Blink reflex abnormalities in children with Tourette syndrome

R. Raffaele[a], L. Rampello[a], I. Vecchio[a], A. Alvano[a], R. Rizzo[b], P. Pavone[c], T. Maci[a] and V. Perciavalle[d]

[a]*Department of Neurosciences, University of Catania, Catania, Italy;* [b]*Department of Pediatrics, University of Catania, Catania, Italy;* [c]*Pediatric Unit, Ragusa Hospital, Ragusa, Italy; and* [d]*Department of Physiological Sciences, University of Catania, Catania, Italy*

Keywords:
blink reflex, tics, Tourette syndrome

Received 30 April 2005
Accepted 7 September 2005

Tourette syndrome (TS) is a common disorder which typically occurs during childhood or early adolescence. There is no definitive diagnostic test for TS. The objective of this study was to demonstrate whether neurophysiological abnormalities of the blink reflex can be observed in children with TS. We enrolled 15 children with TS, diagnosed according to DSM IV Diagnostic Criteria, and 15 controls. The blink reflex was elicited by stimulating the supraorbital nerve in order to measure the early response (R1), homolateral and contralateral R2 (late) responses, amplitude of R1 and duration of R2. The mean duration of R2 was significantly longer in TS patients than in the controls ($P < 0.001$, Student's *t*-test). An abnormal pattern of the blink reflex can be, even in childhood, an early neurophysiologic marker of TS, which is not related to the duration of TS or to the age of onset.

Introduction

Tourette syndrome (TS) is a neurological disorder characterized by involuntary movements and uncontrollable vocal sounds called tics. Tics must involve both the voice and a body part, especially neck or head [1,2]. The disorder was first described by Georges Gilles de la Tourette [3], a French neurologist, who published a study describing the disorder in a French noblewoman (the Marquise de Dampière) and in other eight similar cases. TS can affect patients of all ethnic groups, and males are affected three times more often than females [4]. Symptoms onset typically occurs during childhood or early adolescence[4], and the natural course of TS varies from patient to patient [5]. Although the cause of TS is unknown, current research [6] suggests that there is a genetic abnormality affecting the brain metabolism of neurotransmitters (dopamine, serotonine and noradrenalin). Many patients with TS also develop associated behavioural problems, such as obsessions and compulsions, inattention and hyperactivity [7]. The genetics of TS are not well understood. However, genetic analysis of numerous pairs of siblings has shown several loci with genes that, when mutated, may give rise or increase susceptibility to TS [2,6,8]. There is evidence that TS is inherited from both parents (bilineal transmission). Typically, the father is affected with childhood tics and the mother is affected by symptoms of obsessive–compulsive behaviour [9].

The diagnosis of TS is based upon a thorough clinical evaluation and a careful patient and family history. There is no definitive diagnostic test for TS [10]. Neurophysiological abnormalities, including abnormalities of the blink reflex, have been reported in TS [11–14]. These studies have revealed a significant increase in the mean duration of the R2 response in TS adults with a long mean disease duration (>16 years). We studied patients with TS with mean age 10.2 and a brief mean disease duration (3.73 years), and healthy volunteers with a similar mean age and no history of neurological disease. The aim of our study was to disclose neurophysiological abnormalities of the blink reflex since childhood.

Patients and methods

We enrolled 15 TS patients (11 boys and four girls) with a mean age of 10.2 years (±3.05 standard deviation, SD); the mean disease duration was 3.73 years (±1.46 SD). All these patients fulfilled all of DSM IV Diagnostic Criteria [15]. Tic severity was measured using a standard clinical rating instrument for TS, the Yale Global Tic Severity Scale (YGTSS) [16]. Clinical features of TS patients enrolled for this study are reported in Table 1. Controls were 15 healthy children (10 boys and five girls), with no history of neurological disease, having a mean age of 9.87 years (±2.82 SD).

No subject was taking medication. We obtained the informed consent from legal tutors of both patients and

Correspondence: Prof. Vincenzo Perciavalle, Department of Physiological Sciences, University of Catania, Viale Andrea Doria 6, 95125 Catania, Italy (tel.: (+39) 095 339095; fax: (+39) 095 330645; e-mail: perciava@unict.it).

