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Tracking Multifocal Epilepsy With Automated Electric Source Imaging in a Patient With Triple-X Syndrome

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Dear Editor,

Pharmacoresistant epilepsy with polymorphic behavior remains a great challenge in clinical epileptology. Here we present a 20-year-old female with triple-X syndrome who was admitted because of variable seizures and the suspicion of nonepileptic events. Absences with deep breathing, wagging of the left arm, yawning, nausea, aggressiveness, and amnesia were replaced by turning the head to the left, stretching the left arm, and bending the right arm ("figure-of-4 sign"), followed by confusion. Similar seizures occurred up to seven times per day on up to 20 days per month, resulting in numerous consultations at the emergency department. Tonic-clonic seizures had occurred during her 3rd year of life, and at 8 years old she started to also show focal nonaware cognitive seizures, sometimes with bilateral spread. At that time, several routine electroencephalography (EEG) recordings revealed a right, paracentral epileptic focus. Valproic acid (1,500 mg daily) resulted in a seizure-free period of 6 years, but this had to be discontinued due to weight gain and hirsutism, and was subsequently changed to levetiracetam (2,000 mg daily), lamotrigine (100 mg daily), and lacosamide (200 mg daily), which failed to control the seizures and increased behavioral problems. Brain magnetic resonance imaging (MRI) findings were normal.

The patient underwent long-term overnight video-EEG with a 25-channel montage (2017 IFCN guidelines), which revealed several epileptogenic foci with sharp waves in the right inferotemporal (T10−F10) region, in the right central region at C4−P4, and in the left central region (C3−P3) (Fig. 1A-C). We then ran the fully automatic EPILOG® PreOp algorithm (Epilog NV, Ghent, Belgium) in order to quantify the interictal epileptic discharges and localize their electric source according to the patient's own brain anatomy (Fig. 1D-F). To this end, we used the full 88-hour-long low-density EEG track together with the patient's own 3-T magnetization prepared rapid gradient echo MRI scan, allowing for an anatomical head model with six tissue compartments (gray matter, white matter, CSF, skull, air cavities, and scalp). The electrode positions were estimated by calculating distances over the head after marking specific landmarks such as the inion, nasion, and auricular points.[1,2] EEG source analysis was done using sLORETA as the inverse technique to localize each spike according to its onset, half height, and peak. A patient-specific head model was constructed from the MRI data, and the finite-difference method was used to calculate the lead fields that linked neuronal currents in the brain to the measured scalp potentials.[1,2]

After demonstrating the presence of multifocal epilepsy in our patient, we changed the pharmacologic treatment to brivaracetam (100 mg daily), higher-dose lamotrigine (500 mg daily, serum level of 8.7 mg/L; ref. 3−14 mg/L), and low-dose valproic acid (300 mg daily), which subsequently resulted in a remarkable improvement of seizure control.

Overnight video-EEG combined with fully automated electric source imaging was successful in confirming the hypothesis of different epileptic foci causing the changing seizure semiologies in our patient. The previously reported triple-X aberration additionally orient-

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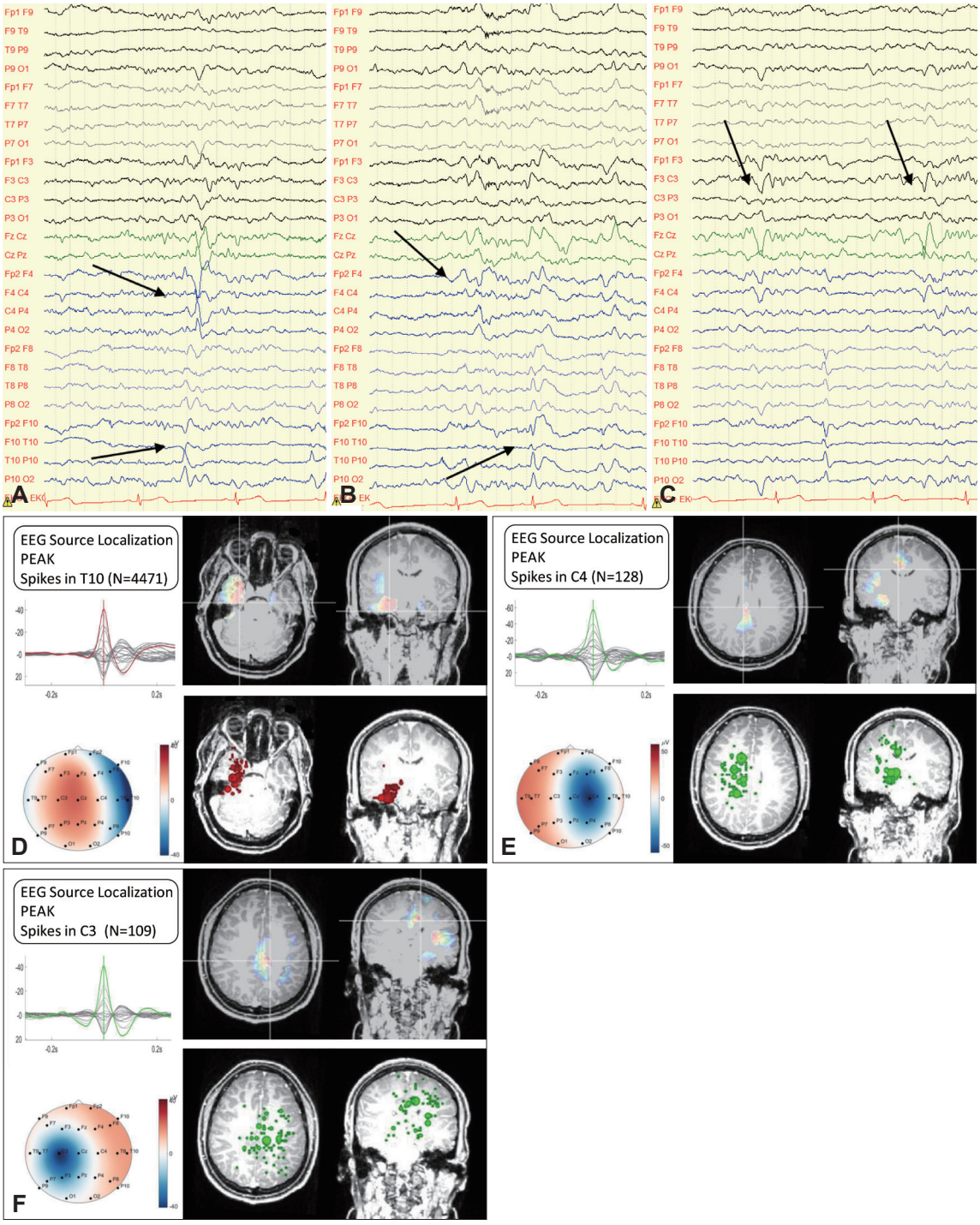

