Clinical Neurophysiology 129 (2018) 1121–1129

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Rapid exhaustion of auditory neural conduction in a prototypical mitochondrial disease, Friedreich ataxia

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ARTICLE INFO

Article history:
Accepted 13 March 2018
Available online 27 March 2018

Keywords:
Friedreich ataxia
Auditory brainstem
Conduction velocity
Neurodegeneration

HIGHLIGHTS

- Friedreich ataxia patients can have ABRs in response to short but not long series of stimuli.
- Prolonged averaging leads to gradual increases in latency of ABR waves.
- ATP shortage is a likely explanation for Friedreich-ataxia's auditory neuropathy.

ABSTRACT

Objectives: In patients with Friedreich ataxia (FRDA), mitochondrial failure leads to impaired cellular energetics. Since many FRDA patients have impaired hearing in noise, we investigated the objective consequences on standard auditory brainstem-evoked responses (ABRs).
Methods: In 37 FRDA patients, among whom 34 with abnormal standard ABRs, hearing sensitivity, speech-in-noise intelligibility and otoacoustic emissions were controlled. ABR recordings were split into four consecutive segments of the total time frame used for data collection, thus allowing the dynamics of ABR averaging to be observed.
Results: Most ears showed features of an auditory neuropathy spectrum disorder with flattened ABRs and impaired speech-in-noise intelligibility contrasting with near-normal hearing sensitivity and normal preneural responses. Yet split-ABRs revealed short-lived wave patterns in 26 out of 68 ears with flattened standard ABRs (38%). While averaging went on, the pattern of waves shifted so that interwave latencies increased by 35% on average.
Conclusions: In FRDA, the assumption of stationarity used for extracting standard ABRs is invalid. The preservation of early split-ABRs indicates no short-term dyssynchrony of action potentials. A large decrease in conduction velocity along auditory neurons occurs within seconds, attributed to fast energetic failure.
Significance: This model of metabolic sensory neuropathy warns against exposure of metabolically-impaired patients to sustained auditory stimulation.

1. Introduction

The importance of neural processing of temporal cues by the auditory system has been stressed by the discovery of auditory neuropathy spectrum disorders (ANSD) (Starr et al., 1996; Rance and Starr, 2015), in which disrupted auditory-nerve conduction leads to a characteristic pattern of hearing disorder. One striking

Abbreviations: ABR, auditory brainstem-evoked response; ANSD, auditory neuropathy spectrum disorder; ATP, adenosine triphosphate; OAE, otoacoustic emissions; FRDA, Friedreich's ataxia; ICARS, International Cooperative Ataxia Rating Scale; PTA, pure-tone average.

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https://doi.org/10.1016/j.clinph.2018.03.005
1388-2457/

complaint of ANSD patients is the presence of impaired speech understanding out of proportion with what the auditory sensitivity would predict, particularly in the presence of noise (Kraus et al., 2000; Zeng and Liu, 2006). Other timing-related perceptive tasks such as gap detection, pitch determination at low frequencies and sound localization using interaural time differences are impaired in ANSD patients (Zeng et al., 2005). Conversely, in ANSD, the micromechanical cochlear pre-processing of sounds remains normal or near normal as evidenced by the frequent preservation of otoacoustic emissions (OAEs), sounds reemitted by active cochlear outer hair cells (Starr et al., 1996). For the subcategory of ANSDs that result from primary afferent (cochlear nerve) dysfunction, intervention must follow non-conventional guidelines because amplifying hearing aids are of questionable relevance and electric stimulation of cochlear neurons by cochlear implants, although sometimes giving encouraging results (Sininger and Trautwein, 2002), may not completely restore their synchrony (Harrison et al., 2015). It would thus be of the utmost importance to explain how and why, in post-synaptic ANSD, cochlear neurons lose track of timing cues so that auditory perception is easily disrupted by noise. Two mechanisms are currently hypothesized, a loss of neurons and/or temporal jitter among spiking patterns of auditory neurons (Berlin et al., 2003; Zeng et al., 2005). In patients, objective evaluation of neuronal synchrony can only be indirect, using averaged auditory brainstem-evoked (ABR) to a brief stimulus. The presence and size of ABR waves provide an estimate of the number of neurons able to keep responding in synchrony over the whole averaging procedure, and ABRs are typically flat or severely distorted in ANSDs (Starr et al., 1996).