Table 1 Clinical features of Tourette syndrome (TS) patients enrolled for the present study

TS patients	Sex	Age (years)	Onset age (years)	YGTSS score	Facial tics
1	M	10	5.50	11	–
2	M	14	11	17	–
3	M	14	9.5	10	–
4	F	13	10.5	11	–
5	M	14	9	19	+
6	M	9	6.5	12	+
7	M	14	11.5	15	+
8	M	10	2	10	–
9	M	11	7.5	17	–
10	M	7	2.5	16	+
11	F	5	1.5	10	–
12	F	7	3.5	14	+
13	M	7	4.5	10	–
14	F	10	7.5	11	–
15	M	8	4.5	12	+

YGTSS, Yale Global Tic Severity Scale [16].

controls. The study was approved by the ethics committee of our institution.

The blink reflex was elicited by stimulating the supraorbital nerve. A Sierra Cadwell EMG/EP electromyograph (Cadwell Laboratories, Kennewick, WA, USA) was utilized and the responses were recorded using cup electrodes; the G1 electrode was applied to the orbicularis oculi and the G2 to the wing of the nose, with the earth electrode on the chin. The stimulus intensity was 5 mA. The duration of stimulation was 0.3 ms. The sweep ranged from 5 to 10 ms per division. The gain was 500 μV per division. The impedance of recording electrodes was under 10 kΩ. The stimulation rate was dysrhythmic with intervals of at least 10 s. Single shocks were given to measure the early response (R1), homolateral and contralateral R2 (late) responses, amplitude of R1 and duration of R2. The amplitude of the R1 response was measured from peak to peak and average amplitude was calculated. Statistical analysis has been performed by using a two-tailed Student's *t*-test (SYSTAT, version 11, Systat Software Inc., Richmond, CA, USA). *P*-value was considered as statistically significant.

Results

Figure 1 illustrates the two typical blink reflex responses observed in the present research – the upper part shows recording from a subject with TS, whereas the lower part shows recording from a normal subject. It is evident that in the TS patient the duration of R2 responses was much longer than in the control subject.

All data obtained in TS patients and controls are reported in Table 2. As can be seen, no significant differences in the latencies of R1 and R2, nor in the amplitude of the R1 between the patients and the controls were observed. The only observed differences was the mean duration of R2 that was significantly longer in the patient group than in the control group ($P < 0.001$, Student's *t*-test).

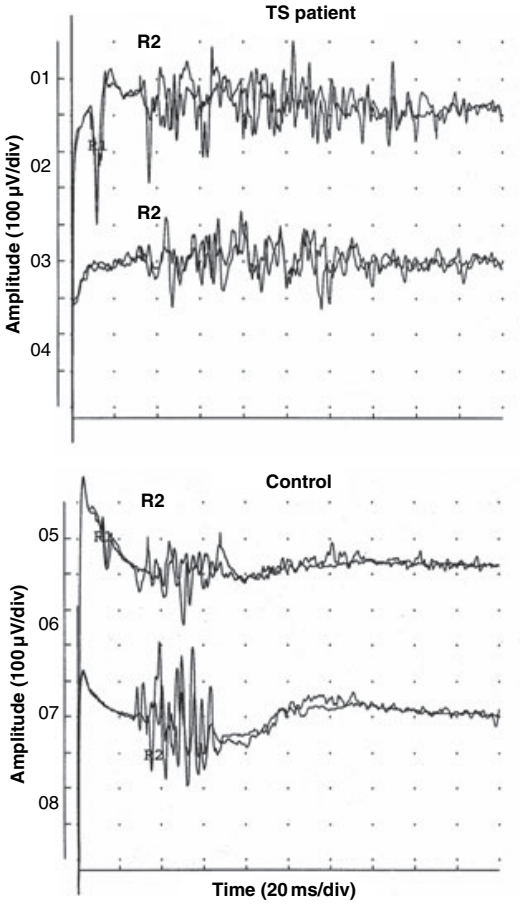

Figure 1 Examples of blink reflexes observed in a Tourette syndrome patient (upper traces) and in a normal subject (lower traces). Onset of R1 and R2 responses are indicated. R1, early response; R2, late response.

