Reflex Sympathetic Dystrophy Associated with Antiepileptic Drugs


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Summary: Reflex sympathetic dystrophy syndrome (RSDS) complicating antiepileptic drug (AED) therapy is not well acknowledged in the neurologic literature. We report 4 patients with reflex sympathetic dystrophy that occurred while they were receiving AEDs. All patients had shoulder and hand involvement, which in 2 was bilateral, and 1 had ipsilateral foot involvement. Two patients did not respond to a change in AEDs, but all improved with a course of prednisone. One patient with phenobarbital (PB)-associated RSDS relapsed on inadvertent rechallenge with secobarbital. A review of the literature showed that several other fibrosing disorders are associated with AED administration, including Dupuytren's contractures, frozen shoulder, plantar and hand nodules, and Peyronie's disease. RSD associated with AEDs is important to recognize because it may result in permanent disability if treatment is delayed. Key Words: Anticonvulsants—Reflex sympathetic dystrophy—Shoulder-hand syndrome—Barbiturates—Antiepileptic drugs—Dupuytren's contractures.

Reflex sympathetic dystrophy (RSD) affects one or more extremities and is characterized by distal pain, tenderness, swelling, and vasomotor instability (Leriche, 1939). RSD is often associated with allodynia, hyperpathia, and patchy demineralization on plain radiography of the affected extremity (Kozin, 1986).

The clinical features were described by Mitchell et al. (1864), who introduced the term causalgia to describe the RSD syndrome (RSDS) occurring in association with peripheral nerve injuries. Many descriptive terms have since been used, each emphasizing one particular clinical facet or etiology (Steinbrocker and Argyros, 1958). The terms reflex dystrophy and RSD were used by Leriche (1939), de Takats and Miller (1943), Evans (1946), and Holden (1948). Although still used in its original sense by some investigators (International Association, 1979), the term causalgia has become almost synonymous with the term RSD.

The association of RSDS with antiepileptic drugs (AEDs, most notably phenobarbital, PB), is unrecognized in most standard texts on epilepsy (Woodbury et al., 1982), although it is alluded to in one (Oxley et al., 1983). There are few descriptions of this entity in the English-language rheumatology literature (Van der Korst et al., 1966; Horton and Gerster, 1984; Reddy, 1985), or neurology literature (Davis, 1977; Janz and Piltz, 1983; Schmidt, 1983; Mattson et al., 1989). In expanding on our original observations (Toly et al., 1988), we wish to emphasize the importance of recognition and early adequate treatment of RSDS in patients receiving AEDs, PB in particular.

CASE REPORTS

The case histories of 4 patients treated by us are described. Physical findings (Table 1) were used to classify patients according to the criteria of Kozin (1986): definite RSDS, pain and tenderness in an extremity with swelling and vasomotor and sudomotor changes; probable RSDS, pain and tenderness with vasomotor and sudomotor changes or swelling; and possible RSDS, vasomotor or sudomotor changes. All patients had radiographs and
bone scans consistent with the radiologic criteria of Kozin et al. (1981).

**Patient 1**

A 56-year-old woman with Parkinson's disease with retropulsion, rest tremor, and cogwheel rigidity of the left arm was treated with ethopropazine and developed episodic sensations of heaviness in this extremity associated with a tight feeling in the throat and subsequent loss of consciousness. PB 150 mg at bedtime was initiated after an EEG showed right temporal sharp waves and spikes and occasional independent left temporal sharp waves. After 3-months treatment, she experienced severe pain in the left shoulder and hand. Physical examination disclosed marked limitation of shoulder movement and non pitting edema of the hand, which was warm and tender. Thickening of flexor tendon sheaths and allodynia were evident (Fig. 1), as were small effusions of the fourth and fifth proximal interphalangeal (PIP) joints. Radiographs of both hands showed diffuse demineralization of the hand. PB was substituted for CBZ. Prednisone 40 mg daily was administered and tapered for 8 weeks, resulting in remission of symptoms. She has remained free of symptoms for 6 years.

