

THE IMPACT OF EPIDEMIOLOGICAL, CLINICAL AND RADIOLOGICAL CHARACTERISTICS ON THE OUTCOME OF INFANTILE AND CHILDHOOD ENCEPHALITIDES

PhD Theses

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INTRODUCTION

Encephalitis is an inflammatory disorder of the brain parenchyma manifesting with neurological dysfunction. It is usually caused by infectious agents, mostly by viruses. The neurological dysfunction can be: cognitive dysfunction (e.g. acute memory loss, speech disturbance), mental change (disorientation, hallucination, psychosis, personality change, agitation), focal deficit, seizures.

The diagnosis is based on the clinical picture, and is supported by modern investigations such as MRI or microbiological diagnostics. All these however, cannot replace the experienced clinician who has to decide on treatment and make rational plans of diagnostic workup.

The inflammation of the brain parenchyma can be the result of direct infection (**infectious encephalitis, IE**), of a postinfectious, immune-mediated process (**acute disseminated encephalomyelitis, ADEM**), may manifest as paraneoplastic syndrome, or is - rarely - caused by other immune mechanisms. Though clinical picture is similar in most cases, the above pathomechanisms are worth to be differentiated in favour of appropriate treatment.

The **pathomechanism** of a neuroinfection is the result of a complex interaction between the infectious agent and host cells. Most viruses reach the nervous system by haematogenous whilst others (rabies virus, some herpes viruses) mainly by neural spread. The arboviruses are inoculated in the skin by arthropods (tick, mosquito), then they invade and infect the nervous system by the bloodstream.

The viruses can lead to neurological symptoms either by direct damaging of neurons or by influencing neuronal functions via modification of the host immune mechanisms. The spectrum of neurological signs and symptoms depends on neurovirulence and neurotropism of the virus on one hand and on host immune response on the other.

Some viruses cause a disease via immune mechanisms (**ADEM**).

Limbic encephalitis (LE) is the result of an immune process, too. First it was taken solely to a paraneoplastic syndrome, based on the immunological similarity of certain tumour antigens and neural cells. The majority of the paediatric cases however, are non-paraneoplastic.

IE is most often caused by viruses, less often by other **microorganisms**. The infectious agent is dependent of geographical region, climate, vaccinations and of the occurrence and density of vectors. Most of them may cause disease in anyone, while some agents - certain herpes viruses, the JC virus (JCV), *Toxoplasma gondii* – result in neuroinfection primarily of immunocompromised hosts.

Most ADEM cases are preceded by upper respiratory or enteric infections of unidentified origin, or – rarely – by immunizations.

The **incidence** of encephalitis is 1.9-7.4 per 100 000, being 1.27/100 000 inhabitants per year in Hungary in 2009. It is more frequent in children. ADEM represents 2 to 15% of all acute encephalitides.

IE is preceded in most cases by unspecific symptoms (**prodroma**) such as malaise, loss of appetite, chills, nausea, vomiting, abdominal pain, diarrhoea, headache, cough, rash, joint or muscle pain. A biphasic course is typical of enteroviruses (EV) and the tick-borne encephalitis (TBE) virus: the febrile prodroma is followed by an afebrile period lasting a couple of days, then neurological symptoms develop with concurrent fever. The peculiarities of the prodroma may help identifying the microorganism. In ADEM the medical literature rather uses the term preceding event (that triggers immune mechanisms) instead of “prodroma”. This occurs in a half to one third of cases. Neurological symptoms follow in 2 to 30 days.

Encephalitis is typically a triad of **fever, headache and disturbed consciousness/mental change** that may be accompanied by **seizures and focal deficits. Motor dysfunction** (palsy, extrapyramidal movement disorder, tremor) occurs in a quarter of cases, but **ataxia, cranial nerve signs and speech disturbance** may be present, too. The **autonomic nervous system, the hypothalamus** may also be involved. **Intracranial hypertension** can develop. Some microorganisms result in specific neurological symptoms. Focal or multifocal neurological symptoms and encephalopathy preceded within 30 days by viral infection or immunization is typical of ADEM.

AERRPS (acute encephalitis with repetitive refractory partial seizures) was first described in 1989. Its diagnostic criteria: an acute phase lasting for at least 2 weeks, repetitive, refractory, similar partial seizures with frequently occurring status epilepticus from the acute phase to convalescence, and lack of a specific etiology.