It is worth noting that, in TS patients, the abnormal R2 duration was not related with duration of the disease (Fig. 2).

Discussion

Tourette syndrome typically appears in children between the ages 2 and 15, with approximately 50% of patients affected by the age of 10 and the symptom onset before the age of 20 [2,4].

The diagnosis of TS is based upon a thorough clinical evaluation and assessment of symptoms, and a careful patient and family history. There is no definitive test for diagnosis of TS and laboratory tests

Table 2 Group statistics: mean and standard deviation of age and blink reflex components in Tourette syndrome (TS) patients and controls

	n	Mean	SD	Student's *t*-test for independent samples (*P*)
Age				
TS patients	15	10.2	3.05	NS
Controls	15	9.87	2.82	
Left R1 latency				
TS patients	15	10.58	1.05	NS
Controls	15	10.25	0.8	
Right R1 latency				
TS patients	15	10.6	0.92	NS
Controls	15	10.23	1.51	
Left homolateral R2 latency				
TS patients	15	31.86	2.53	NS
Controls	15	30.74	3.44	
Right homolateral R2 latency				
TS patients	15	32.13	2.12	NS
Controls	15	30.79	2.44	
Left contralateral R2 latency				
TS patients	15	32	2.01	NS
Controls	15	30.96	2.72	
Right contralateral R2 latency				
TS patients	15	32.58	1.53	NS
Controls	15	31.46	2.63	
Left R1 amplitude				
TS patients	15	226.06	168.7	NS
Controls	15	198.22	76.6	
Right R1 amplitude				
TS patients	15	208.95	72.98	NS
Controls	15	227.81	109.05	
Left R2 duration				
TS patients	15	78.3	31.65	< 0.001
Controls	15	34.26	3.32	
Right R2 duration				
TS patients	15	83.58	36.97	< 0.001
Controls	15	35.6	4.88	

R1, early response; R2, late response; NS, not significant.

and neuroimaging techniques may be conducted only to exclude related disorders with similar symptoms [10]. Indeed the clinical phenomenology of tics has been described in detail, but the pathophysiology of tics is still largely unknown.

Blink reflex abnormalities have been reported in TS adults with a long mean disease duration (> 16 years), showing a significant increase in the mean duration of the R2 response compared with controls [12,13]. This study shows abnormalities of the blink reflex even in childhood. Our data have pointed out an increase in the duration of the R2 component of the blink reflex in children aged 5–14 (mean: 10.2 years $\pm$ 3.05 SD). No differences in the R1 amplitude and latency were observed between the patients and controls. The R1 component is probably relayed from the supraorbital nerve to the homolateral facial nucleus via a oligosynaptic pathway in pons [12], whereas impulses that induce R2 component descend to the facial nuclei through a polysynaptic pathway in medulla [12]. An abnormal duration of the response of R2 component of blink reflex and an abnormal recovery cycle of the R2 component probably indicate an increased excitability of interneurones subserving this part of the reflex [12].

It is well known that, in the human blink reflex, there is a third component that follows the R2 and is known as the R3 response [17]. Initially considered a sporadic and irregular finding in the routine exploration of young people, it was later recognized as a systematic or nearly systematic component of the blink reflex when an appropriate electrical intensity was used [18,19]. The R3 response is bilateral, is supposed to be conducted mainly by nociceptive afferent fibres [18,20] , and shows a mean onset latency of around 80 ms [19]. Upper cervical structures related to spinal trigeminal nucleus appear to be involved as a central part of the reflex arc [21]. Although R2 and R3 responses are generally easily differentiated, pathological conditions (e.g. an hyperexcitable reflexes), may give rise to

