Antiepileptic Drug-Related Ataxia in Children

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Abstract
Ataxia is a complex neurological sign that can have both genetic and acquired etiologies. It has often been described as an adverse drug reaction associated with the use of antiepileptic drugs, both when given at appropriate dose and in case of overdose. Recognizing this clinical sign in children might be challenging. We performed a short literature review of this phenomenon focusing our research on pediatrics cases related to the use of second and third generation anticonvulsants.

ABBREVIATIONS
AED: Antiepileptic Drug; CBZ: Carbamazepine; CI: Confidence Interval; ESL: Eslicarbazepine; GABA: Γ-Aminobutyric Acid; GPT: Gabapentin; GTCS: Generalized Tonic-Clonic Seizures; LAC: Lacosamide; LEV: Levetiracetam; LTG: Lamotrigine; MHD: 10-Monohydroxy Derivative; NMDA: N-Methyl-D-Aspartate; OXCBZ: Oxcarbazepine; PER: Perampanel; PGB: Pregabalin; RFM: Rufinamide; RR: Relative Risk; STP: Stiripentol; TGB: Tiagabine; TPM: Topiramate; ZNS: Zonisamide

INTRODUCTION
Ataxia has often been described as an adverse drug reaction associated with the use of antiepileptic drugs, both at therapeutic dosage and in case of overdose. In older patients, this side effect is well known for its negative impact on the quality of life, whereas it is less frequently considered in the pediatric population [1].

We performed a short literature review of this phenomenon focusing our research on pediatrics cases related to the use of new generation anticonvulsants.

DISCUSSION
Long-term treatment with some antiepileptic drugs (AEDs) has been associated with the development of ataxia and imbalance. Evidence of cerebellar and vestibular toxicity by first and second generation AEDs has been described by Hamed et al., who identified phenytoin, carbamazepine and lamotrigine as medications potentially causing ataxia [2]. Hilgers performed a systematic adverse drug reaction monitoring of patients aged 16-89 years under newer AEDs, recording ataxia in 5.2 % of them; association with this side effect was identified, in descending order, for: eslicarbazepine, lacosamide, oxcarbazepine, zonisamide, pregabalin, levetiracetam and topiramate [3]. In a meta-analysis of placebo-controlled trials performed by Zaccara et al., evaluating central nervous system adverse effects of new AEDs, ataxia was found to be significantly associated with the administration of lamotrigine, oxcarbazepine, pregabalin or topiramate [4]. In a meta-analysis by Sirven et al., including studies selectively evaluating second generation AEDs impact on balance in adolescent and adult patients, pooled analysis of all anticonvulsants found them to be responsible for an increase in imbalance risk at any dose. Most of the medications showed a dose-response effect [5].

SECOND GENERATION AEDS
Gabapentin (GPT) is a γ-Aminobutyric acid (GABA) analog that binds to the α2-8 protein subunit of voltage-gated calcium channels [6]. It is indicated as adjunctive therapy for partial seizures with or without generalization in adults and children over 6 years and as monotherapy for partial seizures with or without generalization in adults and adolescents over 12 years. In a Cochrane review including randomized, placebo controlled, double blind, add-on trials evaluating GPT as add-on therapy for drug-resistant partial epilepsy in patients of any age, ataxia was the second most common side effect after dizziness, developing in 2.01 % of subjects [7]. In a multicenter prospective observational study collecting data from gabapentin exposures reported to poison centers, 50% of the intoxicated patients were children and adolescents. Drug overdose was associated
to minimal toxicity in case of isolated ingestion; side effects included drowsiness, dizziness and ataxia and developed early after intake, frequently resolving by 10 hours [8]. Lamotrigine (LTG) acts by blocking voltage-gated sodium channels, inhibiting glutamate action and serotonin reuptake [9]. It is recommended in children as adjunctive treatment and as monotherapy for partial-onset and secondarily generalized tonic-clonic seizures, for Lennox-Gastaut syndrome and as add-on therapy for primarily generalized tonic-clonic seizures (GTCS). Moreover, it has been proposed as an adjunctive therapy in association with valproic acid for the treatment of absence seizures. In a retrospective study analyzing data on exposures to LTG as a single drug reported to the American Association of Poison Control Centers Toxic Exposure Surveillance System, most of the patients did not experience any intoxication effect. Among the symptomatic ones, most frequently reported effects were drowsiness, gastrointestinal symptoms and ataxia, that developed in 4.9% of subjects [10]. In a recent Cochrane review including randomized placebo controlled trials investigating LTG as add-on for drug-resistant partial epilepsy in patients of any age, ataxia was the second most common side effect after diplopia, developing in 3.34% of subjects [11]. Single case reports of LTG overdose in children manifesting with acute ataxia are described by Briassoulis et al., Grosso et al., and Daana et al., In the first two cases, the intoxication occurred in non-epileptic children who accidentally ingested the drug that was prescribed for a family member; the third case experienced side effects during dose-adjustment [12-14].