EEG is a sensitive indicator of cerebral function. It is usually abnormal early and shows episodic or continuous, focal or generalized slow activity with or without epileptic discharges. It is rarely typical of the underlying pathogen however, in one third to a half of herpes simplex virus (HSV) encephalitis (HSE) cases periodic lateralized epileptic discharges (PLED) can be seen.

MRI is highly sensitive even in the early stage. It should be carried out in the presence of focal deficits, severe or progressive symptoms! It is also useful in excluding other conditions. The MRI abnormalities may refer to the pathogenic role of certain microorganisms. In the first days of ADEM MRI can be normal however, later it becomes abnormal in 100% of cases: focal or multifocal, ill-defined hyperintense lesions of irregular shape are seen in the brain and often in the spinal cord. Radiological follow-up is indispensable, and complete or partial resolution of lesions is seen within 3 to 6 months in ADEM. In LE areas of increased T2 signal are found in the hippocampi and amygdalae, sometimes also in the hypothalamus and the striatum.

CSF cell count is mildly elevated in more than half of both IE and ADEM cases. First granulocytes, whereas later lymphocytes predominate. Red blood cells are found in the CSF of approx. 20% of cases, especially in HSE. CSF protein is increased in a quarter, while IgG/albumin ratio in 25-50% of cases. A normal CSF does not exclude encephalitis!

Microbiological investigations should be rationally tailored upon epidemiological data, immunological and vaccination status of the patient as well as on clinical, radiological and EEG findings. A definite microbiological diagnosis relies upon the detection of the pathogen in central nervous system sample. Investigation of any other sample (throat or nasal swab, blood, faeces) can make the pathogen probable. Evaluation of **serological tests** needs caution and experience. Some microbes are diagnosed upon specific IgM found in the serum. The detection of seroconversion is often time-consuming but very important from the point of view of retrospective diagnosis. The specific IgM against some viruses can be detected in the CSF, too. **Polimerase chain reaction (PCR)** has become part of the routine diagnostics. PCR examination of the CSF has replaced brain biopsy in diagnosing HSE. PCR positivity is most likely detected on day 4 to 7 of symptoms when the virus temporarily enters the CSF space. It is worth to use both PCR and serology. **Viral culture** is labor-intensive and time-consuming but often of diagnostic value in cases of enteroviral (EV) etiology.

Specific treatment is necessary in HSE, and it comes up in encephalitides caused by other viruses, Mycoplasma pneumoniae or other bacteriae. High-dose

methylprednisolone pulse therapy as well as plasma exchange or high-dose intravenous immunoglobulin are regarded as causal treatment in ADEM.

To alleviate **intracranial hypertension** mannitol and furosemide can be administered, mechanical hyperventilation and – in case of imminent herniation - decompressive craniectomy may be undertaken. Phenytoin or other anticonvulsants can be given to stop or prevent seizures. **Respiration, circulation and fluid balance** has to be monitored and supported. **Thrombosis** of the deep veins, disseminated intravascular coagulation, **aspiration pneumonia, secondary bacterial infections and gastrointestinal bleedings** are to be avoided.

With the wide-spread use of measles-mumps-rubella **vaccination** encephalitides caused by these viruses have become preventable. Immunisation can prevent further diseases such as TBE, varicella-encephalitis, rotavirus encephalopathy, rabies or japanese encephalitis.

Prognosis depends on the pathogen, the host immune status, the symptoms and on whether a specific treatment is available. 69-90% of patients recover with minimal or no sequelae. **Postencephalitis epilepsy (PE)** develops in as much as 16% of patients or in a larger proportion of those having seizures in the acute stage. Hippocampal sclerosis resulting in mesial temporal lobe epilepsy may in part be related to viral encephalitis. The shorter the latency of developing PE, the less favourable is its outcome. PE patients often have cognitive deficit. **Motor dysfunction** is expected in 4-40%, **cognitive and/or behaviour disturbance** – depending on the testing method – in 4-50% of ADEM patients, whereas the risk of **multiple deficits** is 9%.

Relapses are not typical of IE however, they are known to occur in HSE. New demyelination event occurs in 8-30% of ADEM patients and it can be either recurrent ADEM, multiphasic ADEM or multiple sclerosis.

