Clinical Neurophysiology 128 (2017) 1142–1147

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Endophenotyping in idiopathic adult onset cervical dystonia

Georg Kägi [a,b,*], Diane Ruge [a,c], Florian Brugger [a,b], Petra Katschnig [a,d], Rafael Sauter [e], Mirta Fiorio [f], Michele Tinazzi [f,g], John Rothwell [a], Kailash P. Bhatia [a]

[a] Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, Queen Square, London, United Kingdom
[b] Department of Neurology, Kantonsspital St.Gallen, St.Gallen, Switzerland
[c] Department of Psychology and Neurosciences, Leibniz Research Centre for Working Environment and Human Factors, Technical University (TU) Dortmund, D-44139 Dortmund, Germany
[d] Department of Neurology, Division of Special Neurology, Medical University Graz, Graz, Austria
[e] Clinical Trials Unit, Kantonsspital St. Gallen, St. Gallen, Switzerland
[f] Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy
[g] Neurology Unit, Borgo Trento Hospital, Verona, Italy

ARTICLE INFO

Article history:
Accepted 10 April 2017
Available online 23 April 2017

Keywords:
Dystonia
Temporal discrimination
Transcranial magnetic stimulation
Mental rotation
Endophenotype

HIGHLIGHTS

- Only multimodal temporal discrimination proves to be an endophenotype of cervical dystonia (CD).
- Multimodal discrimination is abnormal in 36% of healthy 1st degree relatives of patients with CD.
- Unimodal discrimination, mental rotation and paired pulse TMS are unsuitable endophenotype markers.

ABSTRACT

Objective: Idiopathic adult onset cervical dystonia (IAOCD) is considered to be a partially penetrant autosomal dominant genetic condition. Dystonia may result from genetic and environmental factors. In this view, part of the physiology should be an endophenotype stemming from the genetic background. We assessed the most discriminative test to separate patients with IAOCD and healthy controls for further endophenotyping in non-affected 1st degree relatives.
Methods: We included patients with IAOCD, their 1st degree relatives and healthy controls. Tests performed: (1) Sensory temporal discrimination (visual, tactile, visuo-tactile), (2) Paired pulse paradigms using transcranial magnetic stimulation (TMS), (3) Mental rotation paradigms.
Results: 45 patients with IAOCD, 23 healthy controls and 14 non-affected 1st degree relatives were recruited. Visuo-tactile temporal discrimination separated best between controls and patients as well as between controls and 1st degree relatives. 36% of the latter had an abnormal visuo-tactile temporal discrimination. No difference between patients and healthy controls was found for the other paradigms.
Conclusions: Visuo-tactile temporal discrimination separates controls from patients with IAOCD and its 1st degree relatives. 36% of the latter had abnormal visuo-tactile thresholds supporting the role of visuo-tactile temporal discrimination as an endophenotype for IAOCD.
Significance: Even though the study was of exploratory design, our findings expand the understanding of endophenotypes in IAOCD.

1. Introduction

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both (Albanese et al., 2013). Idiopathic adult onset cervical dystonia (IAOCD) is considered to be an autosomal dominant genetic condition due to partially pene-

* Corresponding author at: Department of Neurology, Kantonsspital, 9007 St. Gallen, Switzerland. Fax: +41 71 4946484.
E-mail addresses: georg.kaegi@kssg.ch (G. Kägi), ruge@ifado.de (D. Ruge), florian.brugger@kssg.ch (F. Brugger), petra.katschnig@medunigraz.at (P. Katschnig), Rafael.Sauter@kssg.ch (R. Sauter), mirta.fiorio@univr.it (M. Fiorio), michele.tinazzi@ospedaleuniverona.it (M. Tinazzi), j.rothwell@ucl.ac.uk (J. Rothwell), k.bhatia@ucl.ac.uk (K.P. Bhatia).

http://dx.doi.org/10.1016/j.clinph.2017.04.007
1388-2457/

trant gene/s (Stojanovic et al., 1995; Waddy et al., 1991). Hence most of the cases appear to be sporadic with a positive family history in 15–25% (Waddy et al., 1991). Several genes have been mapped for families, which include members with cervical dystonia (Almasy et al., 1997; Charlesworth et al., 2012; Fuchs et al., 2009, 2013; Leube et al., 1996; Valente et al., 2001; Xiao et al., 2012) but in several other families with cervical dystonia linkage to these known genetic loci has been excluded. Like in many disorders, dystonia is considered to be caused by a combination of genetic factors and environmental modifiers. In this view, at least part of the physiology should be a trait stemming from the genetic background (Hallett, 2011).

The identification of the genetic causation has been difficult because informative families are rare due to low penetrance of the phenotype and absence of surrogate markers. One approach to find the gene(s) is to find a sensitive endophenotype, "*a marker of subclinical gene carriage*" in non-affected relatives. A useful model to study endophenotype markers is inherited generalized dystonia (*DYT1*) because penetrance is low. Compared to controls, both, manifesting and non-manifesting *DYT1* gene mutation carriers share common features like deficient inhibition on a cortical level (Edwards et al., 2003), impaired sensory temporal processing (Fiorio et al., 2007a), and impaired body movement representation in the mental rotation task (Fiorio et al., 2008).

