Immunodeficiency and lymphoma in Jacobsen syndrome

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0777

Key words: Jacobsen Syndrome. 11q Deletion Syndrome. Immunodeficiency. Lymphoma. Hypogammaglobulinemia.

Palabras clave: Síndrome de Jacobsen. Síndrome deleción terminal del 11q. Inmunodeficiencia. Linfoma. Hipogammaglobulinemia.

Jacobsen syndrome (JS; ORPHA:2308) is a rare disorder with an estimated prevalence of 1 in 100,000 births and a female to male ratio of 2:1 [1,2]. First described by Jacobsen in 1973, JS commonly results from partial deletion of the terminal long arm of chromosome 11 (11q deletion). Clinical manifestations are diverse and are frequently associated with Paris-Trousseau syndrome, which is characterized by thrombocytopenia and platelet dysfunction [2]. The clinical presentation varies from growth and psychomotor retardation to severe facial dysmorphia, malformations of the heart, gastrointestinal, genitourinary, ocular, hearing, skeletal and/or central nervous system. Immunological and hormonal problems may also be present [2].

Here we report the case of a patient with dysmorphic features, mental impairment, Paris-Trousseau syndrome and transient immunodeficiency of childhood, who lived with a false diagnosis for many years.

doi: 10.18176/jiaci.0777

Our patient is the second child of a healthy non-consanguineous Swiss couple, with no relevant family history. He was born at thirty-two weeks following a pregnancy complicated by intrauterine growth restriction. In the first year, he presented with failure to thrive, delayed grow and thrombocytopenia in laboratory studies. He only started walking at the age of two and his language and speech development were significantly delayed, with consecutive intellectual disability requiring special educational support. He has short stature, dysmorphic features including bilateral ptosis, strabismus, long philtrum, thin lips, bilateral clinodactyly of the 5th finger and a limited elbow mobility that required surgical correction. Intravenous immunoglobulins replacement therapy (IRT, 0.4 g/kg/monthly) was given for recurrent infectious tonsillitis, otitis and bronchitis that required regular courses of antibiotic treatment from the age of eight until the age of twelve. Thereafter, no relevant infections were observed. At the age of forty-six he presented with dysphagia and tonsillitis resistant to antibiotic treatment. A biopsy of the right tonsil showed a non-otherwise specified (NOS) high-grade B cell lymphoma (CD20+ CD79a+, CD10+ and BCL6+, EBER-, CD30-, IRF4-, CD5- and PDL1), with a proliferation rate of the E3 ubiquitin-protein ligase MIB1 of 100%. PDL1+ tingible body macrophages without necrosis were found. MYC, Bcl-2 or Bcl-6 rearrangements were absent. Serological analyses for active viral infections herpes and varicella zoster, EBV, CMV, parvovirus B19, HIV, and hepatitis B and C were negative.

He received six cycles of R-EPOCH chemotherapy (rituximab 570 mg, etoposide phosphate 75 mg/m^2, prednisone 60 mg/m^2, vincristine sulfate 0.4 mg/m^2, cyclophosphamide 750 mg/m^2 and

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doxorubicin hydrochloride 10mgm^2), four cycles of intrathecal methotrexate (12mg) and two cycles of high dose intravenous methotrexate (3000 mg/m^2) over six months. At follow-up, a PET-CT scan confirmed a successful recovery from the lymphoma, but showed residual bronchiectasis, pulmonary infiltrates and ground glass opacities in the lower lobe of the left lung and the apex of the right lung. The patient suffered from recurring upper and lower respiratory tract infections requiring frequent antibiotic treatments.

The biological work-up revealed thrombocytopenia, hypogammaglobinemia, lymphopenia with low B-cell, CD4+ and CD4+gamma-delta T-cells (table, see supplementary file). Response to pneumococcal polysaccharide vaccination was absent. Monthly IRT (0.6 g/kg) was initiated: IgG through-levels normalized (10.9 g/l) after three months, and the patient reported no more infections. He is currently receiving IRT, and because of neutropenia and lymphopenia, he is receiving prophylaxis with atovaquone.

A diagnosis of Noonan syndrome has been assumed since infancy due to his dysmorphic features, short stature and thrombocytopenia, but this had never been confirmed by genetic testing. With the patient's and his legal guardian's consent, an array-CGH analysis was performed using Human Genome CGH Microarray Kit G3 180 (Agilent Technologies, Palo Alto, USA) with approximately 13KB overall median probe spacing. Labelling and hybridization were performed following the protocols provided by the manufacturer. Graphical

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overview was obtained using the Agilent Genomic Workbench 7.0.4.0. and data analysis was done with UCSC Genome Browser Human Genome build19.

The array-CGH analysis (Figure 1) revealed a heterozygous terminal loss of approximately 10.7Mb on chromosome 11, in the region q24.2q25 between positions 124,170,725 and 134,927,114bp, encompassing 52 Online Mendelian Inheritance in Man (OMIM) genes, including as *ETS1* (ETS Proto-oncogene, transcription factor), *NRGN* (Neurogranin, OMIM602350), with 18 OMIM morbid genes identified, such as *FLI1* (Friend leukemia virus integration 1, OMIM193067). Parental samples were not available.

