Chapter 10
PHYTORELIEF™-CC: A PILOT STUDY IN BEHCET'S SYNDROME

LUZZI R., BELCARO G., HU S.
IRVINE² LABS, CIRCULATION SCIENCES
DIP SC MED OR BIOT, CH-PE UNIVERSITY

Behcet disease (BE-SY; Behcet's syndrome, 'silk road' disease) leads to mucosal ulcerations and other lesions. It has also been defined as *Silk Road disease* because it is most common and more severe in people originating from countries along the Silk Road, the network of trade routes connecting China with the Mediterranean.
The disease is common in Japan, Turkey, and Israel, but considered rare in the USA.
It is also called Behcet's syndrome (**H. Behcet** was a *Turkish dermatologist who* described a *disease* with *inflamed blood vessels* in 1937).
BE-SY is an inflammatory, multisystem, relapsing vasculitis. Oral and genital ulcers, ocular inflammation and skin lesions are common features. Blindness, neurological and gastro-intestinal involvement, venous thrombosis and arterial aneurysms are the most clinically important problems.
Diagnosis is mainly clinical using some defined criteria.
Treatment is mainly symptomatic, including corticosteroids for acute or severe manifestations (ocular and neurological manifestations). Immunosuppressant can be used for severe

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The cause is still unknown; immunological, bacterial or viral origins have been suggested and observed.
Hla-b51 is associated with cases from the Mediterranean area, Turkey, Iran, Korea, Japan and China. BE-SY is considered uncommon in the USA.
Vasculitic alterations and thrombosis can be observed at histology. The disease may start around 20 years of age and may be equally distributed between sexes (some sources report a male prevalence). Children with BE-SY have been observed.

First manifestations my be recurrent, painful oral ulcerations (aphthae-type) stomatitis. Comparable ulcers at the penis,

scrotum and vulva (very painful) may be observed. Vaginal ulcers cause less pain.
Ocular disease generally occurs after years: relapsing iridocyclitis is associated to pain, photophobia, hazy vision. Hypopyon with a visible layer of pus visible in the anterior chamber is specific but not common. Posterior segments may be involved (choroiditis, retinal vasculitis, papillitis decreasing visual acuity). Untreated posterior uveitis may lead to blindness.

SKIN LESIONS: vescicles, folliculitis, papules, pustules are seen in some 80% of patients. *Erytema nodosum*-like lesions are suggestive to BE-SY; in some 40% of patients, pustular inflammatory reactions to minor trauma (needles), mild, self limiting arthralgias, neutrophil-mediated arthritis (knees, larger joints) in 50% of patients may be observed.
Recurrent superficial or deep venous thrombosis may be observed in some 25% of patients and may lead to vena cava obstruction. CNS involvement as chronic meningoencephalitis, small vessel-disease with a multiple-sclerosis pattern can occur.
Paralyzing, life-threatening brain stem and spinal cord lesions are seen in some patients. Gastro-intestinal manifestations are variable from minor abdominal discomfort to real pain and diarrhea with ulcers that may be comparable to the lesions seen in Chron's disease. A clinical picture of generalised vasculitis may cause aneuryms or thrombosis in different localizations including the lungs. Focal glomerulonefritis is considered rare and may be asymptomatic.

DIAGNOSIS

BE-SY should be suspected in adults with:
- recurrent, oral aphthae-like ulcers,
- unexplaided ocular findings,
- genital ulcers.

The diagnosis is clinical and may require long periods of observation. International criteria indicate for diagnosis:
- recurrent oral ulcers,
- two of the following:
  - recurrent genital ulcers,
  - eye lesions,
  - skin lesions,
  - positive *pathergy test* in absence of any other clinical explanation.

PATHERGY TEST: this is a papular or pustular reaction to skin puncture with a 20-gauge needle.