**Patient 2**

After closed head injury, a 38-year-old woman exhibited mild expressive aphasia and right hemiparesis. Posttraumatic epilepsy developing after 6 months was treated with carbamazepine (CBZ) and PHT. Eighteen months later, PB 180 mg daily was substituted for PHT because of recurrent generalized seizures that occurred despite therapeutic drug levels. She soon developed pain in the left shoulder as well as pain and swelling of the left hand and foot and, to a lesser extent, the contralateral hand. Examination 6 months later, showed allodynia of the left hand accompanied by diffuse warmth, edema, longer fingernails and hair, and contractures of the shoulder, wrist, metacarpophalangeal, proximal, and distal interphalangeal joints (Fig. 2). The foot was swollen and tender. A radiograph showed soft tissue swelling and mild demineralization of the left hand. A [99Tc]MDP bone scan showed diffuse uptake in the left hand and forearm. Several weeks of intensive physical therapy and a single stellate ganglion block effected little change, but rapid improvement followed treatment with prednisone 60 mg daily in a tapering dose for 8 weeks, during which time PHT was substituted for PB. Mild relapse 2 weeks after discontinuation of steroids occasioned a second shorter course of prednisone with symptomatic benefit, but slight residual contractures persisted.
Symptoms remained stable for 2 years and then suddenly worsened. Close questioning showed that she had been receiving secobarbital capsules several times a week at bedtime for 3 months before exacerbation of symptoms. The capsules had been prescribed by another physician unaware of her previous history. Symptoms subsided gradually without prednisone when triazolam was substituted for secobarbital.

Patient 3
A 52-year-old man with a history of primary generalized epilepsy from age 4 years, receiving CBZ, mephenytoin, metharbital, and valproate (VPA), experienced painful swelling of both index and middle fingers, progressing to diffuse painful swelling of both hands and shoulder pain over the next several months. Sedimentation rate, rheumatoid factor, and antinuclear antibody tests were normal or negative.

**FIG. 1.** Left hand of patient 1 showed swelling and shiny skin.

**FIG. 2.** Left hand of patient 2 showed swelling, loss of wrinkles, longer fingernails, and mild hyperpigmentation of the skin overlying the proximal and distal interphalangeal joints of the left hand.
A bone scan showed diffusely increased uptake in both hands. There was no response to physical therapy and a trial of tolmetin. Pain and swelling disappeared during treatment with prednisone 40 mg daily, tapered for 4 weeks. During this time, VPA was discontinued.

**Patient 4**

After a left frontoparietal intracerebral hemorrhage in November 1987, a 65-year-old man developed right-sided focal motor seizures, treated with PB 150 mg daily, and exhibited residual mild right upper extremity weakness. Two months later, he experienced aching in the right shoulder and wrist. Examination 1 month after onset of symptoms showed edema with mottled erythema of the palm, with shiny atrophic skin and inability to make a fist. Shoulder movement was markedly limited. Radiographs disclosed severe patchy demineralization of the right humerus and periarticular demineralization of wrist, metacarpophalangeal joints (MCP), and PIP. A [18F]FDG bone scan showed increased uptake at all sites of demineralization.

The patient was treated with 3 weeks of intensive physical therapy after PB dosage was reduced to 60 mg/day and CBZ was added. He had increased mobility and less pain in the shoulder, but little improvement in flexion contractures of the hand. PB was discontinued. Persistent edema, motting, contractures, and functional disability on follow-up 3 weeks later prompted treatment with prednisone 60 mg daily, tapered for a 3-week period. Definite reduction in swelling and improved mobility were evident at 2 weeks, with 90% recovery of function by 9 weeks and subsequent full functional recovery despite minimal persistent contractures.

**DISCUSSION**

The symptoms of RSDS were first described in association with barbiturate therapy in 1934 (Béreil and Barbier, 1934), although features were described in case reports as early as 1925 (Maillard and Renard, 1925). Several other French language reports have subsequently appeared (Sauden et al., 1971; Camus and Paul, 1972; Blanquart et al., 1974). The few reports in the English language literature (Van der Korst et al., 1966; Schmidt, 1983; Horton and Gerster, 1984; Reddy, 1985), strengthened this association. In the neurologic community, recognition of a relation between RSDS and administration of AEDs has been evident only in the last few years (Mattson et al., 1988; Toly et al., 1988; Mattson et al., 1989; Taylor and Posner, 1989).

RSDS may not be rare, but only rarely recognized. Taylor and Posner (1989) noted shoulder-hand syndrome in 12% of patients with brain tumor treated with PB as compared with 5% in patients not so treated. Van der Korst et al. (1966) reported one third of patients with shoulder-hand syndrome had been receiving PB.

