Lhermitte-Duclos Disease caused by a novel germline PTEN mutation R173P in a patient presenting with psychosis

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Running title: R173P mutation in LDD

Keywords: Lhermitte-Duclos, PTEN, schizophrenia

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This is an Accepted Article that has been peer-reviewed and approved for publication in the Neuropathology and Applied Neurobiology, but has yet to undergo copy-editing and proof correction. Please cite this article as an "Accepted Article"; doi: 10.1111/j.1365-2990.2009.01041.x
Due to the common replacement of the inner granular layer or its most superficial region by hypertrophic ganglion cells, it has been hypothesized that aberrant granule cell migration and hypertrophy may play a role in Lhermitte-Duclos disease (LDD), while cell proliferation apparently does not. The abnormal neuronal cells send their hypertrophic and hypermyelinated axons into an enlarged molecular layer and may thus represent hypertrophic granule cells\textsuperscript{1,2}. Mitoses have not been found in these cells. Despite the benign nature of LDD, surgical excision appears to be the only effective treatment to relieve the symptoms\textsuperscript{2}, such as headache, dizziness, vomiting, tremor, ataxia, unstable gait and seizures. Sometimes LDD occurs in the context of Cowden syndrome (CS), an autosomal dominant hamartoma tumour syndrome, with a high risk of malignant tumours\textsuperscript{3}. Therefore, patients have to be monitored for additional lesions, indicating the development of CS.

Germline mutations in \textit{PTEN} (\textit{Phosphatase and TENsin homolog deleted on chromosome TEN}), on 10q23.3, are found in 80-85\% of individuals with CS\textsuperscript{4,5}. PTEN is a tumour suppressor dual-specificity phosphatase. Its lipid phosphatase activity antagonizes the action of PI3-kinase (\textit{phosphoinositide-3 kinase}), which activates the kinase Akt. Akt promotes proliferative, anti-apoptotic and pro-survival pathways\textsuperscript{6}. In an unselected series of 18 patients presenting with LDD, 15, all adults, were found to carry \textit{PTEN} mutations\textsuperscript{5}. At least 4 with \textit{PTEN} mutations only had LDD, without other clinical features of CS. All 18 presented with cerebellar signs and/or signs consistent with space occupying lesions. In the present study, we describe a patient with LDD and a novel germline \textit{PTEN}-mutation presenting with psychosis.

The 42-year old woman had a 12-year history of several admissions to the department of psychiatry of Magdeburg University. She suffered from mild mental retardation, alcohol addiction and frequent suicidal ideation and attempts. In 2005, paranoid schizophrenia was diagnosed because of acoustic hallucinations, i.e.
imperative voices telling her to perform suicide. In 2008, she was readmitted to the department after a suicide note was found. She complained about episodic headache, nausea, drowsiness and dizziness with a tendency to fall, and still suffered from alcohol addiction.

She was obese, macrocephalic and had a neglected appearance. Hirsutism, multiple cutaneous facial papules and a papillomatous growth on the tongue were observed during examination of skin and mucosa. Palmoplantar keratosis and verrucoid papules were present on dorsal hands and feet. A scar from thyroid goitre resection was visible. No abnormal distortions, swelling or nodules were found in the breasts (mammography was refused). Apart from hypertension, no cardiovascular abnormalities were detected. Examination of the respiratory, gastrointestinal and genitourinary system showed no pathological findings. Apart from suspected swelling of the optic papillae, neurological examination showed signs of cerebellar ataxia, such as a dysmetric finger-nose / heel-shin test, dysdiadochokinesia and a negative Romberg’s test. Psychiatric assessment found mild to moderate death thoughts, suicide ideation, affective lability and dysphoria. Acoustic hallucinations with imperative voices were present again. The family history was positive for mood disorders (mother suffered from major depressive disorder). However, typical features of CS were absent in parents, brother and son.

Brain MRI revealed a space occupying mass in the cerebellum with early obstruction of the fourth ventricle and signs of increased intraventricular pressure (Figure 1A). The lesion was successfully removed in the neurosurgery department. Histology revealed a dysplastic gangliocytoma (Figure 1B). After resection, headaches as well as the suicidal syndrome with affective lability and psychotic symptoms remitted, while ataxia remained unchanged. Clinical follow-up examination after five, ten and
fifteen months showed a stable remission of psychiatric symptoms without further need for antipsychotic or antidepressant medication.