The **mortality rate** of encephalitis is 1 to 12%.

AIMS OF THE PRESENT STUDY

I was seeking answers to the following questions:

- What is the frequency and outcome of childhood encephalitis in the leading infectious diseases hospital of Hungary?
- What is the frequency of IE and ADEM, respectively?
- What is the morbidity and mortality of encephalitis?
- What are the differences between the clinical picture and the outcome of IE and ADEM?
- In what proportion of cases can a microbiological diagnosis be verified?
- What is the frequency of certain microorganisms?
- Do clinical, electrophysiological, radiological findings and outcome differ according to the underlying pathogens?
- How do clinical, electrophysiological and radiological findings influence the outcome?
- What are our findings like compared to literature data?

PATIENTS AND METHODS

I analysed data of patients less than 18 years of age treated for encephalitis between 1998 and 2009 at the Departments of Paediatrics, Paediatric Intensive Care, Paediatric Haematology and Bone Marrow Transplantation and Paediatric Neurology Outpatient Service of Szent László Hospital, Budapest.

To diagnose encephalitis I simultaneously used criteria proposed by several authors if conditions resulting in similar clinical picture could be excluded. I established the diagnosis of encephalitis, if **≥1 of the following** signs revealing dysfunction of the brain parenchyma was present: encephalopathy, seizure(s), paresis, ataxia, **plus ≥2 of the following**: fever, abnormal CSF findings, microbiological proof of infection, abnormal EEG, CT or MRI typical of encephalitis.

I personally took case histories of all patients. In the majority of them the first neurological exam was also done by myself. I documented epidemiological, clinical data, results of complementary investigations and followed-up the patients after their discharge for as long as I could.

Microbiological tests were performed in the Microbiological Labs of Szent László Hospital and of the National Centre of Epidemiology, respectively.

Immunofluorescent assays (IFA) for HSV and EV were routinely performed from both serum and CSF samples, as was HSV PCR from 2003 onwards and viral culture from CSF, throat swab and faeces until 2008. When clinically suspected serum and CSF IFA for adenovirus, Epstein-Barr virus (EBV), varicella-zoster virus (VZV), parainfluenzavirus (PIV), TBEV as well as complement fixation test for *Mycoplasma pneumoniae*, influenza viruses, ELISA (enzyme-linked immunosorbent assay) for cytomegalovirus (CMV), and – in immunocompromised patients - multiple PCR for the following microbes were undertaken: HSV1-2, VZV, EBV, CMV, human herpesvirus 6 (HHV6), *Toxoplasma gondii*, JCV. At one patient with cerebral toxoplasmosis PCR had to be done on brain biopsy specimen, too. When rotavirus encephalopathy was suspected, antigen test from faeces was performed.

I established the **definite pathogenic role** of a microorganism if

- encephalitis was in relation with a prodroma obviously attributed to that microbe (varicella, rotavirus enteritis, leptospirosis),
- specific antibodies were detected both in serum and CSF,
- the pathogen could either be cultured or detected by PCR from the CSF,
- the pathogen could be detected in biopsied central nervous system tissue.

I established the **probable pathogenic role** of a microorganism if

- an acute neurological syndrome followed exanthema subitum (HHV6),
- specific antibodies were solely detected in serum, but either IgM and/or IgA revealing recent infection were present or a 4-fold rise in the titre of specific IgG was found in the convalescent sample,
- the pathogen could be cultured or detected by PCR from extraneural sample (throat swab or faeces) but not from the CSF.

EEG recordings were made by a 16-channel computerised equipment of the Szent László Hospital EEG Lab, or at the Paediatric Intensive Care Department by a 16-channel computerised, portable device. All recordings were analysed according to uniform regards.

Abnormal EEG changes were classified as follows: mild to moderate diffuse dysfunction, severe diffuse dysfunction, focal change, paroxysmal sign, periodicity (PLED).

Cranial CT scans were performed at Heim Pál Children's Hospital, at Szent István Hospital or in the referring institute. Cranial and spinal **MRIs** were carried out by 1,0 and 1,5 T MR devices of Budapest MÁV Hospital, National Institute of Psychiatry and Neurology, Szent István Hospital, Semmelweis University Central Radiology Diagnostics, respectively; whereas from May 2006 onwards by the 3,0 T equipment of Semmelweis University MR Research Centre. I reviewed all images,

and if my opinion differed from that of the radiologist, I proposed personal discussion or consulted with a neuroradiologist.

