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Review

Systematic review of oral and craniofacial findings in patients with Fabry disease or Pompe disease

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Abstract

Fabry disease and Pompe disease are rare lysosomal storage disorders that belong to a heterogeneous group of more than 200 distinct inborn metabolic diseases. Mutations followed by loss of function of enzymes or transporters that are localised in the acidic environment of the lysosome may result in degradation of many substrates, such as glycosaminoglycans, glycosphingolipids, glycogen, cholesterol, oligosaccharides, glycoproteins, and peptides, or the excretion of the products degraded by the lysosome. Our aim was to identify the oral signs and symptoms of Fabry disease and Pompe disease from a systematic review made using MEDLINE/PubMed, and a hand search for relevant articles, following the PRISMA guidelines. Both diseases show various craniofacial and oral changes, including supernumerary teeth, dental agenesis, angiokeratoma, and telangiectases in Fabry disease; and macroglossia, teeth fusion, and taurodontism in Pompe disease. Common clinical signs of Fabry disease include hyposalivation, hypohidrosis, and xerophthalmia, and a generally reduced physical resilience was apparent in patients with Pompe disease. Oral and craniofacial changes in patients with both diseases extend over their entire lifetime and can be detected even in an infant. Lysosomal storage diseases should be taken into consideration in the differential diagnosis of relevant diverse symptoms, because treatment, when available, is most effective when started early. The main therapeutic concepts are enzymatic replacement for Pompe disease, whereas patients with Fabry disease require additional oral chaperone treatment or enzyme replacement.

Keywords: Fabry disease; Pompe disease; Interdisciplinary dentistry; Rare diseases; Oral manifestations; Craniofacial findings

Introduction

Initially, we wished to draw attention to specific aspects in the search and evaluation of publications that reported rare disorders with orofacial involvement. In particular, we felt that the individual quality of the publications and the resulting problem of reviewing the published data had to be pointed out. As Fabry disease (Online Mendelian Inheritance in Man, (OMIM) number 201500) and Pompe disease (OMIM number 232300) are orphan diseases,[1] all the case reports mentioned were from single centres, and published as case reports or as small numbers of cases. The reason that we have

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looked closely only at these two diseases is that their phenotypic presentations are not as noticeable at first glance as, for example, those in patients with mucopolysaccharidosis type IV A (Morquio disease).[2] Here, the dysmorphia is particularly noticeable in the head and neck, which possibly explains the extensive number of publications available in MEDLINE concerning oral and skeletal structures for affected patients. We have been unable to find such wide-ranging descriptions for cases of the lysosomal diseases presented here.

Lysosomal storage diseases are inherited metabolic disorders that affect a number of organs, and a characteristic feature is that they are progressive, which means that symptoms and clinical signs can occur early (in infants or toddlers), and become worse in adulthood if untreated. Among the various lysosomal storage diseases (and also within each genetic defect) there is great clinical variability that makes diagnosis more difficult. Each of the diseases is rare but, taking them all together, about 1 in 8000 newborns are affected.[3] Heredity of the lysosomal storage diseases occurs mainly in an autosomal recessive manner, except for Fabry disease and Hunter disease (mucopolysaccharidosis type II), which follow an X-chromosomal inheritance.

Various definitions classify a disease as "rare". In the European Union (EU), a disease is considered "rare" if fewer than five in 10 000 people have it.[4] Accordingly, an estimated 30 million people have a rare disease in the 28 EU member states, of which 4 million live in Germany. Globally, around 8000 rare diseases are known, of which 80% have a genetic basis.[5] They are all complex (making their diagnosis extremely difficult) and their initial symptoms can develop at birth, in early childhood, or over the course of life. Because of the small number of patients who have a given rare disease, clinical trials with evidence-based results can hardly ever be conducted.

Studies have shown that ~15% of all rare diseases are accompanied by orofacial signs and symptoms.[1,6] Of the over 5000 syndromes with a genetic basis, more than 900 have been described as having dental, oral, or maxillofacial involvement.[7] Changes to the oral cavity or perioral region can be of special relevance in the early diagnosis of a rare disease.[8] Dentists, orthodontists, and oral/maxillofacial surgeons need to make an early diagnosis and provide prompt treatment of orofacial disease to improve a person's quality of life.