Levetiracetam (LEV) is a piracetam analog that works by blocking high-voltage gated activated calcium channels; it has been approved as monotherapy for partial seizures with or without generalization in adults and adolescents over 16 years, as adjunctive therapy in subjects over 1 month of life with epilepsy, as treatment for myoclonic seizures in patients over 12 years with Juvenile Myoclonic Epilepsy and as therapy for primary GTCS in subjects over 12 years with Idiopathic Generalized Epilepsy. In a 11-year review of LEV accidental ingestions in children younger than 6 years, excluding cases of multiple ingestions, most of the adverse effects were neurological, with ataxia developing in 2.4% of the patients. No dose-effect relationship was noticed, although the odds of developing this symptom in a LEV naïve patient was 6 times higher than in a patient already taking the medication [15]. Oxcarbazepine (OXCBZ) is the 10-ketoanalog of carbamazepine (CBZ), developed in the attempt to improve tolerability to CBZ; it is extensively metabolized to MHD (10-monohydroxy derivative). It is prescribed as monotherapy and adjunctive therapy in generalized tonic-clonic seizures and partial seizures with or without secondary generalization in children and adolescents. A multicenter, randomized, placebo controlled trial was performed by Glauser et al., to evaluate the safety and efficacy of OXCBZ as adjunctive therapy in children with inadequately controlled partial seizures on two or more concomitant AEDS. The study included children and adolescents aged 3-17 years; most of the adverse effects were recorded during the double-blind treatment phase, which was reached after a titration period of 14 days, and mainly involved the nervous system. Ataxia developed in 14% of the subjects treated with OXCBZ and 5% of the children that were administered placebo, whereas abnormal gait occurred in 10% of the treated patients and in 3% of the ones receiving placebo. Ataxia, dizziness and abnormal gait were among the side effects that lead to discontinuation of the drug and were judged to be related to the medication. Both Glauser et al., and Kalis et al., proved that ataxia and headache incidence is directly related to plasma MHD concentration [16,17]. In a single-center retrospective analysis evaluating the efficacy of OXCBZ in patients aged 6 months to 17.8 years receiving OXCBZ monotherapy for partial epilepsy, ataxia incidence was quite low, with symptoms occurring in 1.7% of subjects [18]. In a meta-analysis of randomized, double blind studies evaluating neurological adverse events of new generation sodium-blocker AEDs, at higher recommended doses Oxcarbazepine caused significantly more withdrawals due to adverse effects and significantly more frequent in coordination and ataxia than eslicarbazepine (ESL) and lacosamide (LAC) [19]. Tiagabine (TGB) exerts its antiepileptic effect by selectively inhibiting GABA reuptake by glia and presynaptic neurons. It was approved as adjunctive therapy for patients of 12 years or older with focal-onset seizures with or without generalization. In a study by Vossler et al., prospectively collecting data of safety and efficacy from TGB use mainly as adjunctive therapy in patients aged 0-75 years, ataxia was among the most common side effects and developed in 8% of the patients [20]. Topiramate (TPM) works by modulating voltage-gated sodium channels, enhancing GABAergic inhibition on the GABAA receptor, inhibiting carbonic anhydrase isoenzymes and possibly acting on the non-N-methyl-D-aspartate (NMDA) receptors. It is prescribed as monotherapy in patients over 6 years with partial seizures with or without generalization or with primary GTCS, as adjunctive therapy in subjects over 2 years with partial-onset seizures with or without generalization or primary GTCS and for Lennox-Gastaut Syndrome. In a prospective study conducted by Fröschler on patients aged 16-70 years with poorly controlled epilepsy under therapy with TPM, mainly in combination with other anticonvulsants, ataxia was one of the side effects. Drug dosage (mg/kg) and plasma drug concentration were significantly different between the group experiencing side effects, included ataxia, and the asymptomatic one [21].

Zonisamide (ZNS) is structurally related to sulfonamides; it has several mechanisms of action including blocking T-type calcium channels and sodium channels and weakly inhibiting carbonic anhydrase activity [22]. It is recommended as monotherapy for partial seizures with or without generalization in adults and as adjunctive therapy for partial onset seizures with or without generalization in patients over 6 years. In a Cochrane review including randomized, placebo controlled, add-on trials of ZNS in people of any age with drug-resistant epilepsy, no study found a significant effect of zonisamide on ataxia independently, but there was a significant effect when study date were combined; CI was 3.77 [23].