Several of these characteristics can also be found in patients with cervical dystonia:

(i) *sensory discrimination*: studies have shown that spatial (Molloy et al., 2003; O'Dwyer et al., 2005; Walsh et al., 2007) and temporal sensory discrimination (Bradley et al., 2009; Scontrini et al., 2009; Tinazzi et al., 2004; Kimmich et al., 2014) is impaired in patients with cervical dystonia with the latter being more discriminative (Bradley et al., 2009, 2010; Walsh et al., 2007). Impaired sensory discrimination has been found in 1st degree relatives of patients with cervical dystonia (Bradley et al., 2009; Walsh et al., 2007; Kimmich et al., 2014).

(ii) *impaired inhibition:* Impaired intracortical inhibition using transcranial magnetic stimulation is present in both hemispheres (ipsi-and contralateral to the dystonic hand) suggesting that this abnormality is likely to be a substrate or trait for dystonia (Ridding et al., 1995a). In cervical dystonia, there are conflicting reports with reduced short interval intracortical inhibition only when measured from the sternocleidomastoid muscle or only when magnetic stimulation was performed on the contralateral side of head deviation (Hanajima et al., 1998; Kanovsky et al., 2003).

(iii) *The mental rotation paradigm:* Similar to real movements, mentally simulated movements require an intact specific cortico-subcortical motor network (Ionta et al., 2007) as well as intact sensory systems (Cohen et al., 1996; Vingerhoets et al., 2002). Patients with idiopathic dystonia are slower in mentally rotating corporal objects (Fiorio et al., 2006, 2007b, 2008). In patients with focal hand dystonia, slower mental rotation was observed on the affected and unaffected side (Fiorio et al., 2006).

The aim of this study was to determine the most discriminative test between IAOCD and healthy controls with the idea that an endophenotype marker should be present in subjects presenting with the phenotype and absent in controls. According to the literature we selected temporal sensory discrimination, short intracortical inhibition and mental rotation paradigms. In a second step we applied the test(s) discriminating patients from controls to non-affected 1st degree relatives to decide whether it is part of the phenotype or an endophenotype.

2. Patients and methods

We recruited patients with IAOCD who were attending the Movement disorders or botulinum toxin clinics at the National Hospital for Neurology and Neurosurgery, London, their healthy first degree relatives as well as healthy controls without a family history of dystonia. After giving written informed consent, eligible subjects were clinically examined by an experienced Movement disorders specialist (GK). Participants with clinical evidence for polyneuropathy or carpal tunnel syndrome were excluded. Dystonia severity was quantified with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). The study was approved by the local research ethics committee. Five healthy controls are also part of the control group ofKatschnig et al. (2010).

2.1. Temporal discrimination thresholds

Sensory temporal discrimination thresholds (TDT) were assessed by pairs of visual, tactile and visuo-tactile (crossmodal) stimuli according to the published protocol (Fiorio et al., 2003; Kagi et al., 2013). In short, pairs of stimuli were delivered with progressive increase of the interstimulus interval (ISI). The order of the stimulation paradigms was randomized. Visual stimuli were delivered through light-emitting-diodes (LED) positioned on a black board. Two LEDs in each visual field at 7° from central fixation point. Tactile stimulation consisted of electrical stimuli (constant current) through surface electrodes positioned on the volar side of the index and middle finger of the right and left hand. The anodes were located 1.5 cm distally to the cathodes. Stimulation intensity for tactile stimulation was determined for each subject starting at 2 mA and an increment of 1 mA unless 10 out of 10 stimuli were perceived. Each run started with an ISI of 0 ms with progressive increase by steps of 10 ms. TDT was considered the first (i.e. the shortest) out of three consecutive ISI at which the two stimuli were recognized as asynchronous. Each run was repeated 4 times with the mean taken as the TDT. Additionally, subjects were asked to judge, which stimulus preceded (or followed) the other. The first (i.e. shortest) out of three consecutive ISI at which subjects also reported correctly the temporal order in a pair of stimuli was termed temporal order judgment (TOJ). Again the mean of 4 runs was taken for further analysis.

2.2. Transcranial magnetic stimulation

Subjects were seated with the hands relaxed (audiovisually controlled) on a pillow. Surface electrodes were placed on the FDI muscle of the dominant hand. Stimulation was performed using 2 Magstim 200 stimulators and a figure-of eight-shaped coil, external wing diameter 9 cm (Magstim, Dyfed, UK). The coil handle was positioned to evoke an anteriorly directed current in the brain. Optimal coil position was defined as the position with the lowest threshold to evoke a response in the FDI muscle of the contralateral hand. Resting motor threshold was then defined as the intensity to evoke MEPs (>50 uV amplitude) in more than 5 out of 10 runs. Active motor threshold was defined likewise but with a minimal background muscle activity (10–15% of maximum). Test MEP intensity was set in order to evoke a MEP of ~1 mV. Short intracortical inhibition-/facilitation paradigms followed the protocol described by Kujirai et al. (1993) We used interstimulus intervals of 2 and 3 ms for short intracortical inhibition, of 6 and 8 ms for intermediate and of 10, 12, 15 ms for intracortical fascilitation. The intensity of the conditioning stimulus was set at 80% of active motor threshold. For short intracortical inhibition-recruitment curve a fixed interstimulus interval of 2 ms with increasing intensity of the conditioning stimulus (70%, 80%, 90% of test pulse inten-