Public focus on rare diseases has increased in the EU since 2009 when the EU Council recommended that member states develop and implement plans and strategies for managing rare diseases at appropriate stages, or validate such measures for rare diseases within the scope of other health protection strategies, to ensure that patients with rare diseases have good medical care.[9] In particular, member states were required to develop and accept a corresponding plan by the end of 2013.

In addition, in 2009, a study commissioned by the German Ministry of Health presented measures that were aimed at improving the health of people with rare diseases in the Federal Republic of Germany.[10] This report estimated the relevance of rare diseases as being considerable and was followed, in October 2010, by the foundation of the "Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen" (National Action League for People with Rare Diseases), which was aimed at implementing the EU Council's recommendations. In 2013, the German Cabinet adopted the National Action League for People with Rare Diseases (NAMSE), which comprises 52 suggested measures and seven action strategies, one of which concerns the development of registers or databases.[11] Accordingly, in 2011 a project was initiated to develop a database for the "Recording of Orofacial Manifestations in People with Rare Diseases" (ROMSE).[11] This database should supply general practitioners, dentists, orthodontists, oral surgeons, oral and maxillofacial surgeons, and patients and their relatives, with targeted information concerning intraoral, perioral, and extraoral changes, diagnostics, and specialised area-related therapeutic options based on case reports and published reviews that are associated with treating rare diseases.[12]

Fabry disease

A deficiency of the lysosomal enzyme α-galactosidase causes Fabry disease, a rare, X-linked, metabolic disorder.[13] The continuing accumulation of glycosphingolipids containing α-galactosyl results from the deficit of this catabolic enzyme and presents in various organs. Anderson and Fabry were the first ones to describe cases in 1898. Heterozygous female patients usually have less pronounced disease than hemizygous boys or men. While some patients are diagnosed in adulthood, the primary neuropathic symptoms of Fabry disease are usually noticed during infancy.[14,15]

Patients can have painful acroparaesthesia, or digestive problems, or both. An accumulation of glycophospholipids may result in diverse systemic complications: strokes in childhood, a dysfunctional kidney, corneal dystrophy (cornea verticillata), dermal and oral angiokeratomas, cardiovascular disease, febrile episodes, and anhidrosis attributable to a functional disorder of the sweat glands.[16] Life expectancy is reduced, as varied organs are ultimately affected.[17]

Diagnosis can be confirmed by sural nerve and skin biopsy and consecutive laboratory analyses. These include urine tests to check the amount of globotriaosylceramide, the examination of α-galactosidase A activity in white cells, and dry-blood-spot analysis.[18,19] The main therapeutic concepts consist of viral-mediated gene treatment, replacement of the missing enzymes, or transplantation of bone marrow.[20–22] Since 2015, migalastat has been approved as monotherapy; it is an investigational oral small-molecule drug designed to bind to, and stabilise, endogenous α-galactosidase A to enable its trafficking (that is, as a "pharmacological chaperone") to lysosomes.[23] The prevalence of the disease is 1:100 000 births, although data from newborn screening indicate a significantly higher prevalence (about 30:100 000).[24]

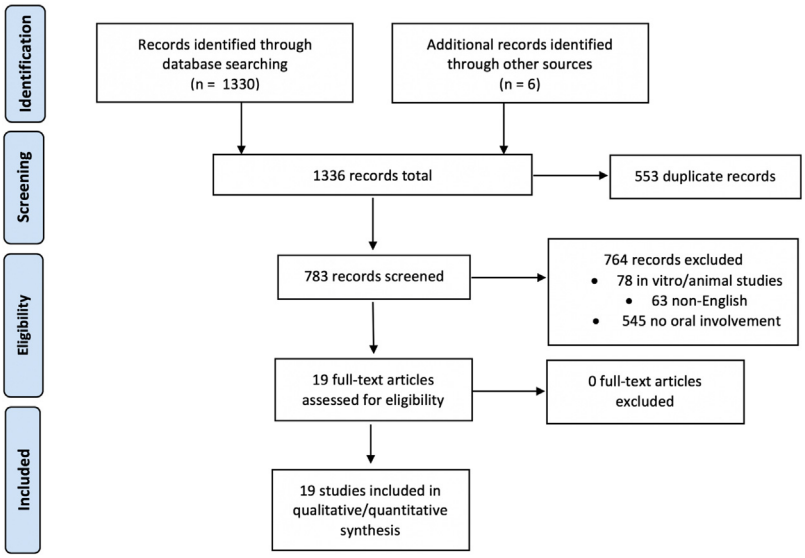

Figure 1. Flow chart for selection of records.