Several other musculoskeletal disorders have been associated with PB. Frozen shoulder without reference to RSDS was described in connection with PB and primidone (PRM, Janz and Piltz, 1983; Schmidt, 1983; Mattson et al., 1989). Many cases were noted to subside spontaneously despite continued therapy with PB and PRM.

RSDS and frozen shoulder may represent only a portion of the spectrum of fibrosing disorders associated with AEDs (Reynolds, 1975; Fröschler and Hoffman, 1983; Schmidt, 1983); i.e., Dupuytren’s contracture affected 50% of male epileptic patients receiving PB (Lund, 1941; Critchley et al., 1976) with a prevalence as high as 88% in the subgroup of males aged >60 years (Critchley et al., 1976). Unlike the idiopathic variety, PB-associated Dupuytren’s contracture was reported to improve or resolve in >50% of patients in the studies described when PB was discontinued.

Less common fibrosing conditions associated with PB include hand nodules overlying the dorsal PIP joints, plantar nodules (Ledderhose syndrome) (Schmidt, 1983), and Peyronie’s disease (Reynolds, 1975). When occurring in association with PB, these disorders are frequently accompanied by Dupuytren’s contracture. The relation between these fibrosing conditions and AED-induced RSDS is unknown, although pathologic changes indistinguishable from those that occur in Dupuytren’s contracture have been reported in RSDS due to other causes (Steinbrocker and Argyros, 1958). Our patient 1 developed palmar thickening in association with RSDS.

The association of RSDS with AEDs other than PB is less well established. Although specifically sought, no definite association could be identified for PHT and CBZ (Janz and Piltz, 1983; Horton and Gerster, 1984; Mattson et al., 1989; Taylor and Posner, 1989). Our patient 3 had resolution of symptoms with a course of prednisone therapy and discontinuation of VPA, despite continuation of metharbital. As compared with PB, with other AEDs the occurrence of RSDS appears to be very uncommon.

As in RSDS due to other causes, there is no clear consensus regarding the best mode of therapy. Previous studies emphasized the need for drug discontinuation and physical therapy (Horton and Gerster, 1984; Sánchez Navarro et al., 1987) although one study, in which details of therapy were not provided, showed no difference in prognosis whether...
or not PB was discontinued, although almost all patients developed atrophy and contractures of the hands (van der Korst et al., 1966). Resolution of pain despite continued administration of PB in most patients, as reported by Taylor and Posner (1989), is not always accompanied by improvement in mobility; fibrous ankylosis persisted in 8 of 20 of their cases.

In view of the current theories regarding pathogenesis of RSDS (Schwartzman and McLellan, 1987), several of the known pharmacologic effects of barbiturates are noteworthy. Unlike other CNS depressants, barbiturates cause hyperalgesia at low dosages, a property attributed to disinhibition of lower level pain control neurons. In neuronal cell culture, barbiturates at low concentrations paradoxically increase the frequency of spontaneous discharge. In addition to their effects at the level of the sympathetic ganglia (Harvey, 1985), these effects could be related to the pathophysiology of RSDS and could represent areas for future research.

RSDS associated with AED therapy is an important complication to recognize since it usually responds rapidly to treatment but can result in permanent disability if not addressed promptly. Previous reports have cited discontinuation of the offending drug and physical therapy as sufficient treatment, but our experience suggests that a course of corticosteroids may be necessary in some cases to prevent significant residual deficits. RSDS is only one of a spectrum of musculoskeletal disorders observed with increased frequency in patients prescribed AEDs.

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REFERENCES


RESUMEN
El síndrome de distrofia simpática refleja (RSDS) como complicación de medicaciones antiepilépticas (AED) no está bien definido en la literatura neurológica. Se describen cuatro pacientes con RSDS que ocurrió durante un tratamiento con ADS. Todos los pacientes mostraron afectación del hombro y de la mano que fue bilateral en dos casos y uno tenía también una participación homolateral de un pie. Dos pacientes no mejoraron al cambiar la AED pero sí durante un tratamiento con prednisona. Un paciente con RSDS asociado a fenobarbital presentó nuevos síntomas tras un tratamiento inadvertido con secobarbital. La revisión de la literatura revela que varios otros trastornos con fibrosis se asocian a la administración de AED incluyendo las contracturas de Dupuytren. El RSDS asociado a AEDs debe ser reconocido porque puede conducir a una discapacidad permanente si el tratamiento se prolonga.

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