Absolute and relative frequencies of data concerning qualitative clinical characteristics and neuroimaging were estimated. The majority of continuous variables (e.g. hospital days, laboratory parameters) are of non-normal distribution, thus their medians and quartiles, in some instances the min-max. values are given. Statistical comparisons were made in these cases by the Mann-Whitney probe. Comparison of qualitative data was done by the chi-square and z-probe, or – in case of low frequencies – by the Fisher's exact-test. Statistical comparisons were performed by two-sided probes on $p < 0.05$ significance level, whereas at multiple comparisons, to make significance level more strict, the Bonferroni method was applied. The role of the analysed clinical, laboratory and radiological attributes in the outcome of the disease was examined by uni- or multivariate logistic regression. The odds ratio (OR), the 95% confidence interval (95%CI) and the significance level is communicated. In case of multivariate logistic regression the stepwise (forward) method was also used.

RESULTS

In the 12-year-period 178 children were treated at Szent László Hospital for **179 encephalitis episodes**. This represented 0.2% of the patient turnover of the Paediatric, while 5% of that of the Paediatric Intensive Care Department. **47% of all children communicated with encephalitis in Hungary** were treated at our hospital. 3 patients were immunocompromised. The median age of patients was 7 y, the ratio of infants and toddlers was 12 and 12%, respectively. The ratio of boys was 57%. 103 patients (**57%**) required **intensive care**.

85% of patients had **IE**, **13%** had **ADEM**. 3 patients (1 LE, 2 Kawasaki syndrome) had a different immune mechanism in the background.

In **68%** of cases related to infection (IE and ADEM) the **infectious agent was found definite (40%) or probable (28%)**. 16% of the verified pathogens was HSV, 38% was EV, 11% was VZV, 7 and 7% were TBEV and adenovirus, respectively. There were cases related to rotavirus, EBV, CMV, HHV6, influenza A virus, PIV, JCV, T. gondii, M. pn., Leptospira and diphtheria-pertussis-tetanus vaccine.

Special diseases: In a 14-y-o girl the clinical picture corresponded to **AERRPS** (acute encephalitis with refractory, repetitive partial seizures), a severe syndrome of unknown pathomechanism however, EV-specific IgM, IgA and increasing amount of IgG was detected in her serum. A 9-y-o boy was diagnosed with **devastating epileptic encephalopathy in school-aged children (DESC)**. Three patients had **LE**. In 2 of them causative role of HSV was proved, in 1 case no etiology was found in the acute stage, but later she developed an autoimmune disease (SLE). An adolescent AIDS patient had **progressive multifocal leukoencephalopathy (PML)**. Four children had **bilateral striatal laesion (BSL)**, a peculiar form of ADEM, where both clinically and radiologically bilateral involvement of the striatum predominates: cessation of verbal communication, negativism, whining cry, extrapyramidal rigour, sometimes dystonia is present. In 3 of these cases etiological role of varicella was proven. An adolescent girl with adenovirus encephalitis developed reversible lesion in the callosal splenium, which corresponded to the clinical and radiological entity of **mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)** described in 2004 by Japanese authors.

In 65% of patients (more often in ADEM) neurological symptoms were preceded or followed by a **prodroma**. In ADEM focal deficits, confusion and severe disturbance

of consciousness were more common than in IE. Seizures occurred more often in encephalitis caused by HSV than by other pathogens. Paresis, pyramidal signs, speech disturbance and ataxia were more typical of VZV.

While “routine” testing of the **CSF** (protein, glucose and cell count) was abnormal in 72%, the examination with estimation of protein ratios was abnormal in 85% of patients. Peripheral blood WBC and IgG/albumin ratio was significantly higher in ADEM as compared to IE, which may reflect more marked systemic inflammation and intrathecal humoral immune reaction. CSF protein was significantly higher in HSE as compared to EV encephalitis.

EEG was abnormal in 93% of cases. Severe diffuse dysfunction occurred more often in ADEM than in IE. Seven of the 8 patients showing periodic EEG changes (PLED) had HSE, and PIV was the pathogen in one. Only 35% of HSE cases had PLED. Both focal, paroxysmal changes and PLEDs were more common in HSE than in cases of other etiologies.