Pompe disease

Pompe disease (glycogen-storage disease type II or acid maltase deficiency) is a rare autosomal recessive muscular disorder. It is characterised by a deficiency of acid α-glucosidase (GAA) leading to an accumulation of glycogen in the lysosomes, primarily in cardiac and skeletal muscle cells.[25] Phenotypes of glycogen storage disease (GSD) type II include the late-onset form, which develops after the age of a year and includes juvenile and adult-onset subtypes that are considered to be part of a continuous clinical range. In addition there is the severe classic infantile form that is characterised by muscular weakness and fatal hypertrophic cardiomyopathy, plus a "non-classic" form that presents between the ages of 1 and 2 years.[26]

The adult-onset form, in particular, presents with slowly progressive paraspinal muscular weakness, or proximal lower limb weakness, or both. It is often followed by restrictive respiratory failure that can be life-threatening, as it is in infants and children.[27] Nevertheless, the range of the adult-onset form is wide, and includes patients who are symptom-free with increased creatine kinase on the one hand, and patients with rigid-spine syndrome or muscular cramps and pain syndrome on the other.[28] Additionally, clinical severity and progression of disease can lead to considerable variability.

Diagnosis is made from an increased creatinine kinase value, measurement of reduced activity of the enzyme acid α-glucosidase, and a biopsy of muscle or skin. In Europe, the rare glycogen storage diseases occur in about 1/20 000 to 25 000 births. Depending on ethnicity, GSD II makes up about 15% of the most common of the 11 previously known muscle glycogen-storage diseases, with an incidence of 1/40 000 to 1/300 000 births.[29–32]

The above symptoms have been described in only a few case reports, as we will show. Such descriptions should help us to obtain an overview of the current status of the database and will underline the relevance of dental medicine in the diagnostics and treatment of rare diseases, because orofacial involvement has been reported for both groups of patients. It is important to raise awareness of these two diseases, as early diagnosis is essential for initiating treatment. The main problem with both is delay in treatment, as symptoms are often recognised too late or not at all.[33–37] The more practitioners from a wide range of disciplines who are familiar with the symptoms, the more likely it is that the patient can be successfully treated.

Methods

We made this systematic review with the aid of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1).[38] All data were extracted from published papers, so that ethics approval was not required from our institution's ethics committee.

Search strategy and selection criteria

Our aim was to identify the oral signs and symptoms of Fabry disease and Pompe disease within a systematic review, which we made using MEDLINE/PubMed. This was followed by an additional hand search in which the same synonyms were used and combined. The search strategy included various combinations of the keywords "Fabry disease", "Pompe disease", and "lysosomal storage disease", together with maxilla, mandible, jaw, oral, dental, craniofacial, skeletal, and mouth. Inclusion criteria were met if the topic of an abstract related to the diseases was mentioned, if the paper was in the English language, and if a full text of the paper was available.

Table 1
Summary of clinical features recorded in patients with Fabry disease.