The underlying pathophysiology of post-synaptic ANSD is known to be diverse (Rapin and Gravel, 2003) and incompletely understood. The critical metabolic needs of auditory neurons that hinge upon mitochondria have been identified as a possible target of several hereditary neurological entities that share ANSD-related auditory dysfunction (Cacace and Pinheiro, 2011). Among them, Friedreich ataxia (FRDA) is the most frequent autosomal recessive cerebellar ataxia in Europe, with a prevalence of between 1 and 9/100,000. In FRDA, most patients are homozygous carriers of an abnormally expanded GAA-repeat in the first intron of the mutated gene (*FXN*; OMIM 606829). The decreased level of frataxin, a mitochondrial protein, leads to a general deficiency of mitochondrial and cytosolic iron-sulfur protein activity, with two consequences, underproduction of adenosine triphosphate (ATP), mainly produced by mitochondria, and hypersensitivity to oxidative stress (Rotig et al., 1997; Lodi et al., 1999; Pandolfo, 2008; Martelli et al., 2012). FRDA patients have been reported to show abnormal speech intelligibility in the presence of noise (Rance et al., 2008, 2012a) and a sizeable proportion of them have ABR abnormalities, e.g., a decreased relative amplitude of wave V (Rance et al., 2008), a pattern that satisfies the definition of ANSD. However, the relative implications in the ANSD profile of irreversible neuronal degeneration resulting from oxidative stress (Spoendlin, 1974) and reversible energetic failure inducing excessive fatigability is unknown in FRDA. The reason why an ANSD-like pattern might emerge from temporary energetic failure stems from textbook neurophysiology. The seminal work of Hodgkin and Huxley proved that the propagation velocity of action potentials essentially depends on the Nernst electrochemical potentials of Na^+ and K^+ (Hodgkin and Huxley, 1952), determined by the ratios of their intra- and extracellular concentrations. These concentrations are modified by action-potential generation and restored by Na^+/K^+ ATPases whose function is jeopardized by frataxin deficiency, particularly in auditory neurons that enlist among the most active in the nervous system (Winter et al., 1990). Hodgkin and Huxley's equations indicate that a 25% departure of K^+ and Na^+ concentrations from their resting values (Sangrey and Levy, 2005; Woo et al., 2009), the result of a few thousand action potentials once Na^+/K^+ ATPases have run out of ATP, would considerably modify the conduction velocity along auditory neurons, and this within only a few tens of seconds.

Time-averaging procedures become invalid if the signal under investigation loses stationarity during data collection. Hence, the action-potential slow-down expected in FRDA challenges the adequacy of the standard ABR recording method in FRDA patients and calls for a modified ABR procedure averaging over shorter time intervals, the goal of the present work. One anecdotal complaint of our FRDA candidates to enrollment, i.e., the need to change sides every few minutes when using a telephone, indicated that the time course of ABR collection, about one minute, should be adequate for spotting abnormally labile neural-conduction velocity. We thus investigated ABRs using a dynamic analysis of ABR responses to 80-dB clicks in consecutive blocks of 250 repetitions in order to document the effect of sustained stimulation on neural synchrony in auditory pathways. It is noteworthy that a similar procedure applied to the rare DFNB59 deafness had successfully spotted its ANSD identity due to peroxisomal failure (Delmaghani et al., 2015), peroxisomes being another prominent actor of neuronal energetics. Because ABR wave identification may become increasingly contentious with decreasing number of averages, and as energetic failure would preclude repeated testing, a method for identifying ABR patterns, rather than individual waves, was developed by looking at ABR-pattern signatures in the spectral domain.

2. Methods

Thirty-seven FRDA patients (14 males, 23 females; mean age 37.3 years ± 11.2, range 12–63) were enrolled after signing their informed consent. Neurological examination in search of typical signs (e.g., (Durr et al., 1996)), such as progressive cerebellar ataxia and dysarthria, ocular square wave jerks and pyramidal signs, included determination of the ICARS score (International Cooperative Ataxia Rating Scale (Trouillas et al., 1997)) that evaluates motor disorders on a 0–100 scale. The protocol for auditory investigations received approval from the Institutional Review Board (CPP Sud-Est VI).

2.1. Subjective tests

After normal otoscopy and tympanometry had excluded middle-ear dysfunction, pure-tone audiometry (Grason-Stadler GSI 38) evaluated monaural hearing thresholds to air-conducted tones (0.25–8 kHz; octave steps). The average of pure-tone auditory thresholds at 0.5, 1, 2 and 4 kHz (PTA, for pure-tone average) served as index of hearing sensitivity because the 0.5–4 kHz range of frequencies is essential for phoneme identification. Speech-in-noise testing was performed in patients with sufficiently moderate dysarthria to be able to repeat speech tokens within a few seconds, so as to avoid results contamination (n = 24; mean age 36.9 ± 12.3 years, range 17–63). Twenty-six normally-hearing subjects (mean age 39.3 ± 13.4 years, range 14–61) served as controls, their inclusion criterion being that all pure-tone hearing thresholds from 0.125 to 8 kHz had to be <20 dB HL. Series of 10 disyllabic, phonetically balanced French words (Fournier list, male voice) were presented binaurally at 60 dB above perception threshold. They were mixed with acoustic noise made of randomly mixed speech from multiple talkers so as to lose any identifiable temporal envelope (babble noise). The spectral contents of babble noise and tested speech being identical, their levels were fully comparable. Here, babble noise was set at −5, 0, 5 and 10 dB relative to the average level of tested speech, and the percentage of correctly repeated words was registered.