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Herpes Viral Origin of the Parsonage-Turner Syndrome: Highlighting of Serological Immune Anti-Herpes Deficiency Cured by Anti-Herpes Therapy

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Key Words
Parsonage-Turner syndrome · Neuralgic amyotrophy · Bilateral phrenic paralysis · Neurotropic herpes virus occurrences · Appropriate anti-herpes therapy

Abstract
In 2012, a 50 year-old athletic male presented with weakness, pain and unilateral phrenic paralysis, followed by bilateral phrenic paralysis with deep dyspnea. In 2013, the Parsonage-Turner syndrome was diagnosed. When the patient was seen in September 2014 for the first time, he was facing phrenic neuromuscular failure, which led to the hypothesis of neurotropic herpes viruses. A control of the global serological anti-Herpes immunity to analyze his antibody (Ab) levels confirmed herpes immune genetic deficiency. An appropriate herpes chemotherapy treatment was proposed. Immediately, a spectacular recovery of the patient was observed, and after a few weeks, the respiratory function tests showed normal values. The hypothesis of the inductive role of viruses of the herpes family in the Parsonage-Turner syndrome was thus substantiated. The patient's immune deficiency covers the HSV2, HHV3, HHV4, HHV5 and HHV6 Ab levels. This led to the control of herpes in the family lineage: indeed, his daughter presented alterations of her serological herpes Ab levels.

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Introduction

Parsonage-Turner is a clinically defined neuralgic amyotrophic syndrome. Affected patients present a characteristic pain followed by flaccid paralysis of some muscles, with an incidence peak between 30 and 50 years of age and a slight male predominance. The etiology remains unknown [1]. 'Parsonage-Turner is notoriously unrecognized and is usually diagnosed with delay', as reported by Verhasselt et al. [2].

Case Presentation

Here we report the case of a 50-year-old athletic male who regularly participated in marathon competitions. In 2012, he presented with a unilateral phrenic paralysis, followed by a bilateral phrenic paralysis in 2013 that has persisted until today. The related clinical observations were a very deep dyspnea, disability to work, sleep disorder, neuropathic pain and weakness. In 2014, the Parsonage-Turner syndrome was diagnosed [3].

Respiratory function tests revealed a deep pulmonary deficiency; the patient's great weakness remains his inability to climb stairs [4]. The essential muscular respiratory exercises were followed daily with a physiotherapist. This patient, as all other adults with the Parsonage-Turner syndrome, has been followed for the past 2 years by neurologists, pneumologists and immunologists who attempted to identify the causes of the syndrome. At the beginning, the treatment was symptomatic. The patient was treated with corticosteroids, analgesic drugs and physical therapy.

He felt absolutely exhausted and hopeless when he was first seen in dermatological consultation to treat a facial skin tumor. It is important to underline that looking at the blood analysis, a lasting monocytosis of >10% (standard: 3–5%) for the last 2 years was a warning of a possible viral infection. As scientists involved in virology and immunology related to cancer research and facing a neuromuscular failure, this suggested the idea of the potential occurrence of a neurotropic virus, but what kind of neurotropic virus remained to be seen. Herpes viruses were the first eligible, since the sensory nerves are almost invariably the target cells, and motor neurons may be involved in herpes diseases. As the patient has never been to tropical areas, other rare exotic tropical neurotropic viruses such as rhabdoviruses, arenaviruses, flaviviruses, bunyaviruses, togaviruses and paramyxoviruses did not need to be considered further.

As stated recently by Marvisi et al. [5], 'viral infections have been identified as the most likely etiology and in some cases a genetic mechanism may be involved'. Gariani et al. [6], examining a herpetic rash with an acute left shoulder pain and a simultaneous limb monoparesis, attributed these features to the Parsonage-Turner syndrome and questioned: could it be a herpes zoster neuropathy? Chebbi et al. [7] described a similar relationship between varicella-zoster infection followed by weakness, sensory symptoms, motor deficits and pain; the Parsonage-Turner syndrome followed a varicella-zoster virus infection. Consequently, for the last 4 years, neurologists have postulated the involvement of herpes viruses in the Parsonage-Turner syndrome but without providing proof and/or anti-herpes therapy to cure this infection.