No. of cases	First author and reference	Sex	Age (years)	Dental findings	Oral hard and soft tissue findings	Skeletal findings	Type of study
1	Regattieri [42]	M	18	Supernumerary teeth	-	-	Case report
1	Brindley [17]	NA	NA	Supernumerary teeth	Angiokeratoma of gingiva, soft palate, tongue	-	Case report
1	Young [43]	M	18	Heavy accumulation of plaque	Gingival enlargement Lateral margins erythematous Gingivitis granulomatosa Cobbled tongue Glossitis granulomatosa Cheilitis granulomatosa	-	Case report
1	Chesser [44]	M	40	-	Telangiectases	-	Case report
13	Baccaglini [45]	M	21-51	Dental agenesis (1/13) Malocclusion (7/13) Diastema (5/7) and complete edentulism (2/7) Delayed eruption, dental impaction (2/13) Dental discolouration (1/13) Enamel waves (1/13)	Cysts/pseudocysts of the maxillary sinus (8/13) Angiokeratomas and telangiectases (8/13) Generalised fissuring of tongue (3/13) Localised tongue fissuring (8/13) Erythematous fungiform papillae (9/13) Pronounced papillae Xerostomia (6/13)	Mandibular / maxillary prognathism (10/13) Mouth breathing (NA)	Case series
11	Larralde [46]	5F/6M	19-56	-	Angiokeratomas (4/11)	-	Case series
1	Bidra[47]	M	41	Diastemata Severe attrition and erosion Minimal wear of mandibular incisors compared with canines Bruxism	Hypermobile maxillary lip Angiokeratomas Telangiectases Xerostomia	Bimaxillary prognathism 5 mm vertical overlap Large jaw Angle-Class I	Case report

Records were excluded if no original case reports were described, if no dental or oral involvement was mentioned, or if inadequate information about the patient was provided. Publications were identified, and abstracts evaluated by two reviewers (KB and JJ) by formal consideration of inclusion criteria and whether the content matched the purposes of the search. Agreement about inclusion or exclusion of publications by the two reviewers was expressed by calculation of Cohen's Kappa statistic (K). In total, 19 titles consisting of five series of cases and 14 case reports were selected for inclusion for further analysis after full agreement between the reviewers.

Results

The results are summarised in Tables 1 and 2, both of which show various craniofacial and oral changes that might extend over the entire lifetime and can be detected as early as in infancy.[39] The overall inter-observer agreement of methodological quality assessment was $K = 0.95$, which was deemed almost perfect agreement.[40,41]

Discussion

Most patients with Fabry disease had intraoral and perioral angiokeratomas and telangiectases on the tongue, gingiva, and soft palate. Studies reported alterations to the mucous membranes including glossitis, cobbled tongue, punctate angiectases, and angiokeratomas.[17,43,47,59] Although not pathognomonic for Fabry disease, angiokeratomas, small macules, or dark-red papules were among the most typical features.[60] They were detected periorally in most cases, the buccal mucosa being less often affected.[44] They were also found on the soft palate and gingiva, although rarely on the tongue.[17,45,47] These symptoms can appear as early as childhood, and increase throughout the lifespan, according to the "Interdisciplinary Guideline for the Diagnosis and Therapy of Fabry's Disease" by the German Society of Neurology.[61] They are characterised histologically by cytoplasmic inclusions within endothelial cells, together with vascular dilatation and fibroblasts.[44] Cheilitis granulomatosa is found not only in Fabry disease, but also in atypical tuberculosis, Crohn disease, allergic reactions, and Melkersson-Rosenthal syndromes; Fabry disease should therefore not be confused with these conditions.[62–66]

Table 2
Summary of clinical features in patients with Pompe disease.

First author and reference	No. of cases	Sex	Age (years)	Dental findings	Oral hard and soft tissue findings	Skeletal findings	Type of study
Felice [48]	2	F/M	46/53	-	Macroglossia (2/2) Weakness of tongue (2/2)	-	Case report
Metzl [39]	1	M	2 mths.	-	Macroglossia Protruding tongue	-	Case report
Jones [49]	13	6F/7M	0,53-16,10 weeks	-	Dysphagia (8/13)	-	Case series
de Gijt [50]	1	F	8	-	Massive gingival overgrowth	-	Case report
Dubrovsky [51]	19	6M/F13	14 - 78	-	Lingual weakness (19/19) Dysphagia (6/19) Dysarthria (2/19) Atrophy of tongue (1/19)	-	Case series
Hobson-Webb[52]	3	F/M/F	39/54/57	-	Oropharyngeal dysphagia	-	Case report
Maggi [53]	3 (siblings)	M/F/F	47/56/53	-	Atrophy of tongue Weakness of tongue Difficulty in swallowing Weakness of orbicularis oris	-	Case report
Jones [54]	30	22F/8M	8-72	-	Lingual weakness (24/30) Dysarthria (25/30)	-	Case series
Karam [55]	1	M	38	-	“Bright tongue sign” on magnetic resonance image	-	Case report
Milisenda [56]	1	F	66	-	Atrophic tongue Benign tumour composed of muscle Lingual pseudohypertrophy	-	Case report
Ceyhan [57]	1	M	18 mths.	Teeth fusion 51&52 Irregular tooth eruption	Macroglossia Respiratory problems Gingival swelling	-	Case report
Drazewski [58]	1	M	17	Taurodontism	Weakness of tongue	Prognathism Malocclusion	Case report