Differential diagnosis include:
- Reactive arthritis
- Steven-Johnson syndrome
- SLE
- Crohn's disease
- Ulcerative colitis
- Ankylosing spondylitis
- Herpes symplex infections (expecially with recurrent aseptic meningitis)

BE-SY has no specific findings excluding other clinical possibilities; it is characterised by its relapsing course and multiple organ involvement.

Laboratory tests are non-specific, or characteristic of inflammatory diseases (elevated ESR, alfa2, gamma-globulins, mild leucocytosis).

PROGNOSIS,TREATMENT

BE-SY is chronic but controllable. Signs-symptoms tend to decrease over time. Remisions and relespes may last from week to years and even decades. Blindnedss caval obstruction, paralysis may complicate more severe cases. Death is possible for severe neurologic, vascular (aneurysms-thrombosis) or gastro-intestinal involvement.

Treatment. Is mainly symptomatic. Needle puncture cause more inflammation and skin lesions and should be avoided.

Oral colchicine 0.5 mg/die bid decrease the frequency and severity of oral/genital ulcers.
Topical corticosteroid may relieve ocular and oral symptoms. However topical corticosteroids do not change the frequency of relapses.
Patients with severe uveitis or CNS involvement respond to high-dose systemic corticosteroids (oral prednisone 60-80 mg bid/die). Posterior uveitis not responding to prednisone can be treated with azathioprine (50-150 mg per os once/day or cyclosporine 5 mg/kg per os once/day, increasing – if needed – to 10 mg/kg until a response is observed.

Cyclosporine levels should be maintained between 50 and 200 ng/mL. In refractory disease cyclophospamide and chlorambucil have been used; other treatments include: interferon alpha, thalidomide, pentoxifylline, etanercept, infliximab and PGE1 to improve perfusion.

CASE REPORT: *8 CASES WITH BE-SY USING PhytoRelief™-CC (Alchem)*

BE-SY is considered a rare immune-mediated small-vessel *systemic vasculitis* often presenting with mucous (oral) ulceration and ocular problems.

CASES IN THIS REPORT: 8 subjects (37.5;3.6; 5 females) with diagnosis of BE-SY were evaluated. Subjects' predominant problem was the presence of minor oral ulcerations and minor ocular problems (dry eye, redness).
At the moment of this registry evaluation subjects were not using any corticosteroid.

MANAGEMENT: for the oral ulcerations patients used PhytoRelief™-CC (Alchem, India) gummy tablets to dissolve slowly in the mouth 5 times/day for two weeks. Each gummy tablet included dantabija (polmgranate stone - Punica granatum) 20 mg, haridra (Curcuma longa) 50 mg, zingiber officialis 5 mg.

RESULTS. After 2 weeks of supplementary management with PhytoRelief™-CC a decrease in the number of ulcerations (from 14 to 4; $p<0.05$) was observed. Also a decrease in the apparent size of the ulcerations (-74.3%) was observed ($p<0.05$).
All patients described a significant, subjective decrease in symptoms (mainly pain due to ulcerations), on average -44.3% (measured on a analogue, visual scale line ranging from 0 to 100) ($p<0.05$) and an improvement in 'dry mouth' (-39.5%) ($p<0.05$).
Also in 6 out of 8 subjects eye dryness was subjectively improved (on a 0 to 10 symptom scale the decrease was on average from 7.4;1.1 to 3.4;2.1 at 2 weeks).
No tolerability problems or side effects were observed during the supplementation period.
A comparative sample of 6 subjects, also followed for 2 weeks and using different symptomatic products (excluding corticosteroids) did not show any decrease in the number of size of the ulcers or improvements at eye level.

Conclusion: an apparent, significant improvements (in mouth ulcers and eye dryness) were observed in these subjects who have very limited management options.
Larger and more prolonged studies may show the potential of this new supplement in BE-SY. The study is still in progress.

References

1. Luzzi R, Belcaro G, Pellegrini L, Cornelli U, Feragalli B, Dugall M. PhytoRelief™-CC: prevention of cold episodes. Control of signs/symptoms and complications. Minerva Gastroenterol Dietol. 2015 Oct 22.