The diagnosis led to the hypothesis of herpes as a genetic immune deficiency. A serological evaluation was requested for all herpes viruses: human herpes virus 3 (HHV3), also known as varicella-zoster virus (VZV); herpes simplex virus 1 and 2 (HSV1/HSV2); human herpes virus 4 (HHV4), also known as Epstein-Barr Virus (EBV); human herpes virus 5 (HHV5), also known as cytomegalovirus (CMV); human herpes virus 6 (HHV6), also known

as roseolovirus, and human herpes virus 8 (HHV8) (table 1). Many large serological anomalies were found, confirming the hypothesis of a herpes genetic immune deficiency.

As a first step and awaiting the results of the herpes serological evaluation (1 week), the patient started a daily non-herpes-specific treatment: retinol DCI (vitamin A 313): 50,000 international units (IU) × 1 pill/day × 8 days; vitamin D3: 2,000 IU, 50 μg = 10 drops/day × 1 month, and niacinamide (vitamin B3): 500 mg × 1 pill/day × 3 weeks. One week later, after receiving the herpes viral serology results, the patient started the classical herpes chemotherapy with valacyclovir: 500 mg × 2 pills/day × 5 days (an equivalent chemotherapy as used below would be acyclovir: 200 mg × 5 pills/day × 5 days). After a few days of appropriate treatment, the patient reported that he was recovering day after day: 'for the first time after 2 years, I am able to drink a glass of wine' (very important for a French patient). Constant revival followed: his pain disappeared, he recovered his sleep and his breath and was able to climb stairs, experiencing week after week the pleasure of recovering his health after 2 years of terrible discomfort.

Discussion

It was necessary to focus on herpes as a genetic immune deficiency in the family lineage. The family history revealed that the father and mother did not have any kind of herpes disease. The patient's children, two girls and one boy (20, 15 and 12 years old, respectively), were examined. Only the 15-year-old girl presented alterations of the serological herpes balance as had her father; she started with a mononucleosis infection diagnosed in May 2014. She felt totally exhausted but received no treatment until her consultation at the dermatological office in September 2014. It was decided to control her genetic immune status with regard to herpes and to compare it with that of her father.

The serological herpes immunoglobulin G (IgG) blood controls showed the genetic immune deficiency of the father concerning the HSV/HHV antibody (Ab) levels for HSV2, HHV3, HHV4, HHV5 and HHV6. Differences between the father and his daughter were observed in particular in the IgG levels to the Epstein-Barr nuclear antigen (EBNA HHV4) and the viral-capsid antigen (VCA HHV4). The EBNA HHV4 IgG levels of the daughter were negative and unmodified by the infectious mononucleosis compared to her elevated VCA HHV4 IgG levels, while the father presented both elevated VCA and EBNA HHV4 IgG levels. Did this suggest that the daughter was unscathed of the genetic immune defect of the father?

Both the father and his daughter presented unusually high titers of anti-HHV3 Abs, although this Ab response was not neutralizing.

Concerning the HHV4 Ab levels, the father's serological IgG blood controls showed an unexpected genetic immune deficiency: the VCA IgG level was 727 IU/ml on September 3, 2014, and showed a very important decrease after anti-VZV therapy and vaccination. On October 22, 2014, the level decreased to an unexpected level of 46 IU/ml, but when repeated on December 17, 2014, the VCA IgG level was 701 IU/ml, thus similarly high as the level observed on September 3, 2014. The EBNA IgG level was elevated and remained unmodified due to administration of the anti-VZV therapy and the anti-VZV vaccination; before it, the level was 166 IU/ml and increased to 182 IU/ml. What is the prognosis of elevated HHV4? We do not know how the future of the patient holds for him.

