and during sleep (Fig. 4), but no language improvement was observed, either at that time or during the subsequent months. A trial of ACTH i.m. 0.5 g/daily for two weeks followed by 1 mg depot for three months was administered with the aim of treating the underlying encephalopathy. This was followed by prednisone per os at a dosage of 5 mg titrated to 25 mg, but this treatment was discontinued after three months because no changes were noted. Valproate was maintained constant throughout.

At a follow up, one year later at the age of 7½ years, normal EEG recording was confirmed; clinically, only minor progress was noted and, in spite of intensive speech therapy, the child was uttering only a few new words. A Leiter test was administered to the child in order to evaluate his cognitive level after exclusion of the impaired verbal domain (14). He scored in the normal/mildly retarded range, confirming the presence of a specific impairment in language development. The child’s social skills varied depending on the situation and the emotional context; under proper guidance from his carers, he was showing better social reciprocity. Representative play had not yet been achieved and, as a whole, he remained within the autistic disorders spectrum.

**Discussion**

Currently, there is growing concern over so-called autistic regression, both because of the percentage of children presenting this feature and because of the question of its relationships with other disorders in which there is language regression. Since autistic regression usually occurs before two years of age, when expressive language may still be limited to a few words, it frequently goes unnoticed by the parents of otherwise healthy children. On the contrary, regression of language in LKS is rarely missed because it occurs in older children who have acquired a wider vocabulary, and whose parents soon become aware of the loss of previously acquired speech and language comprehension (15). Furthermore, children with AER should be easy to distinguish from those with LKS due to the more obvious deterioration of social, emotional and representative/symbolic play in the former. This is not always the case, however, because behavioural abnormalities and autistic traits may also be evident in LKS (7,10,15). The children described in this report were both considered, at onset, as cases of AER, but at follow up they showed a distinct course and outcome. The two children were most impaired in the areas of social relatedness and language, and this impairment was associated with epileptiform discharges in the centrottemporal regions. Although the EEG findings in AER and LKS present similarities, there is a prevalence of multifocal epileptiform activity mainly in centro-temporal regions in the autistic disorder, whereas in LKS, the abnormalities are more frequently subcontinuous and localized in the temporal region (10,12).

In case 1, the disappearance of the autistic behaviours was quicker than the recovery of expressive language (after the disappearance of the autistic behaviours it was a further six months before the girl regained some words). This kind of dissociation has been documented and related to epileptiform discharges interfering with neural pathways at critical stages of brain development (11,12). The characteristics of the girl's language during her recovery phase were not suggestive of verbal auditory agnosia, which is a kind of dysphasia for acoustically but not visually presented language (16), because her phonology and fluency were only mildly affected, and not severely defective as they usually are in that condi-
tion. The girl showed a progressive increase in language skills with good overall comprehension, features indicating a different type of language disorder.

A neuropsychological basis of epileptic regressions has recently been suggested. In LKS, the abnormalities primarily affect the perisylvian areas, whereas in AER, multifocal epileptiform activity with the involvement of several brain areas including the perisylvian regions has been demonstrated (17). Both conditions may be included in the group of the epileptic encephalopathies because epileptiform abnormalities are thought to play a role in altering brain functions independently of seizures, which may even be lacking (18). The localization of the epileptiform activity did not differ in children with autistic spectrum disorders with or without regression and thus does not help to explain the putative distinct pathophysiology of AER. In spite of these conflicting findings, regression does influence the outcome, as a worse cognitive and behavioural profile is expected when a developmental regression is demonstrated, as opposed to when it is not. Moreover, onset at a younger age was more frequently associated with a global impairment typical of the autistic spectrum than with acquired aphasia alone (3,7,15).

The therapeutic approach to AER is still controversial and only case reports and studies on small groups are currently available (19,20). Valproic acid has been used in autistic children with epileptiform abnormalities, with and without seizures (21,22), but no clinical trials have yet been carried out, and treatment is chosen mainly on the basis of subjective clinical findings. In our patients, valproate, which we have previously used as an anti-convulsant and mood stabilizer, was used to treat seizures and behavioural disorders. In case 1, an improvement in behaviour following valproate treatment was observed, leading to disappearance of the autistic traits within a period of 4 to 6 months. The current literature contains only a few descriptions of cases in which AER improved with anti-epileptic therapy. Case 2 did not show any change in his EEG pattern following valproate treatment until it normalized at the age of 6 years; his autistic symptoms attenuated over time, whereas his verbal difficulties did not. This child suffered from a severe language disorder, and the effectiveness of the pharmacotherapy was difficult to establish as the epileptiform discharges did not disappear until he had received 18 months of treatment, and this disappearance was not associated with any significant changes in his language skills. The effect of valproate on behavioural symptoms in autistic disorders is being examined. The question of whether it affects epileptiform components, with possible language and behavioural changes as secondary gains, or whether, instead, it might modify behavioural disorders through a mood stabilizing effect, is still debated. Controlled studies in large samples are needed in order to demonstrate its true efficacy.

Given the similarities between AER and LKS, corticosteroids could be an alternative treatment option; they have not yet been tested in AER, although partial or complete recovery after treatment has been described (23-25). Steroids have been used successfully in LKS even when EEG abnormalities were not demonstrated (26). Corticosteroids have not been suggested as a therapy for AER. Case 2, at the age of 6 years, was given a trial of ACTH and then of prednisone as a further attempt to obtain an improvement in his speech, but no appreciable changes were noted.

More aggressive treatment, such as surgical intervention by means of multiple subpial resections, has been performed in cases of autistic regression associated with epilepsy, with the aim of reducing the spreading of paroxysmal discharges (27-28). Language improvement and a reduction in the frequency of seizures were reported but the surgical approach is strongly debated. The risks related to surgical procedures warrant caution and discourage this approach in AER with or without seizures, leaving it as an option only in cases of intractable epilepsy refractory to pharmacological treatments (19,20).

At present, in the absence of reliable predictors of the outcome of AER, a clinical developmental approach seems appropriate. Multiple prospective evaluations and further research are needed to clarify the possible therapeutic interventions and treatments of choice.