Central nervous system imaging (echography, CT or MRI) was performed in 77% of patients. Cranial CT scan was abnormal in 41 of 93 cases (44%), whereas MRI showed abnormalities in 61 of 96 (63%). CT was followed by MRI in 56 patients, and proved abnormal after a normal CT scan in 24 (43%)! MRI more often showed pathologies in patients who had multiple seizures. CT scan was abnormal in 50 while the MRI in 96% of ADEM cases. These proportions were 44 and 53% for IE. I found significant differences so between ADEM and IE as among the most frequent 3 pathogens (EV, HSV, TBE) in regard to certain MR abnormalities.

58% of all and 79% of ADEM patients required **intensive care**. The median duration of it was 11 while that of the overall hospital stay was 13 days. In ADEM patients these were 17 and 24 days, respectively. There was a higher likelihood of an HSV patient to require intensive care and for a longer duration, in contrast to patients with EV, VZV or TBE encephalitis.

Acyclovir **treatment** was administered in 47% of patients - for a median of 9 days and for a median of 20 days in patients with proven HSE. The 2 patients with toxoplasmosis were given clindamycin, sulfadiazin, pyrimethamin and co-trimoxazol. High-dose methylprednisolone pulse therapy was applied in 22 cases; besides ADEM patients one with LE and – of different considerations - 6 IE patients. 3 ADEM patients responded unsatisfactorily to methylprednisolone, thus in them plasma exchange was added. High-dose intravenous immunoglobulin (IVIG) was given to 5 children (2 with Kawasaki disease, 1 with AERRPS, 1 with encephalitis+Guillain-Barré syndrome and 1 with ADEM). Medical dehydration with mannitol or/and furosemide was used in 134 (75%). In 4 patients decompressive craniectomy was also carried out and was life saving in one. 43 patients (24%) were given – often combined - anticonvulsive therapy. Occipital lobe resection was performed because of intractable seizures in the girl with AERRPS, unfortunately with no effect. 60 patients (33%, or 58% of those requiring intensive care) needed mechanical ventilation, for a median of 7 days. Respiratory insufficiency was more likely in cases with HSV etiology, severely disturbed consciousness, seizures, severe dysfunction, paroxysmal and periodic changes of the EEG and abnormal MRI. Mechanical ventilation was of significantly longer duration in cases with focal and/or periodic EEG changes, abnormal MRI and CSF result.

Mortality was 3% (6 patients). Of the surviving 172 I could follow-up 169 patients. **71%** of patients **completely recovered**.

Sequelae (26%) occurred more often after ADEM than after IE, following severely disturbed consciousness, seizure(s), severe diffuse dysfunction, focal, paroxysmal and periodic changes of the EEG and abnormal MRI.

Motor dysfunction (8%) was more likely following HSE, while severe motor dysfunction occurred more often in patients less than one year of age, in those with repeated seizures, focal, paroxysmal EEG signs or abnormal MRI.

Cognitive dysfunction (20%) was more frequent after ADEM and HSE, severe disturbance of consciousness, seizure(s), or when WBC was less than 10,0 G/L, CSF protein was increased or the MRI was abnormal. Patients under 1 year of age, those without focal deficits, with multiple seizures, focal or paroxysmal EEG changes were more prone to moderate to severe cognitive dysfunction.

The median latency of developing **epilepsy** (14%) was 78 days and postencephalitic epilepsy (PE) was more likely to be severe after shorter latency. PE occurred more often in case of acute seizure(s), severely disturbed consciousness, WBC lower than 10,0 G/L, severe diffuse dysfunction, focal and paroxysmal EEG changes. PE was more likely to be severe in patients less than 1 year of age, those with HSV etiology and focal deficits.

Multiple handicap (11%) was more frequent following HSV etiology, in patients less than one year old, in those with severely disturbed consciousness, WBC less than 10,0 G/L, repeated seizures, severe dysfunction, focal, paroxysmal and periodic EEG changes or abnormal MRI.

Relapses occurred in 2 ADEM patients (1 multiphasic ADEM, 1 multiple sclerosis) and in 1 infant with HSV encephalitis.