Pronounced papillae have been described, as well as variable severity of localised or even generalised fissuring of the tongue.[43,45] The subepithelial capillary vasodilatation might create a clinical effect of increased size and colouring of the fungiform papillae. Some patients have “prominent lips” or even “thick moustaches” as a consequence of the inherent prognathism of their apical skeletal bases. The abnormal soft tissue is gauged to be secondary to that. Gordts et al,[67] detected cysts, or polyps, or both, by magnetic resonance imaging (MRI) in the maxillary sinuses of 21% of all their study participants; these have also been detected in 61% of the cases of another study group.[45] Retention cysts or mucocoeles have been found on panoramic radiographs in 1.4% to 9.6%.[68,69] Malocclusion was also a common finding. Baccaglini et al[45] as well as previous investigators [17,42]reported delayed eruption, general discolouration, and dental agenesis as single conditions as well as in combination with widely spaced teeth and multiple supernumerary, unerupted, and impacted teeth in patients with Fabry disease.

Another lysosomal storage disease that shares findings with Fabry disease, such as abnormal eruption or dentofacial development, is Krabbe disease.[70] Scanning electron microscopic studies of primary teeth have predominantly shown wavy enamel surfaces, enamel hypoplasia, and hypomineralisation. The primary teeth of these patients contain lysosomal inclusions in the pulpal cells, as well as an increased agglomeration of trihexosyl ceramide, a perivascular periodic-acid-Schiff-positive glycosphingolipid.[70] Consequently it has been suggested that analysis of the dental, and particularly pulpal, tissue could serve as a diagnostic test.[59] Saliva and buccal epithelial cells have also been suspected to contain increased amounts of ceramide trihexoside.[59] Future studies are planned to address these issues.

Reports of skeletal abnormalities included increased head size, an extended sella turcica, and an acromegalic-like phenotype.[17] In two studies patients had mandibular or maxillary prognathism (or both).[45,47] Cephalometric abnormalities such as these had not been described in previous studies. Because of the small number of published cases, however, no general statement can be made as to whether a connection with the disease can be derived.

Rather than abnormal dentition, diastemata of dentate patients who have not previously had orthodontic treatment can be ascribed to a discrepancy in dentoalveolar size.[45,47] As a result of involving the nervous system, hyposalivation, hypohidrosis, and xerophthalmia have been noted in patients with Fabry disease.[71] Facial paraesthesia, impairment of taste and smell, odontogenic-like pain, glossomotor dysfunction, and trigeminal neuralgia have nevertheless been reported.

Their origin lies in neurological alterations of the cranial nerves.[71]

The clinical presentation of macroglossia governs most of the reported changes in patients with Pompe disease. For example, in one case, hypertrophy of the gingiva was reported,[50] and a benign tumour was diagnosed in another.[56] A reduction in muscle tone leads to increased mobility of the tongue, which can also be reproduced by a manual muscle test. These data suggest lingual weakness, and occur relatively often and early in those with late-onset Pompe disease.[51] One patient described by Hobson-Webb et al noted feeling that her tongue sometimes did not react "like it should".[52] Although further study is necessary, the finding of lingual weakness might be an important observation in the differential diagnosis of late-onset Pompe disease.

This diagnosis is often difficult and may include several forms of muscular dystrophy or other diseases of muscle. Weakness of the tongue is not a presenting symptom of Pompe disease, although it might be an important early clinical hint found only through careful investigation. As enzyme replacement has been available for roughly 10 years, and because the data suggest that early intervention improves outcomes, this is now particularly relevant.[72–74] Some patients can develop functional consequences of lingual weakness, such as dysphagia and dysarthria.