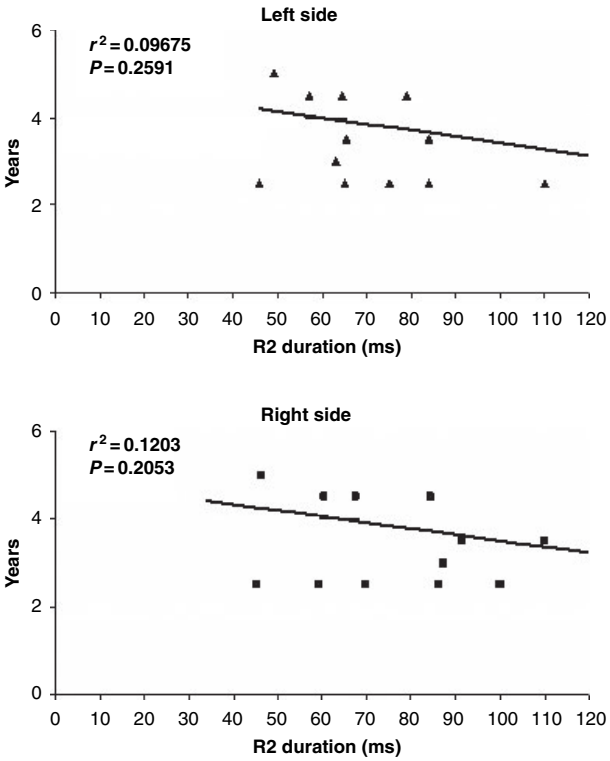

Figure 2 Distribution of R2 duration in function of disease length. R2, late response.

insuperable difficulties in truly identifying the two components [22].

Tulen *et al*. [23] reported a significantly higher blink rate in TS patients than in controls. An initial symptom of TS is often an increased eye blinking that suggests an increase in central dopaminergic activity [24,25]. Although a positive correlation between tics and blink rate has been reported [23,26], few non-definitive data exist on eye tics and their relation to blinks [23,27]. TS causes hyperexcitable trigeminal blink reflex [12] and reduces pre-pulse inhibition of these blinks [28].

It can be, therefore, suggested that in TS patients the hyperexcitability of central structures involved in blink reflex could induce an easier elicitation of R3 response; in this way, this latter component is incorporated in the R2 response and appears as its prolongation.

In conclusion, the abnormalities of the blink reflex in TS suggest enhanced excitability of brainstem interneurones, possibly due to a disturbance of input from the basal ganglia [29]. This hyperexcitability reveals itself for an easier and constant appearance of R3 response that fuses with the R2 one. This feature, not related to the duration or the onset age of TS, can be considered a neurophysiological marker of TS, since childhood.