The most important predictors of **unfavourable outcome** (sequelae and death) were: immune pathomechanism (ADEM), HSV etiology, severe disturbance of consciousness, focal seizures, paresis, pyramidal signs, WBC<10,0 G/L, paroxysmal EEG changes, cortical, subcortical abnormal signal on MRI.

SUMMARY OF THE MOST IMPORTANT RESULTS

1. Combining recommendations of several authors I introduced **unified criteria** to establish the diagnosis of encephalitis.
2. In the study period of 12 years I saw a **high number of encephalitic children**, approximately one half of the patients communicated throughout the country. The majority of patients could be followed-up. Complex clinical, epidemiological, electropysiological and radiological analysis of such a high number of encephalitic children has not been carried out in Hungary before.
 - 2.1. 2% of our patients were immunocompromised.
 - 2.2. 85% of cases were of infectious (IE), whereas 15% were of immune pathomechanism.
3. The **infectious cause** or trigger could be **verified or made likely in two thirds** of cases: a high proportion even compared to international data.
 - 3.1. 38% of these were *enterovirus*, what is very high compared to international data and may be a local particularity.
 - 3.2. In the ADEM group the participation of *varicella-zoster virus (VZV)* as a trigger was outstanding - 25%.
4. I have diagnosed some **special conditions**:

- 4.1. The ADEM cases related to varicella included 3 children whose clinical picture corresponded to *bilateral striatal laesion (BSL)*. The likely causal relationship between this peculiar clinico-radiological entity and varicella has been first described by me.
- 4.2. I diagnosed *acute encephalitis with refractory, repetitive partial seizures (AERRPS)* in a 14-y-o girl. According to serological tests enterovirus might have had an etiological role.
- 4.3. I established and published *progressive multifocal leukoencephalopathy (PML)* in an adolescent AIDS patient.
- 4.4. I diagnosed the rare syndrome of *mild encephalitis/encephalopathy with a reversible splenial lesion (MERS)* in an adolescent girl with adenovirus-encephalitis.
- 4.5. So the presence and characteristics of the prodroma as the general signs are incapable to differentiate between **IE and ADEM** however, confusion, severe disturbance of consciousness and some focal deficits are more typical of ADEM than of IE.
5. **Clinical signs typical of certain microbes:** seizures rather characterize HSV and EV encephalitis, whereas paresis, pyramidal tract signs, speech disturbance and ataxia are more common in VZV encephalitis.
6. Adding **IgG/albumin ratio** to “routine” CSF testing decreased “negative CSF results” to nearly the half.
7. **WBC and IgG/albumin ratio** was **higher in ADEM** than in IE.
8. I introduced **MRI in routine workup** of more severe cases, relying upon which both immune therapy of ADEM and antiviral treatment of HSE is started at an earlier stage.
9. **More than half of the patients required intensive care**, especially ADEM and HSE patients.
10. **Risk factors of respiratory insufficiency were** HSV etiology, abnormal MRI, certain EEG changes particularly periodicity. ADEM, focal and periodic EEG changes, abnormal MRI and CSF predisposed to a more lengthy course of mechanical ventilation.
11. Due to severe intracranial hypertension 4 patients underwent **surgical decompression**, which is not routinely applied in encephalitis. One patient could be saved by it, thus we recommend immediately performing it in all cases of intracranial hypertension not responding to conservative treatment, even in patients with encephalitis.
12. **Morbidity:**
 - 12.1. *In cases of ADEM, severely disturbed consciousness, seizures, severe dysfunction, focal, paroxysmal or periodic EEG changes, abnormal MRI* made sequelae more likely.
 - 12.2. The most severe sequelae occurred more frequently following encephalitis in *infancy*.
 - 12.3. All patients with encephalitis due to *Mycoplasma pneumoniae* recovered completely.

- 12.4. The *latency of postencephalitic epilepsy was inversely related to its severity*. This has been previously established by only two groups, based upon experiences with markedly smaller number of patients.
- 12.5. Patients with *brainstem symptoms* had a lower risk of PE.
13. Among **the most important predictors of unfavourable outcome (permanent sequelae and death)** we found **lower** peripheral blood **WBC**, that has not yet been emphasized by others.

A DOLGOZAT ALAPJÁUL SZOLGÁLÓ SAJÁT KÖZLEMÉNYEK PUBLICATIONS RELATED TO THESE

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