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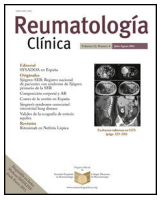

Letter to the Editor

Is "Joker" syndrome a distinctive characteristic of neuro-Behçet's disease☆

¿Síndrome del Guasón, característica distintiva de neuro-Behçet?

Dear Editor,

Laughter is an inherent and essential part of human behaviour. Its impact throughout our culture may be observed from the texts of the great civilisations, from classical Greece, to today's popular culture. The beneficial impact of laughter in medicine has been widely demonstrated in, for example, cardiovascular health, behaviour patterns and learning.[1–4]

On the other end of the laughter type classification spectrum is abnormal laughter. This is defined as something which occurs without any previous stimulus and which is of inappropriate intensity. Similarly, to the first type of laughter, there are many references to abnormal laughter. One recent reference is the *Joker* antihero, whose distinctive trait is his scandalous, abnormal, and on occasions, malevolent laughter.

The aetiology of abnormal laughter, which is a component of pseudobulbar syndrome, is extensive and includes neurodegenerative, tumoral, traumatic and even vascular diseases. In Behçet's disease, primary systemic vasculitis of variably sized blood vessels and involvement of the central nervous system at disease onset is rare and occurs less frequently than that of other organs. Inappropriate laughter as part of the neuropsychiatric symptoms has been infrequently reported.[5–7]

We report 2 cases of patients with Behçet's disease and with "joker syndrome" traits.

Case 1

Male, 23 years of age, previously healthy, with 6-month onset of constitutional symptoms, ataxia, dysmetria and dysarthria. Three months later additional symptoms of polyarthritis, pustular dermatosis, and oral and genital ulcers presented. Diagnosis ruled out infectious aetiologies and confirmed the existence of retinal vasculitis in fluorescein angiography and in magnetic resonance imaging, which showed predominantly mesencephalic inflammatory lesions. Behçet's disease was considered and was treated with methylprednisolone and cyclophosphamide with favourable response. During the course of the disease the patient again presented with ataxia, dysphagia, and dysarthria, accompanied by episodes of intense laughter. His mother reported that the laughter even occurred in situations such as when he was bathing or eating and when his attention was captured. The patient again received methylprednisolone by IV and cyclophosphamide, with subsequent maintenance therapy of azathioprine with partial response. Gait disorders persisted which led to the patient becoming bed-ridden, with dysphasia and a continuation of the inappropriate laughter. Treatment was changed to anti-TNF, but shortly after initiation of treatment the patient died from respiratory infectious complications.

Case 2

Male, 39 years of age, previously healthy. He presented with a 4-month history of constitutional symptoms of low-grade fever, polyarthritis, oral and genital ulcers. Behçet's disease was diagnosed for which the patient was treated with glucocorticoids and cyclophosphamide. During follow-up, his family members, and the patient himself commented upon changes to his behaviour characterized by the appearance of involuntary and irrepressible laughter, even in serious situations or without any stimuli. The most dramatic event presented during the funeral of his daughter aged 12 where, despite being grief stricken, the patient burst into uncontrollable laughter and preferred to vacate the premises. The patient continued with immunosuppressant treatment based on methotrexate, with remission of symptoms.

Behçet's disease, a chronic multisystemic inflammatory disease, is included in the Chapel Hill classification as vasculitis of blood vessels of varying size.[8] An extremely high percentage of patients with this vasculitis, ranging from 5% to 50%, may present with neuropsychiatric symptoms. There are two suggested mechanisms to explain the clinical symptoms: parenchymatose inflammatory lesions (with involvement of the brain stem, mesodiencephalic union, cerebellar and cerebral hemispheres) and the thrombotic phenomenon. Pseudobulbar paralysis syndrome has been previously reported in this disease, but uncontrollable laughter being predominant as a symptom is extremely rare. This finding presented in both patients. In the first case there was mesodiencephalic involvement despite immunosuppressant treatment and evolution was not favourable.

Different disorders have received eponyms from other, non-medical areas. One such known case, the Pickwickian syndrome, was established by Charles Dickens in his novel *The Posthumous Papers of the Pickwick Club* published in 1837. Might we then speak of the "Joker syndrome" in the case of the inappropriate laughter in our patients with this neuropsychiatric expression related to Behcet's disease?

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Growth factors: Do they play a role in entheseal involvement in psoriatic arthritis and undifferentiated spondyloarthritis patients?