Fig. 1. Three episodes in the patient's EEG recordings demonstrating multiple epileptic discharges displayed in a 25-channel montage. A: Sharp waves with phase reversal over C4-P4 and over T10-P10 (arrows). B: Slow waves with phase reversal over C4-P4 and over T10-P10 (arrows). C: Slow waves with phase reversal over C3-P3 (arrows) and over T10-P10. D-E show the results from fully automated spike detection and electric source localization using EPILOG® software. We used the full 88-hour-long low-density EEG track together with the patient's own 3-T MRI scan. D: The 4475 discharges over T10 allowed precise localization in the right anterior mesiotemporal region. E: The 129 discharges over C4 pointed to a focus in the right anterior cingulate cortex. F: The 109 discharges over C3 indicated a focus in the left anterior cingulate cortex. For each source localization (D-F), the average spike and the average spike topography are plotted on the left. On the right, the probability map of the corresponding electric source localization over the patient's MRI data is shown in the two top panels. The two right bottom panels display the localization of single spikes that belong to the same cluster, using the 100 single events that are most alike the average spike (the size of the dot is scaled by the number of single spikes localizing to that position). Radiologic images are displayed according to the usual radiologic convention, meaning that the patient's right side is on the left of the image.

ed toward multifocal epilepsy in the context of a genetic encephalopathy.

Triple-X syndrome (47,XXX) occurs in 1 out of 1,000 females, although this is probably an underestimation due to it often being undiagnosed,[3,4] and the prevalence of epilepsy is increased by 11%−15%.[4] Nevertheless, our literature search yielded only a few single case reports,[3] and while various localizations of epileptic discharges and seizure semiologies have been reported,[4-6] a specific epileptic pattern is not known. Similar to our patient, all previously reported patients had cognitive deficits with normal brain MRI findings and no mesiotemporal abnormalities.[5-8]

The prevalence of epilepsy is also reportedly increased in other chromosomal aberrations: in females with Turner syndrome (0X) and often cortical malformations, as well as in males with Klinefelter syndrome (XXY), with both showing a heterogeneous seizure pattern.[5,9,10]

The present case illustrates that using normal overnight video-EEG combined with a fully automated spike detection and electric source imaging tool can clarify a previously unclear situation (nonepileptic events versus multifocal epilepsy) in patients who have not yet undergone a complete presurgical workup with metabolic brain imaging including positron-emission tomography and ictal single-photon-emission computed tomography, and where high-density EEG acquisition is often unavailable.[11] The use of the EPILOG® automated EEG analysis cannot replace a presurgical workup, but it offers a first-step orientation to epileptologists in smaller centers where complex presurgical workups are not possible.

This case reminds clinicians that multifocal epilepsy should be considerend in patients presenting with a changeable seizure semiology. Chromosomal abnormalities are an important cause of genetic encephalopathies.[12,13]

Ethics Statement

This report conforms to the Declaration of Helsinki, and explicit written consent was obtained from the legal representative of the patient.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to patient privacy and confidentiality, but are available from the corresponding author on reasonable request.

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Conflicts of Interest

Pieter van Mierlo is CMO and shareholder of Epilog NV, Ghent, Belgium. The other authors have nothing to declare related to this project.

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