References

1. Marcus D, Kurlan R. Tics and its disorders. *Neurologic Clinics* 2001; **19:** 735–758.
2. Cohen DJ, Jankovic J, Goetz CG. Tourette syndrome. *Advances in Neurology*, Vol. 85. Philadelphia, PA: Lippincott Williams & Wilkins, 2001.
3. Gilles de la Tourette G. Étude sur une affection nerveuse caracterisée par incoordination motrice accompagnée d'écholalie et de coprolalie. *Archives of Neurology (Paris)* 1885; **9:** 19–42; 158–200.
4. Scahill L, Tanner C, Dure L. The epidemiology of tics and Tourette syndrome in children and adolescents. *Advances in Neurology* 2001; **85:** 261–271.
5. Leckman JF, Peterson BS, King RA, Scahill L, Cohen DJ. Phenomenology of tics and natural history of tic disorders. *Advances in Neurology* 2001; **85:** 1–14.
6. Pauls DL. Update on the genetics of Tourette syndrome. *Advances in Neurology* 2001; **85:** 281–293.
7. Kurlan R, Como PG, Miller B,*et al*. The behavioural spectrum of tic disorders: a community-based study. *Neurology* 2002; **59:** 414–420.
8. Walkup JT. Epigenetic and environmental risk factors in Tourette syndrome. *Advances in Neurology* 2001; **85:** 273–279.
9. Hanna PA, Janjua FN, Contant CF, Jankovic J. Bilineal transmission in Tourette syndrome. *Neurology* 1999; **53:** 813–818.
10. Jankovic J. Differential diagnosis and etiology of tics. *Advances in Neurology* 2001; **85:** 15–29.
11. Hallett M. Neurophysiology of tics. *Advances in Neurology* 2001; **85:** 237–244.
12. Smith SJ, Lees AJ. Abnormalities of the blink reflex in Gilles de la Tourette syndrome. *Journal of Neurology Neurosurgery and Psychiatry* 1989; **52:** 895–898.
13. Hatanaka T, Owa K, Hayashi N,*et al*. The excitability of blink reflexes in patients with neurologic and psychiatric disorders. *Electromyography and Clinical Neurophysiology* 1994; **34:** 105–109.
14. Raffaele R, Vecchio I, Alvano A, Proto G, Nicoletti G, Rampello L. Blink reflex abnormalities in Tourette sindrome. *Clinical Neurophysiology* 2004; **115:** 320–324.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* 4th edn. Washington, DC: American Psychiatric Association, 1994.
16. Leckman JF, Riddle MA, Hardin MT, *et al*. The Yale Global Tic Severity Scale (YGTSS): initial testing of a clinician-rated scale of tic severity. *Journal of the American Academy of Child and Adolescent Psychiatry* 1989; **28:** 566–573.
17. Penders CA, Delwaide PJ. Le rèflexe de clignement chez l'homme. Particularités électrophysiologiques de la réponse précoce. *Archives Internationales de Physiologie et de Biochimie* 1969; **77:** 351–354.
18. Rossi B, Pasca SL, Cantucci F, Siciliano G, Murri L. Trigemino.cervical reflex in pathology of the brain stem and of the first cervical cord segments. *Electromyography and Clinical Neurophysiology* 1989; **29:** 67–71.
19. Ellrich J, Hoft HC. The R3-component of the blink reflex: normative data and application in spinal lesion. *Electroencephalography and Clinical Neurophysiology* 1996; **101:** 349–354.
20. Ellrich J, Katsarava Z, Przywara S, Kaube H. Is the R3 component of the human blink reflex nociceptive in origin? *Pain* 2001; **91:** 389–395.

21. Rossi B, Risaliti R, Rossi A. The R3 component of the blink reflex in man: a reflex response induced by activation of high threshold cutaneous afferents. *Electroencephalography and Clinical Neurophysiology* 1989; **73:** 334–340.
22. Esteban A. A neurophysiological approach to brainstem reflexes. Blink reflex. *Neurophysiologie Clinique* 1999; **29:** 7–38.
23. Tulen JH, Azzolini M, de Vries JA, Groeneveld WH, Passchier J, van De Wetering BJ. Quantitative study of spontaneous eye blinks and eye tics in Gilles de la Tourette's syndrome. *Journal of Neurology Neurosurgery and Psychiatry* 1999; **67:** 800–802.
24. Shapiro AK, Shapiro E, Young JG, Feinberg TE. *Gilles de la Tourette Syndrome,* 2nd edn. New York: Raven Press, 1988.
25. Kleven MS, Koek W. Differential effects of direct and indirect dopamine agonists on eye blink rate in Cyomolgus monkeys. *Journal of Pharmacology and Experimental Therapeutics* 1996; **279:** 1211–1219.
26. Karson CN, Kaufmann CA, Shapiro AK, Shapiro E. Eye-blink rate in Tourette's syndrome. *Journal of Nervous and Mental Disease* 1985; **173:** 566–569.
27. Frankel M, Cummings JL. Neuro-ophthalmic abnormalities in Tourette's syndrome: functional and anatomic implications. *Neurology* 1994; **34:** 359–361.
28. Castellanos FX, Fine EJ, Kaysen D, Marsh WL, Rapoport JL, Hallett M. Sensorimotor gating in boys with Tourette's syndrome and ADHD: preliminary results. *Biological Psychiatry* 1996; **3:** 33–41.
29. Mink JW. Basal ganglia dysfunction in Tourette's syndrome: a new hypothesis. *Pediatric Neurology* 2001; **25:** 190–198.