**THIRD GENERATION AEDS**

Lacosamide (LAC) enhances the slow inactivation component of voltage-gated sodium channels [24]. It is approved as adjunctive therapy for partial-onset seizures with or without generalization in adolescents over 16 years and adults. In a trial with LAC as adjunctive therapy in patients aged 14-
74 years with uncontrolled focal-onset seizures, ataxia was one of the most common side effects and was sometimes responsible for LAC withdrawal [25]. Similar conclusions can be drawn for a meta-analysis evaluating LAC as adjunctive therapy for partial-onset seizures both in children and adults; in this study ataxia appeared as the most frequent side effect [26]. A systematic review and meta-analysis of randomized-controlled trials involving patients aged 16 years or older taking LAC was performed with the goal of defining the adverse event profile of this drug. The study identified a significant dose-effect relationship in the odds of developing ataxia [27]. Perampanel (PER) is a non-competitive selective antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor approved in Europe and in the United States of America as adjunctive therapy for patients aged 12 years or older with partial seizures with or without generalization [28]. Ataxia is among the most frequently described side effects and dizziness is very commonly observed. In the report from the first clinical experience with perampanel performed in Kork by Steinhoff et al., patients of 15 years or older were included. The majority were affected by structural or metabolic epilepsies, most of them were taking two AEDs and mean drug dose was 8.8 mg/day. Ataxia was the third most common side effect after somnolence and dizziness [29]. In a meta-analysis performed by Zaccara et al., including patients of 12 years or older taking PER and other AEDs, a significant dose-effect relationship was noticed: no adverse events were associated with the drug at low doses (2 or 4 mg/kg/day), whereas ataxia and dizziness were observed when perampanel was prescribed at the doses of 8 or 12 mg/kg/day. These symptoms are thought to be related to cerebellar or brainstem dysfunction. [30]

Pregabalin (PGB) works by binding to voltage-gated sodium channel [31]. It is recommended as adjunctive therapy for partial seizures with or without generalization in adults. In a Cochrane review analyzing PGB add-on for drug-resistant partial epilepsy, ataxia was significantly associated with the medication, with a RR of 3.9 for any drug dose [32]. In a systematic review and meta-analysis of randomized controlled trials focusing on the adverse effect profile of PGB, ataxia was observed with a RR of 4.77 and a dose-effect relationship [33]. Rufinamide (RFM) is a triazolo derivative that acts by limitation of sodium-dependent action potentials with subsequent membrane potential stabilization. It is approved as adjunctive therapy for epileptic seizures associated with Lennox-Gastaut Syndrome in patients of 4 years of older. As reported in European Medicines Agency literature, the results of blinded and open-label trials conducted on subjects aged ≥ 12 years taking RFM as monotherapy or add-on therapy showed that selected adverse effects including dizziness and ataxia occurred at a higher rate in the group treated with the medication than in the group that was administered placebo. Dizziness was very commonly observed, occurring in more than 10% of patients; it showed a lower rate in younger patients and it was frequently leading to discontinuation of medication. Decreased coordination, tremor, gait difficulty, nystagmus and vertigo were common, occurring in 1-10% of patients. Adverse effects were reported early in the study course, mainly during the titration phase, and decreased or became tolerable later on [34]. Similar findings were reported in a double blind, placebo controlled, randomized, parallel group, multicenter trial by Brodie et al., evaluating the efficacy and safety of RFM as adjunctive treatment of partial seizures in patients of 16 years or older. Most frequently reported adverse effects were dizziness, nausea, diplopia and ataxia; this nervous system toxicity was the main reason for drug discontinuation in the treated group. Adverse effects were mild to moderate in severity and transient in nature, often occurring during dose-adjustment period and subsiding with drug discontinuation [35]. Stiripentol (STP) positively modulates GABAAergic inhibitory neurotransmission, increases the effective concentration of other drugs and enhances benzodiazepines action [36]. It is approved for adjunctive therapy of GTCS refractory to treatment with clobazam and valproic acid in patients with Severe Myoclonic Epilepsy of Infancy. In an open-label study published by Inoue et al., and evaluating the effectiveness of STP add-on therapy in patients with Dravet syndrome aged 1-20 years, ataxia was among the most frequently encountered adverse effects, especially during the early and intermediate period and most frequently in the younger group, including patients between 1 and 8 years of age [37]. In an open-label study evaluating effectiveness of add-on STP to clobazam and valproic acid in patients with Dravet syndrome aged 1-30 years, ataxia developed in 54.2% of subjects, mainly during the titration phase [36]. In another paper of the same authors describing the long-term results of STP use in the same population, ataxia was confirmed again of being a side effect, developing in 58% of subjects. Median time to onset after the start of add-on therapy was 15 days and the symptom lasted long, with a mean of 134 days, but it never determined drug discontinuation [38].

**CONCLUSION**

Ataxia is a complex neurological sign that can have both genetic and acquired etiologies. Recognizing ataxia in children may be challenging. It may be overlooked in infants and erroneously related to a delay of coordination. Physical examination and correct maneuvers are useful for highlighting its clinical sign. Antiepileptic drugs have been recognized as class of medications with a potential risk of causing ataxia, not only in case of overdose but also when given at appropriate doses. Antiepileptic drugs-related ataxia should therefore be considered in the differential diagnostic strategy. Symptoms may occur after the introduction of an AE drug or an increase in dose, within days or weeks. A chronological relationship between AE administration and ataxia appearance is therefore a useful diagnostic clue. Since ataxia tends to disappear after discontinuation or dose-reduction of the drug, physicians should be aware of the possibility that ataxia might be drug-induced, in particular for some antiepileptic drugs with relative high frequency of this particular adverse event.

**REFERENCES**