*PTEN* sequence analysis revealed a G-C-transversion at nucleotide position 110111 of the reference sequence (GenBank entry GI 4240386), which was also present in the corresponding blood sample (Figure 1C). It leads to the substitution of an arginine in codon 173 (exon 6) by proline (R173P). Analysis of the flanking microsatellite D10S541 (Figure 1C) with the 6-FAM labelled forward primer 5’-CACAGACATCTCACAACC-3’ and the reverse primer 5’-GTGAATAGTTCCAGGGATGG-3’ revealed no deletion. Pyrosequencing of the promoter region detected no methylation at any of the five CpG sites analyzed (data not shown). Immunohistochemical investigations showed strong retained PTEN expression in the tumour, as well as increased cytoplasmic and nuclear phospho-Akt immunostaining in dysplastic ganglion cells (data not shown).

The substitution R173P has not been previously associated with CS/LDD. Although arginine 173 is frequently lost by somatic PTEN-mutations in glioblastomas and endometrial cancers, it is not typically affected in CS/LDD. At least one case of a 13-year old boy with CS had been described to harbour the substitution R173C. Even as a somatic mutation in glioblastomas and endometrial cancers, the observed exchanges were usually R173C or R173H. It should be recognized that codon 173 is neither located in exon 5, harbouring the catalytic domain and more than 40% of PTEN germline mutations, nor in the C-terminal exons 7 and 8. Together with exon 5, the latter comprise about 67% of all germline mutations in individuals with CS. However, *in-vitro* mutagenesis of codon 173 and expression of the proteins in E. coli revealed a complete loss of lipid phosphatase activity towards the substrate Ins(1,3,4,5)P₄ for all of the above mentioned mutations in that codon. Functional elimination of PTEN may thus up-regulate the target Akt, which in turn may stimulate
mTORC-1 (target of rapamycin complex 1), a key regulator of protein biosynthesis and cell growth. The kinase complex mTORC-1 may be associated with cell enlargement in LDD. Although recurrence may sometimes occur even after resection of a dysplastic cerebellar gangliocytoma, there is no profound need for pharmacological intervention to supplement surgical therapy, as long as the gangliocytoma remains the only disease manifestation. To ensure this, a long term follow-up is recommended. However, mTOR-inhibitors like temsirolimus may be of some interest in CS. Recently, a mouse model was established, which expressed a PTEN deletion associated with multiple tumours. The mTORC-1 inhibitor rapamycin promoted rapid regression and halted the development of CS-like lesions, when administered prior to disease manifestation\textsuperscript{11}.

According to our knowledge, alcohol dependency, chronic suicidality, psychosis or other psychiatric diseases have thus far not been associated with CS/LDD. The psychiatric disease, however, cannot be conclusively attributed to the mutation, although enhanced intracranial pressure due to constriction of cerebrospinal fluid flow may explain psychotic symptoms\textsuperscript{12}.

\textit{Acknowledgements:} We gratefully acknowledge the excellent technical assistance of Mrs. Ines Schellhase.
**Figure legends:**

**Figure 1A:** Magnetic resonance imaging (MRI) shows an inhomogeneous, non-enhancing tumour mass in the cerebellum with compression of the fourth ventricle and T2-weighted hyperintense (a) and T1-weighted hypointense appearance (b).

**Figure 1B:** Histopathology of dysplastic gangliocytoma.  
- **a** The internal granule layer of the cerebellum (upper part) is filled with dysplastic ganglion cells (H&E). In the molecular layer there is extensive vacuolation of the tissue seen (asterisk).  
- **b** Higher magnification shows irregular arranged dysplastic ganglion cells in the granule layer (H&E)

**Figure 1C:**  
- **Left panel:** Sequence flanking codon 173 of PTEN exon 6, showing a G-C-transversion (stars) in blood and gangliocytoma, leading to the substitution R173P.  
- **Right panel:** The ratio of peak areas for the two alleles of the marker D10S541 (blue), obtained by fluorescent PCR, was identical (1.3) in blood and gangliocytoma. Peak areas were determined by the sequencer software. The smaller red peaks represent markers of fragment length.
References