The terminal loss on the long arm of chromosome 11, including at least five genes, *BSX*, *NRGN*, *ETS-1*, *FLI-1*, and *RICS (ARHGAP32)*, is compatible with JS (OMIM 147791).

JS has recently been recognized as a primary immunodeficiency [3-6]. It is often associated with recurrent respiratory, urinary and ENT infections [1]. JS presents with an antibody deficiency and impaired response to pneumococcal polysaccharide vaccination, or features of combined immunodeficiency. Late-onset of clinical symptoms of immunodeficiency have been reported. Antibiotic prophylaxis and IRT may be necessary to control recurring infection. Genes involved in immune regulation are suppressed in the 11q deletion syndrome. The deletion on chromosome 11 in our patient comprised 52 OMIM genes including 11 genes of pathological significance such as the ETS1, NRGN and FLI-1; a proto-oncogene involved in platelet functions whose deletion is associated with Paris-Trousseau syndrome. ETS-1 knockout in

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mice show significant defects in T, B, and NK cell development. Based on the patient's medical history, including recurrent infections requiring antibiotic treatment and IRT from age eight to twelve, we assume that the patient already suffered from immunodeficiency during childhood. We further hypothesize that chemotherapy led to an exacerbation of this immunodeficiency. Unfortunately, laboratory values prior to chemotherapy treatment were not available.

While there are no reports available on the association between JS and neoplasia in the literature, 11q deletions have been associated with myeloid and lymphoid neoplasia, especially Burkitt-like (MYC-negative) tumors [7]. ETS-1 may play a role in malignant transformation of hematopoietic neoplasms, including B-cell malignancies [8]. The occurrence of these 2 unusual diagnoses (JS and B-cell lymphoma) could be incidental, but an association between chromosome 11q deletion and malignancies is plausible [7,9,10].

We believe that JS patients should be screened for immunodeficiency at diagnosis and during follow-up to prevent recurring infections. A high degree of vigilance is required due to the elevated risk of Burkitt-like lymphomas in patients 11q deletion.

doi: 10.18176/jiaci.0777

Acknowledgements

We thank Emily Wymer for corrections and edits.

Financial Disclosures

All the authors report no disclosures/conflict of interest relevant to this manuscript.

Poster presentation

Swiss Society for Allergology and Immunology (SGAI-SSAI), 19-20 August 2021

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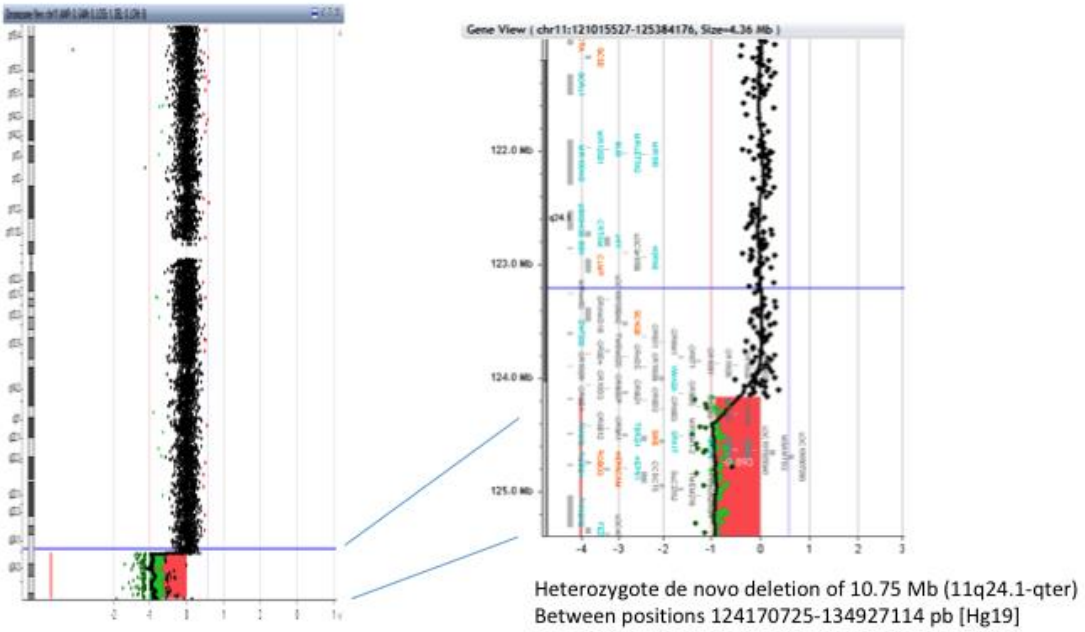
doi: 10.18176/jiaci.0777

FIGURE

Figure 1. Array-CGH analysis showing a heterozygous terminal loss of approximately 10.7Mb on chromosome 11, in the region q24.2q25.



doi: 10.18176/jiaci.0777