Factores de crecimiento: ¿desempeñan un papel en el compromiso enteseal en pacientes de artritis psoriásica y espondiloartritis indiferenciada?

Dear Editor:

The role of growth factors (GFs) in arthritis is rarely investigated, reporting controversial results.[1–4]

To the best of our knowledge, the serum levels of IGF-1, FGF-1, TGFβ in patients (pts) with undifferentiated spondyloarthritis (SpA) or psoriatic arthritis (PsA) have never been described in literature. Partsch et al. described a higher titer of GH in the sera of PsA pts compared to psoriatic pts.[1]

We describe a study designed to evaluate the serum levels of GFs, IGF-1, FGF-1, GH and TGFβ, in PsA pts and SpA pts, with particular focus on the entheseal involvement. Our goal was to assess any differences in the concentration of these GFs between pts with different clinical and instrumental features.

Preliminary data were obtained on 15 pts (all female): 6 with a new diagnosis of PsA,[5] 9 with a new diagnosis of SpA.[6] The control group was formed by 5 age-matched healthy females (HC). The exclusion criteria were intestinal bowel disease, diabetes mellitus, body mass index >30, systemic hypertension, dyslipidemia, alteration of thyroid function.

Serum levels of IGF-1, FGF-1, GH and TGFβ were measured using enzyme-linked immunosorbent assay (ELISA). Moreover, an imaging evaluation was conducted on all pts: the presence of calcific enthesopathy (CE) was assessed using standard radiology; the ultrasound evaluation was conducted according to the Madrid Sonographic Enthesis Index (MASEI) score.[7] Disease activity was assessed by means of Disease Activity Score (DAS28), Disease Activity in PSoriatic Arthritis (DAPSA) and Leeds Enthesitis Index (LEI). Comparisons between groups were made with one-way analysis of variance (ANOVA) (Table 1).

We found that serum levels of IGF-1 and TGFβ were remarkably but not significantly higher in SpA pts compared to PsA pts and HC. In particular, there was a tendency toward higher serum concentrations of TGFβ in pts with CE compared to those pts without and HC (1003.5 ± 208.5 vs. 999.5 ± 156.9 vs. 975.9 ± 61.7; $P = .965$). Furthermore, a statistically significant negative correlation between TGFβ levels and symptoms duration both in SpA and PsA pts was observed ($r^2 = 0.582$; $P = .029$). In addition, subjects with moderate (MA) or high disease activity (HA) according to DAPSA score showed a tendency toward higher GH (low activity

Table 1
Comparison of demographic, clinical characteristics and serum levels of growth factors between groups in study.

Variables	PsA	SpA	HC	*P*
Age	49.1 ± 15.7	43.8 ± 12.3	43.2 ± 13.1	.691
BMI	24.1 ± 3.2	24.2 ± 1.54	22.5 ± 3.6	.233
Symptoms duration	4.6 ± 3.2	4.00 ± 2.0		.424
ESR	16 ± 17.7	19.4 ± 14.6		.688
CRP	0.1 ± 0.2	0.2 ± 0.2		.813
LEI	3.5 ± 1.2	2.3 ± 1.3		.109
DAS28	3.2 ± 0.5	2.6 ± 1.1		.287
DAPSA	24.1 ± 5.7	20.7 ± 6.1		.305
MASEI	6.5 ± 5.6	5.3 ± 4.5		.665
SHARP score	33.3 ± 39.7	50.7 ± 33.9		.474
PARS	4.6 ± 1.1	6.5 ± 8.2		.708
IGF-1	378.3 ± 330.8	859.4 ± 923.4	366.5 ± 280.6	.638
FGF-1	9.6 ± 23.5	13.3 ± 22.5	3.5 ± 7.1	.242
GH	336.1 ± 694.0	991.2 ± 1082.6	593.1 ± 601.6	.679
TGFβ	968.8 ± 189	1024.3 ± 193.3	927.2 ± 121.1	.464

Data are expressed as mean ± standard deviation; significant *P* value was set to ≤ .05.
BMI: BODY MASS INdex; CRP: C Reactive Protein; DAPSA: Disease Activity in PSoriatic Arthritis; DAS28: Disease Activity Score; ESR: Erythrocytes Sedimentation Rate; HC: Healthy Controls; LEI: Leeds Enthesitis Index; MASEI: MAdrid Sonographic Enthesitis Index; PARS: Psoriatic Arthritis Ratingen Score; PsA: Psoriatic Arthritis; SpA: undifferentiated Spondyloarthritis.