Dental abnormalities have also been reported recently; taurodontism and fusion of teeth have been described in case reports concerning two young boys, together with prognathism and malocclusion.[57,58] In addition, the so-called "bright-tongue sign" can be detected by MRI.[55] The bright colour results from fatty infiltration of the tongue.[51]

Another phenomenon that results in the degeneration of the musculature in these patients is the use of respiratory auxiliaries to ensure an adequate supply of oxygen. There is also a general reduced physical resilience that is indicated by frequent pauses during climbing stairs or walking within the rooms of the medical practice. Frequent physiotherapeutic exercises should alleviate motor deficits, prevent contractures, and stabilise weak respiratory muscles.

As with most other muscular disorders, Pompe disease has not yet to our knowledge been the subject of controlled trials or treatment protocols for optimal treatment, even though most patients benefit from regular physiotherapy. A moderate exercise programme adapted to the degree of disability should be undertaken to avoid muscular overload. In addition, as mobility becomes increasingly restricted, sufficient supplies of excipients should be provided to maintain mobility.[25] The importance of dietary measures such as a protein-rich or low-carbohydrate diets, has not been clarified. Gastrointestinal symptoms can also develop as a result of the disease, as a case report with an improvement of chronic diarrhoea, abdominal fullness, and incontinence of stool during enzyme treatment, has shown.[75]

Bone density is reduced, even in juvenile patients, proportionally to the muscle weakness.[76] As in all cases of secondary osteoporosis, no treatment has to our knowledge been validated in studies. A measurement of bone density and the treatment of osteoporotic factors, such as vitamin D deficiency, are useful. Medication – for example, treatment with bisphosphonates - has to be decided in individual cases because of the lack of appropriate studies. If such treatment is necessary, special dental care is needed for the patient because of the risk of a bisphosphonate-associated osteonecrosis of the jaw, as this is an often-reported result after interventions.[77]

The papers investigated have provided a great deal of information about orofacial alterations in affected patients at the time of their examination. Whether the findings were initial signs and symptoms or had occurred years previously (difficult to work out at a later date) was not clear. An exact distinction between early-onset and adult-onset forms of the disease and their specific oral signs could not be made. This might be possible if an early-stage examination of newborns who were diagnosed with either of the diseases is followed up by regular screening at short-term recall sessions.

However, we found no studies that mentioned the course of the respective treatments or any changes that might have occurred. Further clinical studies and long-term observations have to be initiated and will be conducted by our study group in the near future to improve our knowledge of this field of oral medicine and to support patients by recording oral and craniofacial alterations.

Conclusion

Lysosomes are cell organelles that break down complex macromolecules into small fractions. These are degraded by a large number of hydrolases, each of which is specialised for the digestion of a specific substrate. As a result of the disturbed function of multiple organ systems, a genetic defect in one enzyme can lead to the accumulation of substances that cannot be degraded. For all lysosomal storage disorders, the progressive course of the disease is the same: the signs and symptoms include organomegaly, muscular degeneration, and skeletal deformities. Diagnosis is difficult because of the rarity and variability of the symptoms and often ends in unsuccessful and frustrating treatments. Here, any oral findings during the primary diagnosis – such as macroglossia, dysphagia at an early age, or angiokeratoma, can have an important role, because a suspicious diagnosis will lead to the transfer of the patient to a specialist centre.

Interdisciplinary treatment is the focus here, which enables physicians and patients to act early and possibly to prevent or delay deterioration in the symptoms. Early initiation can be life-saving and might prevent irreversible damage.

ROMSE can serve as a register for suspicious diagnoses, as many findings relating to orofacial changes in people with rare diseases are deposited in this database, which is based on searches of published papers and made available to medical specialists.[12] The aim of this project is to avoid the affected patient having unnecessary additional examinations

and treatments. Nevertheless both diseases still require much research and clinical investigation.

To the best of our knowledge, this is the first review that highlights the different presentations of these two lysosomal storage diseases, Fabry disease and Pompe disease. Lysosomal storage diseases should be taken into consideration in the differential diagnosis of diverse symptoms. Because treatment, when available, is most effective when started early in the course of the disease, a high index of suspicion is crucial. A speedy diagnosis might allow both early treatment to prevent irreversible clinical complications, and genetic counselling.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

All the data given in this paper were extracted from published papers, so that ethics approval was not required from our institutional ethics committee. The patient's permission was not necessary.

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