The daughter already presented infectious mononucleosis in May 2014 but received no treatment. Compared to the father, there was an interesting difference between her EBV VCA and EBNA IgG Ab levels. The VCA IgG level was highly positive after two controls: 171 IU/ml (May 2014) and 282 IU/ml (September 2014), while the EBNA IgG level was negative when

controlled twice (3 IU/ml). The daughter with her mononucleosis infection has not been affected by the deep EBNA genetic immune defect of her father (table 1).

In October 2014, the prescription for the daughter was the same non-herpes-specific treatment as for the father: retinol DCI (vitamin A 313): 50,000 IU × 1 pill/day × 8 days; niacinamide (vitamin B3): 500 mg × 1 pill/day × 3 weeks, and anti-herpes chemotherapy with acyclovir: 1,000 mg/day × 5 days (usual dose). In agreement with the father, it was decided to propose anti-VZV vaccination 3–4 weeks later to enhance the efficiency of her herpes defense ability. Vaccination has to be followed by an anti-VZV booster vaccination [8] (according to the classical CDC Atlanta protocol for children) 3–6 months later. A few weeks after the treatment and anti-VZV vaccination, the adolescent quickly recovered.

At the end of October 2014, week after week, the father noticed the efficiency of the herpes disease treatment, which corroborated the assumption of the herpes viral etiology.

The most recent control of the respiratory function showed normal results compared to those of June 2014. On June 30, 2014, a bilateral diaphragmatic paresis respiratory control showed a 30% decrease in vital capacity. On October 24, 2014, checking this diaphragmatic phrenic nerve paralysis, the functional respiratory tests revealed a normal respiratory function.

Conclusion

Our results revealed a potential inductive role of members of the herpes virus family in the Parsonage-Turner syndrome. It is possible to conclude with a therapeutic proposal, which has proved successful in our patient. After the serological herpes Ab controls, a classical anti-herpes therapy was proposed. As a first step, acyclovir or valacyclovir to cure the herpes infection were administered. Three to four weeks later, anti-VZV vaccination to prevent any relapse of herpes infection was delivered given the genetic immune defect of the patient. One question still remains to be answered: is it possible to find a long-term cure to correct a herpes immunological defect? A booster anti-VZV vaccine has been proposed as a necessary complementary therapy 2–3 months later. In the future, the HHV3 and HHV4 serological Ab levels of the patient will be evaluated once a year, as they are early markers of all kinds of evolutionary diseases linked to herpes viruses.

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Disclosure Statement

None of the authors have conflicts of interest to disclose.

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Table 1. Serological IgG blood controls: immuno-luminometric assay (IU/ml)

	HSV1	HSV2	HHV3 VZV	HHV4 EBV	HHV5 CMV	HHV6	HHV8
Father (born in 1964) Parsonage-Turner: 2012–2015 September 3, 2014: no treatment	<0.9 (–)	>8.0 (+)	2,069 (++)	VCA 727 (+++) EBNA 166 (++)	90.3 (+)	20 (+)	(–)
October 7, 2014: anti-VZV vaccination							
October 22, 2014: after anti-VZV vaccination	<0.9 (–)	>8.0 (+)	3,133 (++)	VCA 46 (+) EBNA 182 (++)	101 (+)	40 (+)	(–)
December 17, 2014			2,339 (++)	VCA 701 (+++) EBNA 147 (++)			
Daughter (born 1998) May 9, 2014: infectious mononucleosis, no treatment				VCA 171 (++) EBNA 3 (–)	105 (+)		
September 29, 2014: no treatment	<0.9 (–)	<0.9 (–)	2,511 (++)	VCA 282 (+++) EBNA 3 (–)	124 (+)	40 (+)	(–)
November 11, 2014: anti-VZV vaccination 2015: serodiagnosis expected							

Analysis of the serological herpes Ab qualitative and quantitative values.
HHV3 (VZV) standard = ±1,500 IU/ml. Normal values related to the usual values. Positive to highly positive (++)/(+++) = higher values related to the usual values. (–) = Lower values related to the usual values. HHV4 (EBV): EBNA = Epstein-Barr nuclear antigen; VCA = Epstein-Barr viral capsid antigen.